Effect of Ring Size on Coordination Properties of *trans*-1,2-Cycloalkanediamine Ligands: Synthesis of Dinuclear Platinum(II) Complexes as Potential DNA Cross-Linkers

Sandrine Ongeri,[†] David J. Aitken,*[,†,‡] Henri-Philippe Husson,[†] Jiří Kozelka,[§] and Bernard Viossat[||]

Laboratoire de Chimie Thérapeutique associé au CNRS-UMR 8638, Université René Descartes (Paris V), 4 avenue de l'Observatoire, 75270 Paris Cedex 06, France, Laboratoire de Chimie et Biochimie Pharmacologiques et Toxicologiques associé au CNRS-UMR 8601, Université René Descartes (Paris V), 45 rue des Saints-Pères, 75270 Paris Cedex 06, France, Laboratoire SEESIB associé au CNRS-UMR 6504, Département de Chimie, Université Blaise Pascal (Clermont-Ferrand II), 24 avenue des Landais, 63177 Aubière Cedex, France, and Laboratoire de Chimie Générale, Faculté de Médecine et de Pharmacie, Université de Poitiers, 34 rue du Jardin des Plantes, BP 199, 86005 Poitiers Cedex, France

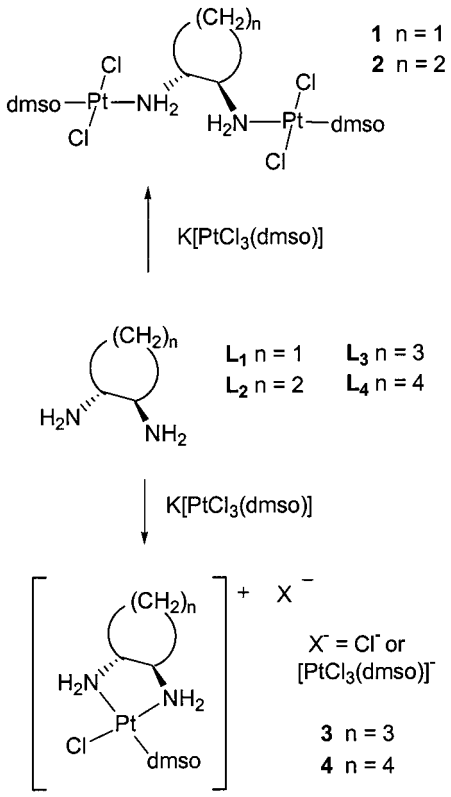
Received March 28, 2000

Introduction

Recently, a novel class of dinuclear platinum complexes has been introduced by Farrell et al. and shown to display interesting antitumor properies.[1] In these compounds, two $PtCl_nN_{4-n}$ centers (N stands for a primary or secondary amino group; $n = 1, 2$) are generally connected by a flexible linker (e.g., an alkyl chain). DNA binding studies have suggested that these complexes form a different spectrum of adducts than does the well-established antitumor drug cisplatin (*cis*-$[PtCl_2(NH_3)_2]$).[2] This may be related to the observation that the antitumor active dinuclear compounds and cisplatin do not show cross-resistance.

An analysis of DNA adducts has revealed that the dinuclear compounds form considerably more interstrand cross-links than cisplatin.[2] Although cross-linking of adjacent guanines—the most frequent DNA-binding mode for cisplatin—is still possible with the Farrell compounds,[3] the amounts of these intrastrand cross-links is significantly reduced as compared with cisplatin. Reducing the number of short-range intrastrand cross-links in favor of long-range (intra- or interstrand) cross-links thus seems to confer to the new dinuclear compounds a therapeutic activity distinct from that of cisplatin. It therefore appeared interesting to us to prepare dinuclear platinum amine complexes which would form long-range cross-links *exclusively*, i.e., which could not form any short-range cross-links at all. To this end, we sought to connect the platinum coordination spheres with a rigid linker that would fix the platinum at remote positions. In the present paper, we report that such fixation has been achieved using *trans*-1,2-cycloalkanediamine ligands. We show here that *trans*-1,2-cyclopropanediamine (**L$_1$**) and *trans*-1,2-cyclobutanediamine (**L$_2$**) readily react with 2 equiv of $K[PtCl_3(dmso)]$ to yield the uncharged dinuclear complexes *trans*-$[\{PtCl_2(dmso)\}_2(\mu\text{-}\mathbf{L_1})]$ (**1**) and *trans*-$[\{PtCl_2(dmso)\}_2(\mu\text{-}\mathbf{L_2})]$ (**2**), respectively (Scheme 1). On the other hand, under the same conditions, *trans*-1,2-cyclohexanediamine (**L$_4$**), a well-known chelator, and *trans*-1,2-cyclopentanediamine (**L$_3$**), whose chelating ability is less well established, yield the mixed complex salts $[PtCl(\mathbf{L_4})(dmso)][PtCl_3(dmso)]$ and $[PtCl(\mathbf{L_3})(dmso)][PtCl_3(dmso)]$, respectively.

Scheme 1



Experimental Section

Reagents and Instrumentation. The racemic ligands *trans*-1,2-cyclopropanediamine (**L$_1$**),[4] *trans*-1,2-cyclobutanediamine (**L$_2$**),[5] and *trans*-1,2-cyclopentanediamine (**L$_3$**)[6] were prepared as their dihydrochloride salts as previously described; *trans*-1,2-cyclohexanediamine (**L$_4$**) was obtained commercially as the free base. The salt $K[PtCl_3(dmso)]$ was prepared according to Kukushkin's procedure[7] and was crystallized from water to give analytically pure material. All NMR spectra were recorded in DMF-d_7 solutions (unless otherwise stated) on a Bruker AC-300 instrument for ^{1}H (300.13 MHz) and $^{13}C\{^1H\}$ (75.43 MHz) or a Bruker ARX-250 instrument for ^{195}Pt (53.63 MHz).

* Corresponding author (at Université Blaise Pascal). E-mail: aitken@chisg1.univ-bpclermont.fr.

† Laboratoire de Chimie Thérapeutique, Université René Descartes.

‡ Université Blaise Pascal.

§ Laboratoire de Chimie et Biochimie Pharmacologiques et Toxicologiques, Université René Descartes.

|| Université de Poitiers.

(1) Farrell, N.; Qu, Y.; Bierbach, U.; Valsecchi, M.; Menta, E. In *Cisplatin*: *Chemistry and Biochemistry of a Leading Anticancer Drug*; Lippert, B., Ed.; Wiley-VCH: Weinheim, 1999; pp 479−496.

(2) Kaspárková, J.; Nováková, O.; Vrána, O.; Farrell, N.; Brabec, V. *Biochemistry* **1999**, *38*, 10997.

(3) Qu, Y.; Bloemink, M. J.; Reedijk, J.; Hambley, T. W.; Farrell, N. *J. Am. Chem. Soc.* **1996**, *118*, 9307.

(4) Wittiak, D. T.; Lee, H. T.; Hart, R. W.; Gibson, R. E. *J. Med. Chem.* **1977**, *20*, 630.

(5) Vergne, F.; Partogyan, K.; Aitken, D. J.; Husson, H.-P. *Tetrahedron* **1996**, *52*, 2421.

(6) Ongeri, S.; Aitken, D. J.; Husson, H.-P. *Synth. Commun.* **2000**, *30*, 2593.

(7) Kukushkin, Y. N.; Vyaz′menskii, Y. E.; Zorina, L. I.; Pazukhina, Y. L. *Russ. J. Inorg. Chem.* **1968**, *13*, 1573.

10.1021/ic000334p CCC: $19.00
Published on Web 11/29/2000

Positive mode electrospray mass spectra were obtained using a Nermag R30-10 quadrupole instrument fitted with an Analytica source. Isotopic peaks with appropriate relative intensities were observed for each fragment, the largest of which is reported.

General Procedure for the Preparation of Platinum Complexes. A solution of K[$PtCl_3$(dmso)] (1.10 mmol) and the diamine ligand (or its dihydrochloride plus 2 equiv of aqueous KOH solution) (0.50 mmol) in water (10 cm^3) was heated at 40 °C for 3−4 h, during which time a solid formed. After cooling, the solid was isolated by filtration, was washed successively with water, ethanol, and ether, and then was dried in vacuo over P_2O_5.

Complex 1: obtained as a pale yellow solid in 75% yield. ^{1}H NMR: δ 1.17 (t, J = 6.8 Hz, 2H), 2.92 (m, 2H), 3.34 (s, 12H), 5.22 (s, 2H), 5.42 (s, 2H). ^{13}C{^{1}H} NMR: δ 15.1, 35.4, 43.1. ^{195}Pt NMR: δ −3110. MS: m/z 799 $[M + K]^+$, 783 $[M + Na]^+$. Anal. Calcd for $C_7H_{20}Cl_4N_2O_2Pt_2S_2$: C, 11.06; H, 2.65; N, 3.68; S, 8.43; Cl, 18.60. Found: C, 11.15; H, 2.53; N, 3.75; S, 8.33; Cl, 18.86.

Complex 2: obtained as a beige solid in 71% yield. ^{1}H NMR: δ 1.79 (m, 2H), 2.10 (m, 2H), 3.33 (s, 12H), 3.68 (m, 2H), 5.42 (m, 4H). ^{13}C{^{1}H} NMR: δ 23.0, 43.0, 57.7. ^{195}Pt NMR: δ −3113. MS: m/z 813 $[M + K]^+$, 797 $[M + Na]^+$. Anal. Calcd for $C_8H_{22}Cl_4N_2O_2Pt_2S_2$: C, 12.41; H, 2.86; N, 3.62; S, 8.28; Cl, 18.31. Found: C, 12.76; H, 2.61; N, 3.42; S, 7.88; Cl, 18.02.

Salt 3·[$PtCl_3$(dmso)]: obtained as a yellow solid in 58% yield. ^{1}H NMR: δ 1.63 (br m, 2H), 1.78 (br m, 2H), 2.18 (br m, 2H), 3.34 (s + d, J = 21 Hz, 6H), 3.47 (s, satellites visible, 3H), 3.49 (s, satellites visible, 3H), 3.57−3.68 (br m, 2H), 5.92 (m, 4H). ^{13}C{^{1}H} NMR: δ 23.8, 26.3, 43.4, 43.5 (s + d, J = 56 Hz), 43.9, 68.1, 68.4. ^{195}Pt NMR: δ −3052, −2964. MS: m/z 408 $[M]^+$. Anal. Calcd for $C_9H_{24}Cl_4N_2O_2Pt_2S_2$: C, 13.71; H, 3.07; N, 3.65; S, 8.13; Cl, 17.99. Found: C, 14.07; H, 2.95; N, 3.66; S, 7.84; Cl, 17.69.

Salt 4·[$PtCl_3$(dmso)]:[8] obtained as a yellow solid in 90% yield. ^{1}H NMR: δ 1.15 (m, 2H), 1.53 (m, 4H), 2.12 (m, 2H), 2.75 (m, 2H), 3.34 (s + d, J = 21 Hz, 6H), 3.45 (s, satellites visible, 3H), 3.47 (s, satellites visible, 3H), 5.80 (s, 2H), 6.28 (s, 2H). ^{13}C{^{1}H} NMR: δ 24.4, 32.3, 32.5, 43.3 (s + d, J = 56 Hz), 43.5, 43.6, 62.3. ^{195}Pt NMR: δ −3268, −2964. MS: m/z 423 $[M]^+$. Anal. Calcd for $C_{10}H_{26}Cl_4N_2O_2Pt_2S_2$: C, 14.97; H, 3.27; N, 3.49; S, 7.99; Cl, 17.67. Found: C, 15.11; H, 3.42; N, 3.51; S, 7.94; Cl, 17.97.

Salt 3·Cl. A solution of *trans*-1,2-cyclopentanediamine (0.50 mmol) and K[$PtCl_3$(dmso)] (0.50 mmol) in water (5 cm^3) was heated at 40 °C for 18 h. After cooling, the solution was filtered and the filtrate was evaporated to dryness. The residue was digested in anhydrous methanol (5 cm^3) and the solution filtered. The filtrate was treated with dry ether until the solution became turbid, and was set aside at 0 °C for 24 h. The product was isolated by filtration and obtained as a white solid in 76% yield. ^{1}H NMR (CD_3OD): δ 1.57 (br m, 2H), 1.90 (br m, 2H), 2.33 (br m, 2H), 3.40 (m, 2H), 3.58−3.62 (m, 6H). ^{13}C{^{1}H} NMR (CD_3OD): δ 24.4, 24.5, 26.8, 44.1, 44.3, 68.4, 68.8. ^{195}Pt NMR (CD_3OD): δ −3058 (major), −3096 (minor).

Salt 4·Cl. The above procedure was repeated using *trans*-1,2-cyclohexanediamine to give the product as a white solid in 84% yield. ^{1}H NMR (D_2O): δ 0.98 (br m, 2H), 1.13 (m, 2H), 1.43 (m, 2H), 1.88 (m, 2H), 2.41 (m, 2H), 3.24 (s, satellites visible, 3H), 3.27 (s, satellites visible, 3H). ^{13}C{^{1}H} NMR (D_2O): δ 23.6, 31.9, 32.2, 43.0, 43.2, 61.5, 61.7. ^{195}Pt NMR (D_2O): δ −3284. Anal. Calcd for $C_8H_{20}Cl_2N_2OPtS$: C, 20.97; H, 4.40; N, 6.11; S, 7.00; Cl, 15.47. Found: C, 20.57; H, 4.26; N, 5.92; S, 6.86; Cl, 15.25.

Crystallographic Structure Determination. An X-ray diffraction study of a single crystal of complex **4**·[$PtCl_3$(dmso)] was performed on a Stoe Imaging Plate Diffraction System (IPDS) using graphite-monochromated Mo Kα radiation. Crystal data: $C_{10}H_{26}Cl_4N_2O_2Pt_2S_2$, fw = 802.44, monoclinic, space group $P2_1/n$, Z = 4, a = 10.345(1) Å, b = 11.306(1) Å, c = 18.083(2) Å, β = 98.93(2)°, V = 2089 Å^3, d_{calc} = 2.55 g·cm^{-3}; 4067 unique reflections were measured and used in refinement. All computations were carried out using Stoe software (IPDS Manual, Version 2.75). No absorption correction was applied. The structure was solved by direct methods using SIR92 and refined by least-squares procedures on F_o with the PC CRYSTALS package program. The final R1 factor was 0.0382 for 3353 reflections with $I > 2\sigma(I)$. The molecule was drawn with the help of CAMERON.

Full details are available as Supporting Information.

Results and Discussion

Each *trans*-1,2-cycloalkanediamine was reacted with 2 molar equiv of K[$PtCl_3$(dmso)] in aqueous solution (Scheme 1). The choice of K[$PtCl_3$(dmso)] as the starting material allowed the unequivocal differentiation between a mononuclear ionic product in which the diamine chelates Pt^{II}, and an electrically neutral dinuclear complex with a bridging diamine ligand, by means of mass spectrometry and NMR spectroscopy. In the former case, the second equivalent of [$PtCl_3$dmso]$^-$ serves as counterion and forms a water-insoluble precipitate.

The cyclopropane and cyclobutane ligands (**L_1** and **L_2**) reacted in comparable fashion, giving respectively complexes **1** and **2** as single products in good yield. Their dinuclear composition was indicated by the electrospray mass spectral data, and their solution state structures were confirmed by NMR data obtained in DMF-d_7: only one type of DMSO molecule (single ^{1}H and ^{13}C NMR signal sets) and one type of platinum center (single ^{195}Pt NMR signal around −3110 ppm) were evidenced, while ^{1}H signal integration indicated a 2:1 ratio of DMSO to diamine in the molecule. The trans substitution pattern of each square-planar platinum center, predicted on account of the strong trans effect of DMSO, was supported by the apparent equivalence of the DMSO methyl groups. The dinuclear structure of **2** was also confirmed in the solid state by an X-ray diffraction study, communicated elsewhere.[9]

In contrast, the cyclopentane and cyclohexane based ligands (**L_3** and **L_4**) reacted to produce salts having chelated mononuclear platinum(II) cations **3** and **4**, as suggested by MS data. In each case, the anion was the second (unreacted) equivalent of [$PtCl_3$dmso]$^-$, easily identified from its NMR data. For each cation, a single ^{195}Pt signal was observed, while the ^{1}H and ^{13}C NMR spectra showed one set of signals each for DMSO and diamine. The proximity of a chiral diamine ligand rendered the DMSO methyl groups nonequivalent. The lack of an in-plane symmetry axis gave rise to distinct signals for the two methyne and the two adjacent methylene centers of the diamine ligands.

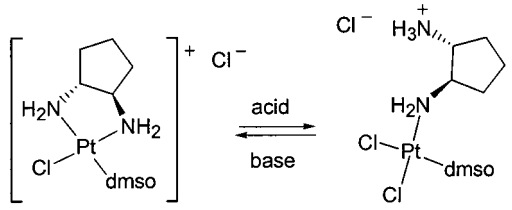
The effect of ring size on ligand behavior became particularly clear when the above reactions were repeated using only 1 equiv of K[$PtCl_3$(dmso)]. Ligands **L_1** and **L_2**, unable to chelate, gave only small amounts of the bridging complexes **1** and **2**, accompanied by a number of other, nonidentified species. On the other hand, **L_3** and **L_4** again yielded the mononuclear cations **3** and **4**, this time as their chloride salts, which were appreciably more soluble in protic solvents than the [$PtCl_3$dmso]$^-$ salts.

A difference in the behavior of salts **3**·Cl and **4**·Cl was noted upon isolation (see Experimental Section). Whereas the latter was obtained in analytically and spectroscopically pure form, the elemental analysis of the former corresponded to the formula **3**·Cl + nHCl, with n ranging between 0.25 and 0.4. The CD_3OD solution of the product displayed a major ^{195}Pt NMR signal at −3062 ppm, corresponding to cation **3**, and a minor signal at −3138 ppm, attributable to the ring-opened dichloro complex with a protonated NH_3^+ group (Scheme 2). Addition of a small amount of nitric acid to the solution inverted the proportions, the upfield signal becoming predominant; subsequent addition of tetrapropylammonium hydroxide redressed the balance and

(8) The cation **4** has been prepared as its nitrate by a different route: Farrell, N.; Kiley, D. M.; Schmidt, W.; Hacker, M. P. *Inorg. Chem.* **1990**, *29*, 397.

(9) Aitken, D. J.; Husson, H.-P.; Nguyen-Huy, D.; Ongeri, S.; Vergne, F.; Viossat, B. *Inorg. Chem. Commun.* **1998**, *1*, 314.

Scheme 2



returned primacy to the downfield signal once again. These observations support the pH-dependent equilibrium shown in Scheme 2. A similar reversible ring opening was observed for $[PtCl(en)(dmso)]^+Cl^-$ by Tobe et al.[10] This tendency of $\mathbf{L_3}$, not observed for $\mathbf{L_4}$, indicates that the five-membered ring of the former involves appreciable strain.

The relative strain induced in the cycloalkane ring of the diamine ligands upon chelation of a Pt^{II} center can be roughly evaluated using simple molecular models. If, in energy-minimized structures of the cycloalkanes,[11] the C−H bonds are replaced by single C−N bonds of 1.48 Å length, the minimum N···N distances between vicinal nitrogens bound in the trans configuration are 3.81, 3.65, 3.16, and 2.93 Å for $\mathbf{L_1}$, $\mathbf{L_2}$, $\mathbf{L_3}$, and $\mathbf{L_4}$, respectively. For the strain-free chelation of a square-planar Pt^{II} center having two Pt−N bonds of 2.05 Å, the required N···N distance is of $\sqrt{2} \times 2.05$ Å = 2.90 Å. Thus, whereas chelation of a platinum center by $\mathbf{L_4}$ involves only minimal strain, the ring strain induced by platinum chelation by $\mathbf{L_3}$ is expected to be somewhat larger, and for $\mathbf{L_1}$ and $\mathbf{L_2}$, the strain would be so large that chelation is impossible. Our experimental observations are fully in line with these model-based predictions.

The solid state structure of the crystal structure of **4**·$[PtCl_3$(dmso)] was confirmed by X-ray diffractometry and is presented in Figure 1. The square-planar geometry, bond distances, and angles around the Pt^{II} centers are unexceptional; in the cation, the *trans*-1,2-cyclohexanediamine ligand adopts a chair conformation with the two amine groups in equatorial positions, as found in other Pt^{II} complexes bearing this ligand.[12]

In conclusion, we have used the diamine ligands $\mathbf{L_1}$ and $\mathbf{L_2}$ to prepare the dinuclear complexes **1** and **2**, respectively, in which the positions of the platinum centers are fixed by the rigid cycloalkane framework. These complexes are stable as solids as well as in DMF solution, which is particularly noteworthy in the case of **1**, in view of the high reactivity of the free diamine.[13] It is interesting to compare these results with the previous work of Tobe et al.,[14] who showed that, with unhindered 1,ω-alkanediamines, separation of the two amine functions by a four-atom carbon chain was required before bridging properties were observed for the ligand.

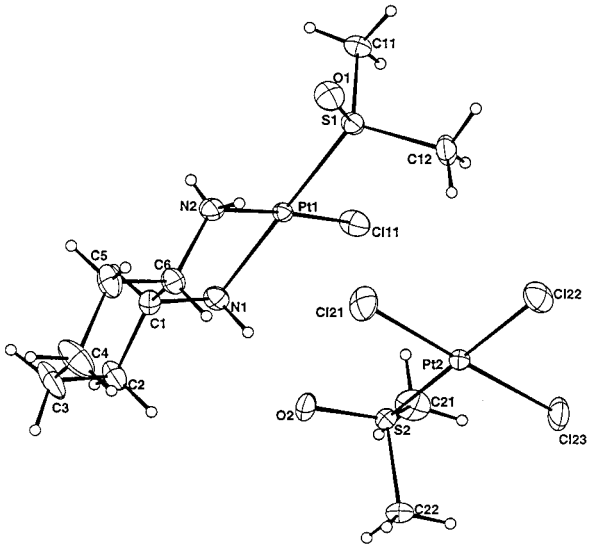


Figure 1. Perspective view of compound **4**·$[PtCl_3$(dmso)] drawn with thermal ellipsoids at the 50% probability level. Selected bond distances (Å) and bond angles (deg): Pt(1)−S(1) 2.203(2), Pt(1)−N(1) 2.067(6), Pt(1)−Cl(11) 2.292(2), Pt(1)−N(2), 2.044(6), S(1)−Pt(1)−Cl(11) 92.41(6), S(1)−Pt(1)−N(1) 174.6(2), S(1)−Pt(1)−N(2) 93.4(2), Cl(11)−Pt(1)−N(1) 92.0(2), Cl(11)−Pt(1)−N(2) 174.1(2), N(1)−Pt(1)−N(2) 82.3(2). Torsion angle (deg): N(1)−C(1)−C(6)−N(2) 51.8(7).

The ligands $\mathbf{L_1}$ and $\mathbf{L_2}$ could be used for the synthesis of other dinuclear platinum complexes, for instance those having two identical or nonidentical $PtClN_3$ centers. Such complexes would resemble the dinuclear Farrell compounds with monofunctional platinum centers but would be capable of cross-linking only remote DNA bases, short-range cross-links being impeded. Synthesis of these compounds is in progress. Finally, we note that reacting a diamine ligand with $K[PtCl_3$(dmso)] represents a straightforward assay allowing the evaluation of the (bridging or chelating) metal binding preferences of the ligand.

Acknowledgment. This work was supported by a grant from the Rectorat des Universités de Paris (to S.O.). We thank F. Libot, Université René Descartes, for recording the mass spectra and B. Donnadieu, Université de Toulouse, for assistance with the X-ray diffraction study.

Supporting Information Available: Crystallographic data for compound **4**·$[PtCl_3$(dmso)] in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

IC000334P

(10) Romeo, R.; Lanza, S.; Tobe, M. L. *Inorg. Chem.* **1977**, *16*, 785.
(11) The energy minimizations were performed with the DISCOVER program using the CVFF force field. The minimum energy conformations of cyclopentane and cyclohexane have envelope and chair conformations, respectively.
(12) Bruck, M. A.; Bau, R.; Noji, M.; Inagaki, K.; Kidani, Y. *Inorg. Chim. Acta* **1984**, *92*, 279.
(13) von der Saal, W.; Quast, H. *J. Org. Chem.* **1996**, *61*, 4920.
(14) Romeo, R.; Minniti, D.; Lanza, S.; Tobe, M. L. *Inorg. Chim. Acta* **1977**, *22*, 87.