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cis-$\{Pt(NH_3)_2(L)\}^{2+/+}$ (L = Cl, H_2O, NH_3) Binding to Purines and CO: Does π-Back-Donation Play a Role?

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The ability of *cis*-$\{Pt(NH_3)_2(L)\}^{2+/+}$, a molecular fragment of the anticancer drug cisplatin, to bind to purines and CO by π-back-donation from Pt to the ligand was examined computationally. Optimized geometries and computed vibrational frequencies suggest that *cis*-$\{Pt(NH_3)_2(L)\}^{2+/+}$ (L = Cl, H_2O, NH_3) is a poor π-donor and that π-back-donation does not play an important role for Pt(II)–ligand interactions in general.

Cisplatin is a potent anticancer drug[1] that is widely used to treat testicular, ovarian, head, and neck cancer.[2] Much is known about its mode of action,[3,4] and guanine (G) in genomic DNA has been identified to be the primary cellular target. Initial electrophilic attack at the N7 position of G is followed by a reaction of the Pt-center with an adjacent purine base to give a 1,2-intrastrand cross-link, which leads to bending and unwinding of DNA.[5] This lesion suppresses DNA replication and transcription, ultimately leading to cell death.[6] Despite much effort to optimize the drug by varying the ligand composition, only three Pt-based drugs have been FDA-approved, namely cisplatin, oxaliplatin,[7,8] and carboplatin.[9,10]

Recently, we[11] and others[12−18] have presented a number of theoretical studies aimed at identifying new leads to rational drug design. Detailed MO-studies revealed the Pt−N bonding to be unusually complicated.[11] In good agreement with experimental data, the calculated Pt−N bond strength is notably greater in the cisplatin-G adduct than in its adenine (A) analogue.[19−21] Whereas there is no controversy over the relative energetics of cisplatin−purine interactions, some disagreement exists about which electronic features are responsible for this behavior. Given the similarity of the two purine bases, the main character of binding is probably identical in both adducts, and the distinction stems from small differences of the purine-based molecular orbitals that promote Pt-binding. Recently, we found that a combination of differences in the strength of hydrogen-bonding and the σ-bond component is at work,[20] whereas π-back-donation from the occupied metal d-orbital to the ligand-based π^*-orbital does not play an important role.[11] We concluded that the distortions in the π-orbital subspace upon platination are due to relaxation effects that do not involve the Pt−N bond directly. Another study,[12] however, proposes that such interaction is present and important for the binding of cisplatin to purine bases. Conceptually, it is reasonable to suspect that π-back-donation plays a role in determining the Pt−N bonding, because the d^8-Pt(II) center should in

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(1) *Platinum and Other Metal Coordination Compounds in Cancer Chemotherapy*; Plenum Press: New York, 1996.
(2) Go, R. S.; Adjei, A. A. *J. Clin. Oncol.* **1999**, *17*, 409.
(3) Jamieson, E. R.; Lippard, S. J. *Chem. Rev.* **1999**, *99*, 2467.
(4) Fuertes, M. A.; Alonso, C.; Perez, J. M. *Chem. Rev.* **2003**, *103*, 645.
(5) Sherman, S. E.; Lippard, S. J. *Chem. Rev.* **1987**, *87*, 1153.
(6) Mello, J. A.; Lippard, S. J.; Essigmann, J. M. *Biochemistry* **1995**, *34*, 14783.
(7) Raymond, E.; Chaney, S. G.; Taamma, A.; Cvitkovic, E. *Ann. Oncol.* **1998**, *9*, 1053.
(8) Spingler, B.; Whittington, D. A.; Lippard, S. J. *Inorg. Chem.* **2001**, *40*, 5596.
(9) Teuben, J. M.; Bauer, C.; Wang, A. H. J.; Reedijk, J. *Biochemistry* **1999**, *38*, 12305.
(10) Wagstaff, A. J.; Ward, A.; Benfield, P.; Heel, R. C. *Drugs* **1989**, *37*, 162.
(11) Baik, M. H.; Friesner, R. A.; Lippard, S. J. *J. Am. Chem. Soc.* **2002**, *124*, 4495.
(12) Deubel, D. V. *J. Am. Chem. Soc.* **2002**, *124*, 5834.
(13) Carloni, P.; Sprik, M.; Andreoni, W. *J. Phys. Chem. B* **2000**, *104*, 823.
(14) Zhang, Y.; Guo, Z. J.; You, X. Z. *J. Am. Chem. Soc.* **2001**, *123*, 9378.
(15) Cochran, K.; Forde, G.; Hill, G. A.; Gorb, L.; Leszczynski, J. *Struct. Chem.* **2002**, *13*, 133.
(16) Burda, J. V.; Zeizinger, M.; Sponer, J.; Leszczynski, J. *J. Chem. Phys.* **2000**, *113*, 2224.
(17) Burda, J. V.; Sponer, J.; Leszczynski, J. *J. Biol. Inorg. Chem.* **2000**, *5*, 178.
(18) Burda, J. V.; Sponer, J.; Hrabadkova, J.; Zeizinger, M.; Leszczynski, J. *J. Phys. Chem. B* **2003**, *107*, 5349.
(19) Reedijk, J. *Proc. Natl. Acad. Sci. U.S.A.* **2003**, *100*, 3611.
(20) Baik, M. H.; Friesner, R. A.; Lippard, S. J. *J. Am. Chem. Soc.* **2003**, *125*, 14082.
(21) Chval, Z.; Sip, M. *Collect. Czech. Chem. Commun.* **2003**, *68*, 1105.

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principle be able to interact favorably with the low lying π*-orbital of the purine ligand. The π*-orbitals of G and A differ slightly owing to the keto and amino groups at the C6 position in G and A, respectively. Thus, on first sight, π-back-donation is a promising distinctive feature that might provide insight into why the platinum binding to these two purine bases is different. It is difficult, however, to provide an unambiguous answer to the question of whether this electronic feature is present. The complexity of the molecular orbital mixing in this intrinsically asymmetric molecule makes it impossible to attribute MO-deformations cleanly to a simple and unbiased feature.

As a part of our ongoing effort to derive a thorough characterization of the electronic properties that determine the binding of cisplatin to purine bases, we examined how the Pt-center in cisplatin interacts with a typical π-acid ligand, carbon monoxide.

In experimental organometallic chemistry, the vibrational stretching frequency of the carbon monoxide ligand is commonly taken as a reliable reporter for the extent of π-back-donation in metal carbonyl complexes.[22−24] As a result of partial occupation of the C−O π*-orbital, notable shifts of the vibrational frequency from its unperturbed value of 2143 cm^{-1} are observed. In addition, C−O bonds in these complexes are expected to be longer than 1.128 Å, which is found in free carbon monoxide.[25] Inspired by the use of this experimental probe, we applied the same logic to test the ability of the *cis*-$\{Pt(NH_3)_2(L)\}^{2+/+}$ (L = Cl, H_2O, NH_3) fragment to serve as a π-donor in general. Thus, we computed[26] the vibrational frequencies of the three hypothetical complexes *cis*-$[Pt(NH_3)_2Cl(CO)]^+$, *cis*-$[Pt(NH_3)_2(H_2O)(CO)]^{2+}$, and *cis*-$[Pt(NH_3)_3(CO)]^{2+}$. Since to the best of our knowledge none of these three carbonyl complexes has been successfully prepared, we cannot compare the computed energies directly with experimental data. Nevertheless, the molecular structures and the vibrational profiles of the related Pt(II) carbonyl complexes *cis*-$[Pt(X)_2(CO)_2]$ (X = F, Cl, SO_3F) have been studied previously[27] and serve as benchmarks for our calculations.

Figure 1 shows the optimized geometries of the three complexes considered in this study. For comparison, the optimized C−O distance of free carbon monoxide and the optimized geometries of $Pt(CO)^{2+/+/0}$ with three different oxidation states of platinum are also included. The C−O bonds in *cis*-$\{Pt(NH_3)_2(L)\}^{2+/+}$ complexes range from 1.130 to 1.136 Å and are therefore slightly shorter than the value of 1.138 Å computed for free carbon monoxide in the same

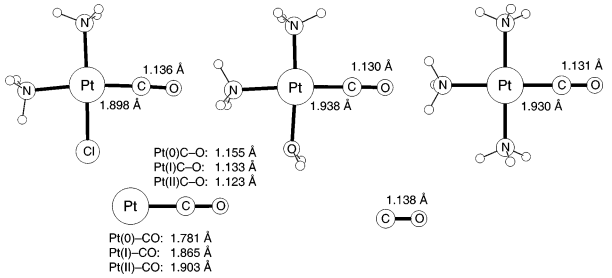

Figure 1. Optimized structures of the three hypothetical Pt complexes, free carbon monoxide, and $Pt-CO^{2+/+/0}$.

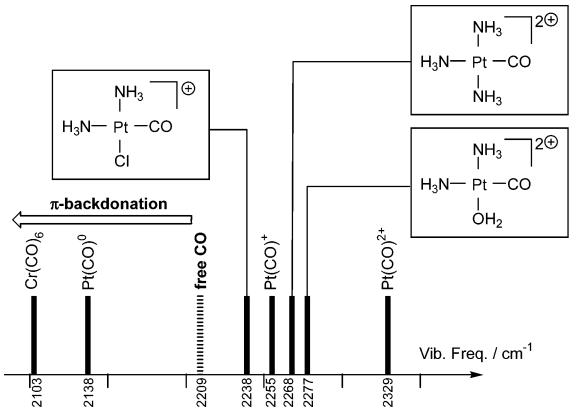

Figure 2. Computed vibrational stretching frequencies of the C−O ligand in putative Pt−carbonyl complexes compared to free CO and $Cr(CO)_6$.

theoretical framework.[28] These trends are in good agreement with C−O distances of 1.130 and 1.103 Å found experimentally in *cis*-$[Pt(SO_3F)_2(CO)_2]$.[27] When compared to free CO the stretching frequencies of all three calculated complexes, presented in Figure 2, do not show a shift to lower energies. Instead, they shift to higher wavenumbers, which means that the C−O bond becomes stronger upon binding to the Pt center. This trend is easy to understand and relates to the fact that the lone-pair orbital on carbon promoting the donor−acceptor σ-bonding between CO and the metal center is antibonding with respect to the carbon and oxygen atoms. Partial removal of electron density from this orbital in forming the Pt−C bond weakens this antibonding interaction and strengthens the C−O bond. Experimentally, the C−O stretching frequencies of *cis*-$[Pt(SO_3F)_2(CO)_2]$ and *cis*-$[PtCl_2(CO)_2]$ are observed at 2202 and 2171 cm^{-1}, respectively, which are similarly shifted to higher wavenumbers when compared to that of free CO at 2143 cm^{-1}.

These results suggest that the *cis*-$\{Pt(NH_3)_2(L)\}^{2+/+}$ fragment is a poor π-base and that π-back-donation does not play a significant role in binding these compounds to π-acids. As a typical example of a transition metal complex where π-back-donation is important, we list the textbook complex $Cr(CO)_6$, where the first IR-active C−O stretching frequency is calculated to be at 2103 cm^{-1} in our theoretical framework.[29] We considered the simple systems Pt(CO), $Pt(CO)^+$, and $Pt(CO)^{2+}$, thus varying the oxidation state of Pt from 0

(22) Cotton, F. A.; Kraihanzel, C. S. *J. Am. Chem. Soc.* **1962**, *84*, 4432.
(23) Kraihanzel, C. S.; Cotton, F. A. *Inorg. Chem.* **1963**, *2*, 533.
(24) Hubbard, J. L.; Lichtenberger, D. L. *J. Am. Chem. Soc.* **1982**, *104*, 2132.
(25) Barnes, L. A.; Liu, B. W.; Lindh, R. *J. Chem. Phys.* **1993**, *98*, 3972.
(26) All calculations are carried out using the program suite: *Jaguar* 4.1; Schrödinger, Inc.: Portland, OR, 2000. These calculations utilized the B3LYP functional (Lee, C. T.; Yang, W. T.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785. Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648.) together with the LACVP** basis set (Hay, P. J.; Wadt, W. R. *J. Chem. Phys.* **1985**, *82*, 270.). Computational details are given in the Supporting Information.
(27) von Ahsen, B.; Wartchow, R.; Willner, H.; Jonas, V.; Aubke, F. *Inorg. Chem.* **2000**, *39*, 4424.
(28) Our computed CO bond length of 1.138 Å is 0.01 Å longer than the experimentally observed 1.128 Å confirming the tendency of the B3LYP functional to give slightly longer bonds compared to experimental values. Similar results were also obtained for CO with correlated wave function methods (ref 25).

to +2. The question of whether there is a π-back-donation component to the binding of a carbonyl to a Pt(0) center has been discussed in the literature in a different context.[30,31] Our calculations indicate that the C−O stretching frequencies in both $Pt(CO)^+$ and $Pt(CO)^{2+}$ are shifted to higher wavenumbers compared to free CO, whereas the neutral Pt(CO) displays a CO stretching frequency of 2138 cm^{-1}, which is 71 cm^{-1} lower than that computed for free CO. The optimized C−O bond length in Pt(CO) is 1.155 Å, further providing evidence for a weakening of the C−O bond upon binding to the Pt center. Thus, Pt is in principle able to participate in metal−ligand bonding including π-back-donation, but does so to a notable extent only in the zero oxidation state, if the bare Pt atom is considered.

Comparing the bond lengths and vibrational stretching frequencies of the CO ligand attached to the bare platinum metal with those attached to the cisplatin fragment, it is clear that the ligands have a profound effect on the electronic behavior of the Pt center. Although the platinum center in *cis*-$\{Pt(NH_3)_2(L)\}^{2+/+}$ is formally in an oxidation state of Pt(II), the C−O bond length of ∼1.13 Å and the vibrational frequency of ∼2250 cm^{-1} are closer to the values obtained for the Pt(I)CO model than to Pt(II)CO. Clearly, the ligands in the *cis*-$\{Pt(NH_3)_2(L)\}^{2+/+}$ fragment donate electron density into the metal center, rendering it a better base than the bare Pt(II) center. However, the set of ligands in cisplatin is not able to make the Pt center sufficiently basic to give rise to a notable π-back-donation component in the metal−ligand bonding. Thus, the hypothetical Pt−carbonyl complex displays the characteristics of a nonclassical metal carbonyl,[32−36] where the σ-component dominates the bonding.

The lack of π-back-donation in the hypothetical carbonyl complex of cisplatin is of course not absolute proof that there is no such interaction in cisplatin−purine adducts. In addition, the relationship between C−O stretching frequencies and the electronic structure has recently been discussed to be more complex than outlined here for conceptual simplicity.[35,37] However, if taken together with the results of the more detailed MO-analysis presented elsewhere,[11] and the trends observed in general for square planar Pt(II) systems to form nonclassical carbonyl complexes, as mentioned above, it is evident that the Pt center in cisplatin is a poor π-base and gives rise to only a weak or no π-back-donation to π-acids. Thus, the presence of such an interaction between the purine bases, which are weaker π-acids than the CO-ligand, and the Pt-center in cisplatin seems improbable. This conclusion suggests that there is little electronic driving force for a coplanar arrangement of the cisplatin moiety with the molecular plane of the purine base. Thus, both the nearly orthogonal arrangement of the cisplatin unit in the bifunctional adduct that is observed experimentally[38] and the computationally suggested noncoplanar arrangement of the monofunctional adduct[11] are electronically not strained with respect to the metal−ligand π-interaction. The lack of such a directing electronic effect is important for understanding the kinetics of the second electrophilic attack to form the bifunctional adduct, which necessitates a significant rotation of the *cis*-$\{Pt(NH_3)_2\}^{2+}$ unit around the Pt−N7 vector from the monofunctional precursor. The exploitation of this electronic detail for the conceptual and rational design of new drug candidates is a challenge for future studies.

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Supporting Information Available: Computational details, coordinates of the structures, and complete list of vibrational frequencies (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(29) Experimentally, the C−O stretching mode is observed at 2000 cm^{-1}. Thus, our calculation overestimates the vibrational frequency by roughly 100 cm^{-1}. A similar error was also found for free CO, with a computed frequency of 2209 cm^{-1} compared to the experimental value of 2143 cm^{-1}, giving a satisfactory agreement with the observed relative trend. This constant shift between theory and experiment is a well-known problem and is often corrected by empirically shifting the computed values. Here, we use uncorrected frequencies.

(30) Aizawa, H.; Tsuneyuki, S. *Surf. Sci.* **1998**, *399*, L364.
(31) Curulla, D.; Clotet, A.; Ricart, J. M.; Illas, F. *Electrochim. Acta* **1999**, *45*, 639.
(32) Hurlburt, P. K.; Rack, J. J.; Luck, J. S.; Dec, S. F.; Webb, J. D.; Anderson, O. P.; Strauss, S. H. *J. Am. Chem. Soc.* **1994**, *116*, 10003.
(33) Lupinetti, A. J.; Strauss, S. H.; Frenking, G. Nonclassical metal carbonyls. *Prog. Inorg. Chem.* **2001**, *49*, 1.
(34) Lupinetti, A. J.; Jonas, V.; Thiel, W.; Strauss, S. H.; Frenking, G. *Chem. Eur. J.* **1999**, *5*, 2573.
(35) Lupinetti, A. J.; Frenking, G.; Strauss, S. H. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2113.
(36) Lupinetti, A. J.; Fau, S.; Frenking, G.; Strauss, S. H. *J. Phys. Chem. A* **1997**, *101*, 9551.
(37) Bach, C.; Willner, H.; Wang, C. Q.; Rettig, S. J.; Trotter, J.; Aubke, F. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1974.
(38) Sherman, S. E.; Gibson, D.; Wang, A. H. J.; Lippard, S. J. *Science* **1985**, *230*, 412.