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On the Competition of the Purine Bases, Functionalities of Peptide Side Chains, and Protecting Agents for the Coordination Sites of Dicationic Cisplatin Derivatives†

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Abstract: The Pt−L bond energies of simple triammineplatinum(II) complexes, $[Pt(NH_3)_3L]^{2+}$, with oxygen-, nitrogen-, and sulfur-containing donor ligands L have been predicted and rationalized using density functional theory. The ligands L have been chosen as models for functionalities of peptide side chains, for sulfur-containing protecting agents, and for adenine and guanine sites of the DNA as the ultimate target of platinum anticancer drugs. Calculation of the Pt−L bond energy in $[Pt(NH_3)_3L]^{2+}$ reveals that the soft metal center of triammineplatinum(II) prefers N ligands over S ligands. This remarkable result has been discussed in light of several interpretations of the hard and soft acids and bases principle. The concept of orbital-symmetry-based energy decomposition has been employed for the determination of the contributions from σ and π orbital interactions, electrostatics, and intramolecular hydrogen bonding to the Pt−L bond energy. The calculations show that considerable differences in the bond energies of the triammineplatinum(II) complexes with N-heterocycles such as 1-methylimidazole, 9-methyladenine, and 9-methylguanine arise from electrostatics rather than from orbital interactions. Surprisingly, the net stabilization by hydrogen bonding between the (Pt)N−H group and the oxygen of 9-methylguanine is as weak as the intramolecular hydrogen bond in the aqua complex $[Pt(NH_3)_3(H_2O)]^{2+}$, challenging the common hypothesis that DNA-active anticancer drugs require carrier ligands with N−H functionalities because of their hydrogen-bonding ability. The influence of a polarizable environment on the stability of the complexes has been investigated systematically with the dependence of the dielectric constant ϵ. With increasing ϵ, the complexes with S-containing ligands are more strongly stabilized than the complexes of the N-containing heterocycles. At $\epsilon = 78.4$, the dielectric constant of water, 9-methylguanine remains the only purine derivative investigated which is competitive to neutral sulfur ligands. These findings are particularly important for a rationalization of the results from recent experimental studies on the competition of biological donor ligands L for coordination with the metal center of $[Pt(dien)L]^{2+}$ (dien = 1,5-diamino 3-azapentane).

Objective

cis-Diamminedichloroplatinum(II) (cisplatin) is with annual sales of 500 million U.S. dollars one of the three most important anticancer drugs.[2] The understanding of the interaction of cisplatin with potential biological targets can rationalize the development of new antitumor agents, which might have less toxic side effects or help to overcome resistance problems.[3] The broad interest in the activity mechanism of cisplatin has created a new interdisciplinary branch of research.[4] Today it is known that, after partial hydrolysis, DNA intra- and interstrand cross-links between the N7 sites of the purine bases are formed, with 1,2-intrastrand cross-links of adjacent guanine moieties being the predominant product (Figure 1).[4,5] Intra-[6] and intermolecular[7] competition studies indicated that the formation of intermediate platinum(II) complexes with functional groups of peptides is

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† Quantum-chemical studies on the interaction of anticancer drugs with DNA. Part I.

(1) URL: http://staff-www.uni-marburg.de/~deubel.
(2) Wong, E.; Giandomenico, C. M. *Chem. Rev.* **1999**, *99*, 2451.
(3) Reedijk, J. *Chem. Rev.* **1999**, *99*, 2451.
(4) (a) Reedijk, *J. Chem. Commun.* **1996**, 801. (b) Jamieson, E. R.; Lippard, S. J. *Chem. Rev.* **1999**, *99*, 2467. (c) Guo, Z.; Sadler, P. *Angew. Chem., Int. Ed.* **1999**, *38*, 1513. (d) Lippert, B., Ed. *Cisplatin*; Wiley-VCH: Weinheim, 1999. (e) Kelland, L. R., Farrell, N., Eds. *Platinum-Based Drugs in Cancer Therapy*; Humana Press: Totawa, 2000. (f) Cohen, S. M.; Lippard, S. J. *Prog. Nucleic Acid Res.* **2001**, *67*, 93. (g) Hambley, T. W. *J. Chem. Soc., Dalton Trans.* **2001**, 2711.
(5) The first crystal structure of a double-stranded DNA adduct is shown in Figure 1b. Takahara, P. M.; Rosenzweig, A. C.; Frederick, C. A.; Lippard, S. J. *Nature* **1995**, *377*, 649.
(6) (a) Lempers, E. M.; Reedijk, J. *Inorg. Chem.* **1990**, *29*, 1880. (b) Van Boom, S. S. G. E.; Reedijk, J. *Chem. Commun.* **1993**, 1397. (c) Barnham, K. J.; Djuran, M. I.; Murdoch, P. D.; Ranford, J. D.; Sadler, P. J. *Inorg. Chem.* **1996**, *35*, 1065. (d) Fröhling, C. D. W.; Sheldrick, W. S. *J. Chem. Soc., Dalton Trans.* **1997**, 4411. (e) Murdoch, P. D.; Kratchowil, N. A.; Parkinson, J. A.; Patriarca, M.; Sadler, P. J. *Angew. Chem., Int. Ed.* **1999**, *38*, 2949. (f) Van Boom, S. S. G. E.; Chen, B. W.; Teuben, J. M.; Reedijk, J. *Inorg. Chem.* **1999**, *38*, 1450. (g) Hahn, M.; Wolters, D.; Sheldrick, W. S.; Hulsbergen, F. B.; Reedijk J. *J. Biol. Inorg. Chem.* **1999**, *4*, 412. (h) Wolters, D.; Sheldrick, W. S. *J. Chem. Soc., Dalton Trans.* **1999**, 1121. (i) Marchan, V.; Moreno, V.; Pedroso, E.; Grandas, E. *Chem.-Eur. J.* **2001**, *7*, 808. (j) Hahn, M.; Kleine, M.; Sheldrick, W. S. *J. Biol. Inorg. Chem.* **2001**, *6*, 556. (k) Kratochwil, N. A.; Parkinson, J. A.; Sacht, C.; Murdoch, P. D.; Brown, T.; Sadler, P. J. *Eur. J. Inorg. Chem.* **2001**, 2743.

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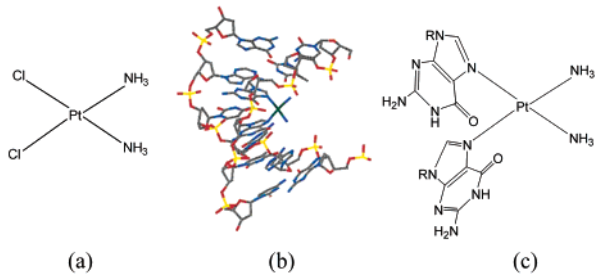


Figure 1. (a) The anticancer drug cisplatin. (b) Structure of a diammineplatinum(II)-DNA adduct with a 1,2-intrastrand cross-link between guanine−N7 sites (Takahara, P. M.; Rosenzweig, A. C.; Frederick, C. A.; Lippard, S. J. *Nature* **1995**, *377*, 649). Pt (green), P (yellow), O (red), N (blue), and C (gray) atoms are shown. Figure reprinted from Jamieson, E. R.; Lippard, S. J. *Chem. Rev.* **1999**, *99*, 2467. Copyright 1999 American Chemical Society. (c) Schematic drawing of the coordination environment at the platinum center in the DNA adduct.

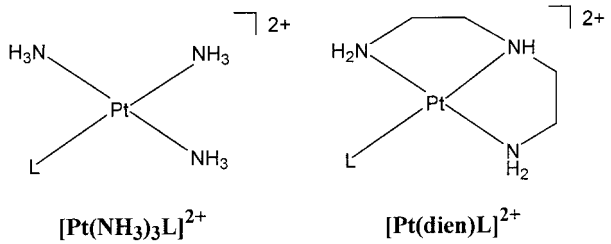


Figure 2. $[Pt(NH_3)_3L]^{2+}$ and $[Pt(dien)L]^{2+}$ (dien = 1,5-diamino 3-azapentane) as simple models for cisplatin-DNA adducts.

kinetically favored, but the ultimate target of the drug is the DNA.

Although considerable research efforts have focused on the interaction of cisplatin with the DNA, the thermodynamic stability of the platinum−guanine(N7) bond has not been understood entirely. The fact that guanine finally wins the competition for the coordination sites of cisplatin derivatives against peptides containing cysteine or methionine side chains[4] is particularly puzzling, given this quotation from Reedijk's recent review,[3] "The well-known HSAB theory predicting a very strong interaction of Pt ions with S-donor ligands in fact would hardly leave any reactivity for the N-donor ligands with so many S donors around in vivo".[3] Bond energies in platinum complexes can be predicted and rationalized using density functional theory (DFT) methods.[8,9] Surprisingly, neither cisplatin derivatives with sulfur ligands have been investigated theoretically nor has a thorough energy analysis of the platinum−ligand bond been carried out.

The objective of this DFT study is to investigate the stability of the platinum−ligand bond in the square-planar complexes $[Pt(NH_3)_3L]^{2+}$. $[Pt(dien)Cl]^{+}$ (dien = 1,5-diamino-3-azapentane, see Figure 2) has been widely used in experimental competition studies[6,7] since it contains only one labile chloro ligand and forms model adducts of the type $[Pt(dien)L]^{2+}$ with donor ligands L under well-defined conditions. In our calculations, the following neutral model ligands L with functional groups of biological relevance have been considered (Figure 3): L = H_2O, MeOH, NH_3, $MeNH_2$, H_2S, MeSH, Me_2S, 1-methylimidazole (MeIm), 9-methylpurine (MePur), 9-methyladenine (MeA), and 9-methylguanine (MeG).[10] Furthermore, complexes with L = MeSNa have been studied, representing the thiolate functionality of deprotonated cysteine residues, glutathione, and protecting agents such as Mesna, which were designed to overcome the toxic side effects of the drug (Figure 3).[3,11]

This work is organized as follows. First, calculated molecular geometries of $[Pt(NH_3)_3L]^{2+}$ and Pt−L bond energies are briefly reported. Second, an energy-decomposition scheme has been employed for the analysis of the Pt−L bond strength in terms of σ- and π-type orbital interactions, electrostatics, and intramolecular hydrogen bonding. Third, model reactions have been developed to discuss the theoretically predicted Pt−L bond energies in light of several interpretations of the HSAB principle. Fourth, environmental effects on the stability of the triammineplatinum(II) complexes have been estimated systematically using

(7) (a) Barnham, K. J.; Djuran, M. I.; Murdoch, P. D.; Sadler, P. J. *Chem. Commun.* **1994**, 721. (b) Barnham, K. J.; Djuran, M. I.; Murdoch, P. D.; Ranford, J. D.; Sadler, P. J. *J. Chem. Soc., Dalton Trans.* **1995**, 3721. (c) Barnham, K. J.; Guo, Z.; Sadler, P. J. *J. Chem. Soc., Dalton Trans.* **1996**, 2867. (d) Fröhling, C. D. W.; Sheldrick, W. S. *Chem. Commun.* **1997**, 1737. (e) Teuben, J.-M.; Reedijk J. *J. Biol. Inorg. Chem.* **2000**, *5*, 463. (f) Volckova, E.; Bose, R. *Biochemistry* **2001**, *40*, 176. (g) Kung, A.; Strickmann, D. B.; Galanski, M.; Keppler, B. K. *J. Inorg. Biochem.* **2001**, *86*, 691. (h) Volckova, E.; Dudones, L. P.; Bose, R. N. *Pharm. Res.* **2002**, *19*, 124.

(8) Dedieu, A. *Chem. Rev.* **2000**, *100*, 543.

(9) Ammineplatinum(II) compounds were studied using quantum-chemical methods, which is mainly due to the anticancer activity of these complexes and their ability to activate C−H bonds: (a) Barber, M.; Clark, J. D.; Hinchcliffe, R. A. *J. Mol. Struct.* **1979**, *57*, 169. (b) Basch, H.; Krauss, M.; Stevens, W. J.; Cohen, D. *Inorg. Chem.* **1985**, *24*, 3313. (c) Basch, H.; Krauss, M.; Stevens, W. J.; Cohen, D. *Inorg. Chem.* **1986**, *25*, 684. (d) Louwen, J. N.; Hengelmolen, R.; Grove, D. M.; Stufkens, D. J.; Oskam, A. *J. Chem. Soc., Dalton Trans.* **1986**, 141. (e) Zuloaga, F.; Arratia-Perez, R. *J. Phys. Chem.* **1986**, *90*, 4491. (f) El-Issa, B. D.; Makhyoun, M. A.; Salsa, B. A. *Int. J. Quantum Chem.* **1987**, *31*, 295. (g) Krauss, M.; Basch, H.; Miller, K. J. *J. Am. Chem. Soc.* **1988**, *110*, 4517. (h) Krauss, M.; Basch, H.; Miller, K. J. *Chem. Phys. Lett.* **1988**, *148*, 577. (i) Allured, V. S.; Kelly, C. M.; Landis, C. R. *J. Am. Chem. Soc.* **1991**, *113*, 1. (j) Kozelka, J.; Savinelli, R.; Berthier, G.; Flament, J.-P.; Lavery, R. *J. Comput. Chem.* **1993**, *14*, 45. (k) Muguruma, C.; Koga, N.; Kitaura, K.; Morokuma, K. *Chem. Phys. Lett.* **1994**, *224*, 139. (l) Muguruma, C.; Koga, N.; Kitaura, K.; Morokuma, K. *J. Chem. Phys.* **1995**, *103*, 9274. (m) Mineva, T.; Russo, N.; Toscano, M. *Int. J. Quantum Chem.* **1995**, *56*, 663. (n) Carloni, P.; Andreoni, W.; Hutter, J.; Curioni, A.; Giannozzi, P.; Parrinello, M. *Chem. Phys. Lett.* **1995**, *234*, 50. (o) Tornaghi, E.; Andreoni, W.; Carloni, P.; Hutter, J.; Parrinello, M. *Chem. Phys. Lett.* **1995**, *246*, 469. (p) Carloni, P.; Andreoni, W. *J. Phys. Chem.* **1996**, *100*, 17797. (q) Cundari, T. R.; Fu, W.; Moody, E. W.; Slavin, L. L.; Snyder, L. A.; Sommerer, S. O.; Klinckman, T. R. *J. Phys. Chem.* **1996**, *100*, 18057. (r) Schulz, L.; Chojnacki, H. *Int. J. Quantum Chem.* **1996**, *60*, 1385. (s) Zilberberg, I.; Avdeev, V. I.; Zhidomirov, G. M. *J. Mol. Struct. (THEOCHEM)* **1997**, *418*, 73. (t) Chval, Z.; Sip, M. *J. Phys. Chem. B* **1998**, *102*, 1659. (u) Mylvaganam, K.; Bacskay, G. B.; Hush, N. S. *J. Am. Chem. Soc.* **1999**, *121*, 4633. (v) Gilbert, T. M.; Ziegler, T. *J. Phys. Chem. A* **1999**, *103*, 7535. (w) Sponer, J.; Sponer, J. E.; Gorb, L.; Leszczynski, J.; Lippert, B. *J. Phys. Chem. A* **1999**, *103*, 11406. (x) Pavankumar, P. N. V.; Seetharamulu, P.; Yao, S.; Saxe, J. D.; Reddy, D. G.; Hausheer, F. H. *J. Comput. Chem.* **1999**, *20*, 365. (y) Pelmenschikov, A.; Zilberberg, I. L.; Leszczynski, J.; Famulari, A.; Siron, I. M.; Raimondi, M. *Chem. Phys. Lett.* **1999**, *314*, 496. (z) Mylvaganam, K.; Bacskay, G. B.; Hush, N. S. *J. Am. Chem. Soc.* **2000**, *122*, 2041. (aa) Carloni, P.; Sprik, M.; Andreoni, W. *J. Phys. Chem. B* **2000**, *104*, 823. (ab) Burda, J. V.; Zeizinger, M.; Sponer, J.; Leszczynski, J. *J. Chem. Phys.* **2000**, *113*, 2224. (ac) Burda, J. V.; Sponer, J.; Leszczynski, J. *J. Biol. Inorg. Chem.* **2000**, *5*, 178. (ad) Chval, Z.; Sip, M. *J. Mol. Struct. (THEOCHEM)* **2000**, *532*, 59. (ae) Moroni, F.; Famulari, A.; Raimondi, M. *J. Phys. Chem. A* **2001**, *105*, 1169. (af) Wysokinski, R.; Michalska, D. *J. Comput. Chem.* **2001**, *22*, 901. (ag) Hill, G.; Gora, R. W.; Roszak, S.; Leszczynski, J. *Int. J. Quantum Chem.* **2001**, *83*, 213. (ah) Sponer, J. E.; Leszczynski, J.; Glahé, F.; Lippert, B.; Sponer, J. *Inorg. Chem.* **2001**, *40*, 3269. (ai) Zhang, Y.; Guo, Z.; You, X.-Z. *J. Am. Chem. Soc.* **2001**, *123*, 9378. (aj) Zeizinger, N.; Burda, J. V.; Sponer, J.; Kapsa, V.; Leszczynski, J. *J. Phys. Chem. A.* **2001**, *105*, 8086. (ak) Burda, J. V.; Sponer, J.; Leszczynski, J. *Phys. Chem. Chem. Phys.* **2001**, *3*, 4404. (al) Berges, J.; Caillet, J.; Langlet, J.; Kozelka, J. *Chem. Phys. Lett.* **2001**, *344*, 573. (am) Sponer, J. E.; Glahé, F.; Leszczynski, J.; Lippert, B.; Sponer, J. *J. Phys. Chem. B* **2001**, *105*, 12171. (an) Baik, M.-H.; Friesner, R. A.; Lippard, S. J. *J. Am. Chem. Soc.* **2002**, *124*, 4495.

(10) Pt complexes of purine bases with a methyl substituent in the 9-position have been studied due to the desoxyribose linkage in DNA. MeIm has been used for comparison with the fused rings; it may also be considered a model for histidine side chains with the alkyl bridge to the amino acid functionality in the 5-position of the N-containing heterocycle. Test calculations show that the $[Pt(NH_3)_3L]^{2+}$ complex with 1-methylimidazole is more stable than the 5-methylimidazole complex by only 1.1 kcal/mol.

(11) Because of the difficulty in comparing calculated energies of molecules with different charges, we decided to consider dicationic complexes and to model the thiolate functionality as an ion pair, $MeS^{-}Na^{+}$.

Table 1. Calculated Bond Distances (X−Y, in Å), Bond Angles (X−Y−Z, in deg), and Pt-L Bond Energies (ΔE, in kcal/mol) of the Complexes $[Pt(NH_3)_3L]^{2+}$ (**0**−**12**)[a]

	0, L = □[b]	**1**, H_2O	**2**, CH_3OH	**3**[d], NH_3	**4**, CH_3NH_2	**5**, H_2S	**6**, MeSH	**7**, Me_2S	**8**, MeSNa	**9**, MeIm	**10**, MePur	**11**[e], MeA	**12**, MeG
Pt−Nα	2.092	2.085	2.083	2.094	2.094	2.098	2.096	2.099	2.084	2.086	2.090	2.084	2.067
Pt−Nβ	2.022	2.054	2.065	2.092	2.107	2.128	2.144	2.157	2.168	2.113	2.110	2.113	2.102
Pt−Nχ	2.089	2.096	2.096	2.095	2.094	2.098	2.095	2.091	2.082	2.087	2.088	2.093	2.100
Pt−L		2.115	2.099	2.097	2.097	2.324	2.317	2.315	2.323	2.033	2.041	2.039	2.046
Nα−Pt−L	86.6[c]	84.4	84.0	89.4	90.5	87.2	86.5	85.6	87.6	88.3	88.1	86.4	87.6
L−Pt−Nχ	86.6[c]	92.8	93.2	90.0	90.2	93.8	94.2	95.0	88.9	88.4	88.0	89.7	90.2
ΔE	0.0	−49.4	−57.2	−71.8	−77.6	−61.9	−73.8	−83.1	−129.1	−103.5	−90.0	−94.1	−117.9

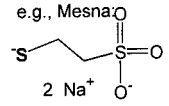
[a] Nα and Nχ are the nitrogen atoms of the ammine ligands cis to L; Nβ is the nitrogen trans to L. Selected structures are displayed in Figure 4. [b] □ = free coordination site. [c] Estimated by Nα−Pt−Nχ 173.3 deg, Nα−Pt−Nβ 93.2 deg, Nβ−Pt−Nχ 93.5 deg. [d] X-ray structure: Pt−Nα 2.057; Pt−Nβ 2.052; Pt−Nχ 2.057; Pt−L 2.052; Nα−Pt−L 89.8; L−Pt−Nχ 90.2. Rochon, F. D.; Melanson, R. *Acta Crystallogr.* **1980**, *B36*, 691. [e] X-ray structure: Pt−Nα 2.052; Pt−Nβ 2.022; Pt−Nχ 2.016; Pt−L 2.000; Nα−Pt−L 91.3; L−Pt−Nχ 87.4; dihedral angle C8−N7−Pt−Nα −107.6 (calcd 111.3). Beyer-Pfnur, R.; Jaworski, S.; Lippert, B.; Schollthorn, H.; Thewalt, U. *Inorg. Chim. Acta* **1985**, *107*, 217.

a polarizable continuum model. The calculated results have been compared to the chemoselectivity of the platination of biomolecules observed in recent experimental competition studies.[6,7] The BP86 functional[12] in combination with a large basis set (VTZP) has been used; computational details are provided in the Computational Methods section.

Molecular Geometries and Stabilization Energies

We have calculated the structures of the fragment $\{Pt(NH_3)_3\}^{2+}$ (**0**) and of the complexes $[Pt(NH_3)_3L]^{2+}$ (**1**−**12**) with all model ligands L shown in Figure 3. The structures of the complexes **0** and with L = Me_2S (**5**), MeSNa (**8**), MeA (**11**), and MeG (**12**) are presented in Figure 4; geometrical parameters of all complexes are listed in Table 1. X-ray crystallographic structures of the complexes $[Pt(NH_3)_3L]^{2+}$ with L = NH_3 and MeA are in good agreement with the calculated geometries, with the theoretically predicted bond lengths being slightly longer than the experimental bond lengths (Table 1).[13,14]

The calculated Nα−Pt−L angles listed in Table 1 show a slight deviation from the square coordination environment in the complexes **1**, **2**, **5**−**7**, which is due to a hydrogen bond between Nα−H and the lone pair at L (Figure 4). The Pt−Nβ bond length in $[Pt(NH_3)_3L]^{2+}$ strongly depends on the nature of the ligand L in the trans position; values between 2.022 (**0**, L = □) and 2.168 Å (**8**, L = MeSNa) have been predicted (Table 1). The comparably long Pt−Nβ distance trans to the sulfur ligand in **5**−**8** indicates a strong trans influence and suggests a potential release of an ammine ligand by coodination of methionine or its derivatives, which was recently observed.[6j,15] In contrast to Pt−Nβ bond lengths, the Pt−Nα and Pt−Nχ bond lengths cis to L are equal in all complexes **0**−**12** (about 2.09 Å), with one exception (Table 1): The Pt−Nα distance in the MeG complex (**12**) is slightly shorter because of a (Pt)Nα−H- - -O(G) hydrogen bond (Figure 3). The O−H distance is

Model Complex	Model Ligand	Biological Relevance
$[Pt(NH_3)_3L]^{2+}$	L =	
1	H_2O	H_2O
2	MeOH	ROH
3	NH_3	
4	$MeNH_2$	RNH_2
5	H_2S	
6	MeSH	Cysteine (Cys)
7	Me_2S	Methionine (Met)
8	MeS^-Na^+	deprotonated thiols
		Protecting agents, e.g., Mesna: 
9	MeIm	Histidine (His)
10	MePur	
11	MeA	Adenine sites of DNA
12	MeG	Guanine sites of DNA

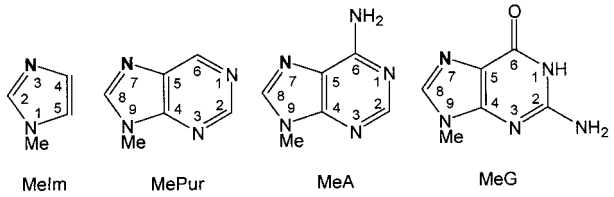


Figure 3. Biological functional groups as potential targets of cisplatin. Me = methyl.

comparable to strong hydrogen bonds, for example, in the water dimer.[16] The net stabilization arising from this hydrogen bond will be determined below. A similar H bridge is also present but apparently much weaker in the adenine counterpart **11** due to the hindered rotation of the amino moiety, the lone pair of which interacts with the π system of the fused ring (Figure 4).

Calculated Pt−L bond energies (ΔE) are also given in Table 1. The aqua ligand stabilizes the $\{Pt(NH_3)_3\}^{2+}$ fragment in the gas phase by 49.4 kcal/mol (**1**). Although the calculated Pt−Nβ distance in the H_2S complex (**5**) is longer than that in the NH_3 complex (**3**), dihydrogensulfide (ΔE = −61.9 kcal/mol,

(12) (a) Becke, A. D. *Phys. Rev. A* **1988**, *38*, 3098. (b) Perdew, J. P. *Phys. Rev. B* **1986**, *33*, 8822.
(13) X-ray structures of $[Pt(NH_3)_3L]^{2+}$: (a) Rochon, F. D.; Melanson, R. *Acta Crystallogr.* **1980**, *B36*, 691 (L = NH_3). (b) Beyer-Pfnur, R.; Jaworski, S.; Lippert, B.; Schollthorn, H.; Thewalt, U. *Inorg. Chim. Acta* **1985**, *107*, 217 (L = MeA).
(14) Although the large VTZP basis set has been utilized, the calculated Pt−N bond distances using DFT are longer than those obtained from X-ray data by about 0.04 Å, which is a well-documented trend (ref 9af). Note that the geometry has a relatively small influence on the energy; the calculated energy using the Pt−N distances from X-ray structures is less stable than the optimized geometry by only 1.2 kcal/mol.
(15) [Pt(H-Met-OH-κ^2N,S)$_2$] was identified as a cisplatin metabolite: Riley, C. M.; Sternson, L. A.; Repta, A. J.; Slyter, S. A. *Anal. Biochem.* **1983**, *130*, 203.
(16) Scheiner, S., Ed. *Hydrogen Bonding: A Theoretical Perspective*; Oxford University Press: Oxford, 1997.

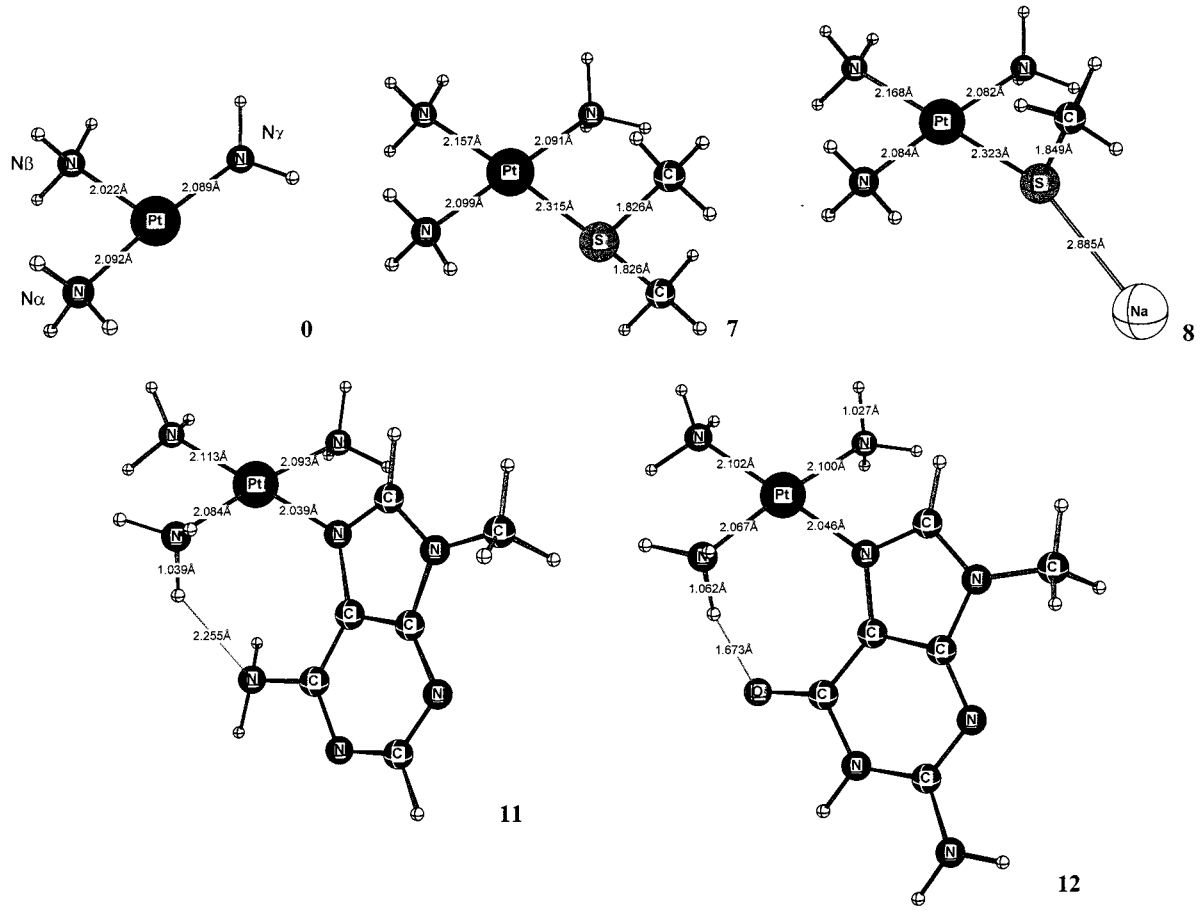


Figure 4. Calculated structures of $[Pt(NH_3)_3L]^{2+}$ with L = □ (free coordination site, **0**), Me_2S (**7**), MeSNa (**8**), MeA (**11**), and MeG (**12**). The structures were optimized without symmetry constraints.

5) forms a weaker bond with the platinum(II) fragment than does ammonia ($\Delta E = -71.8$ kcal/mol, **3**). This is a very interesting result because the Pt^{2+} ion and sulfur ligands are classified by Pearson's HSAB theory as soft acid and bases, respectively, while NH_3 is a hard base.[17] Each methyl group in **2**, **4**, **6**, and **7** leads to an additional stabilization of the Pt−L bond by 6−12 kcal/mol in comparison with **1**, **3**, **5**, and **6**, respectively (Table 1). The strongest Pt−L bond has been calculated for L = MeSNa ($\Delta E = -129.1$ kcal/mol, **8**), representing the thiolate functionality of protecting agents.[3] Because of their high affinity to the platinum(II) center, these compounds help to overcome the toxic side effects of the drug by preventing the metal center from poisoning other donor ligands in vivo.

The theoretically predicted stabilization of the complexes with the N-containing heterocycles is much larger than the stabilization energies of the ammine or methylamine complexes. Even the complexes of the four N-containing heterocycles show comparably large differences in stabilization energies. Fusion of 1-methylimidazole ($\Delta E = -103.5$ kcal/mol, **9**) with pyrimidine yielding 9-methylpurine leads to a considerable destabilization of the complex ($\Delta E = -90.0$ kcal/mol, **10**). While a ΔE value similar to the 9-methylpurine complexation energy is calculated for 9-methyladenine (−94.1 kcal/mol, **11**), 9-methylguanine is apparently strongly stabilized by platination (−117.9 kcal/mol, **12**).[18]

The quantum-chemical prediction of the intrinsic metal−L bond strength in dicationic cisplatin derivatives indicates that the simple classification N-containing versus S-containing ligands is only warranted for similar ligand types such as ammonia and dihydrogensulfide. A discussion of the chemoselectivity of Pt(II) binding to biomolecules, however, requires an improved concept, as demonstrated in the next section.

Energy Decomposition of the Pt−L Bond

To analyze the nature of the Pt−L bond in our model complexes, $[Pt(NH_3)_3L]^{2+}$, we have reoptimized the complexes **1**, **3**, **5**, **7**−**12** in C_s symmetry; the C_s-symmetric complexes are denoted **1s**, **3s**, **5s**, **7s**−**12s**. The energy-decomposition scheme developed by Ziegler and Rauk[19−21] allows for the determination of the contributions from electrostatics and from orbital interactions within the irreducible representations a' and a'' to the bond energy.

Figure 5 displays the calculated geometries of **7s** and **12s**; the results of the analysis are presented in Table 2 and Figure 6. The equilibrium structures of both the ligand L and the metal

(17) (a) Pearson, R. G. *J. Am. Chem. Soc.* **1963**, *85*, 3533. (b) Pearson, R. G., Ed. *Hard and Soft Acids and Bases*; Dowden et al.: Stroudsburg, 1973. (c) Pearson, R. G. *Chemical Hardness*; Wiley-VCH: Weinheim, 1997.

(18) Note that the anti imino tautomer of adenine forms a stronger platinum−N7 bond than does the parent adenine; for details, see ref 9ac and refs therein.

(19) (a) Ziegler, T.; Rauk, A. *Theor. Chim. Acta* **1977**, *46*, 1. (b) Ziegler, T.; Rauk, A. *Inorg. Chem.* **1979**, *18*, 1558. (c) Ziegler, T.; Rauk, A. *Inorg. Chem.* **1979**, *18*, 1755.

(20) Frenking, G.; Fröhlich, N. *Chem. Rev.* **2000**, *100*, 717.

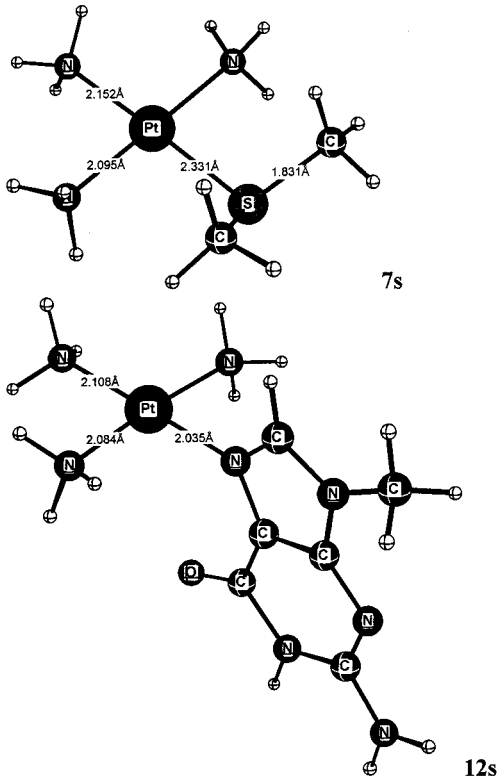


Figure 5. Calculated C_s-symmetric structures of $[Pt(NH_3)_3L]^{2+}$ with L = Me_2S (**7s**) and MeG (**12s**). The difference in the energies of the C_s- and C_1-symmetric structures reflects the net strength of the hydrogen bond.

fragment, $\{Pt(NH_3)_3\}^{2+}$, must be deformed toward their geometry in the complex, $[Pt(NH_3)_3L]^{2+}$; the corresponding energy is denoted strain energy, ΔE_{str}. The analysis indicates moderate strain energies for each fragment (Figure 6b); the largest ΔE_{str} value of 9.6 kcal/mol is required for MeSNa because of the elongation of the S−Na distance in comparison with the free ion pair in our model.[22] The distorted L and $\{Pt(NH_3)_3\}^{2+}$ fragments interact with each other; the corresponding energy is denoted interaction energy, ΔE_{int}. ΔE_{int} can be partitioned into three contributions ($\Delta E_{int} = \Delta E_{Pauli} + \Delta E_{elst} + \Delta E_{orb}$): the repulsion of L and $[Pt(NH_3)_3]^{2+}$ from each other due to the Pauli principle, ΔE_{Pauli}, the electrostatic contribution, ΔE_{elst}, and the stabilizing orbital interactions, ΔE_{orb} (Figure 6a). The sum of strain energy, ΔE_{str}, and interaction energy, ΔE_{int}, gives the Pt−L bond energy ΔE_{Cs} of the C_s-symmetric complexes **1s**−**12s** ($\Delta E_{Cs} = \Delta E_{str} + \Delta E_{int}$).

The stabilizing orbital interactions, ΔE_{orb}, steadily increase from the H_2O complex via the NH_3 complex to the H_2S complex (Figure 6a). The strongest orbital interactions are found in the complex with L = MeSNa. The complexes of the four N-heterocycles also have large ΔE_{orb} values in comparison with the tetrammine complex. It is interesting to learn the contributions from the a' and a'' irreducible representations to the orbital-interaction energy, because the a' orbitals correspond to the σ interactions and the a'' orbitals correspond to the π interactions. The analysis reveals that there is a considerable contribution of π interactions (ΔE_{orb} (a'')) to the Pt−L bond energy in the complexes with the heterocycles (**9s**−**12s**, see Figure 6a). Inspection of the gross populations in the complexes **1s**−**12s** calculated using the fragment orbitals as basis functions indicates that σ donation is much more important than σ back-donation, while π donation and π back-donation are of equal strength. We succeeded in identifying the orbitals which are mainly involved in σ donation and π back-donation, respectively (see Figure 7).[23]

In all dicationic complexes investigated in this work, electrostatics (ΔE_{elst}) provide a larger stabilizing contribution to the Pt−L energy than do orbital interactions (Figure 6a). The difference between ΔE_{elst} and ΔE_{orb} is small in the complexes with hard N ligands and is large in the complexes with soft S ligands. It is interesting to note that the electrostatic contribution reflects the differences in the bond energies (ΔE_{Cs}) in the complexes of the N-heterocycles,[24] whereas the ΔE_{orb} terms in **9s**−**12s** are equal (Figure 6a). The strongest electrostatic stabilization and the strongest orbital-interaction term of all complexes are found in **8s**, which is the complex with the ion pair MeSNa.

ΔE_{CsC1} is the difference between the energy ΔE of the C_1-symmetric complexes **1**−**12** and the energy ΔE_{Cs} of the C_s-symmetric model complexes **1s**−**12s** ($\Delta E = \Delta E_{Cs} + \Delta E_{CsC1}$); ΔE_{CsC1} is also displayed in Figure 6b.[25] ΔE_{CsC1} corresponds to the *net* gain in energy by the formation of the hydrogen bond between the N−H site of the triammine-metal fragment and a donor atom of the ligand L. The ΔE_{CsC1} values are therefore very small in the complexes with the ligands NH_3, MeIm, and MePur. Surprisingly, the largest energy difference between the C_1 and C_s-symmetric structures is found for the aqua complexes **1** and **1s** ($\Delta E_{CsC1} = -4.4$ kcal/mol, see Table 2 or Figure 6b). Note that the stabilization by ΔE_{CsC1} for the 9-methylguanine complexes **12** and **12s** (−4.2 kcal/mol) is not larger than the corresponding value for **1** and **1s**. Rotation of the Pt−N7 bond in the complex with 9-methylguanine (**12** → **12s**) apparently is an interplay between stabilization due to hydrogen-bond formation and destabilization of the remaining interactions, resulting in a net stabilization of only −4.2 kcal/mol. This result is very interesting and scrutinizes the common hypothesis that the presence of at least one N−H group, which binds to the guanine oxygen, is a prerequisite for the drug's anticancer activity.[4] In very recent experimental investigations by Marzilli and coworkers[26] on DNA adducts of dichloro-N,N′-dimethylpiperazineplatinum(II),[27] which lacks N−H functionalities, it was concluded that the forces favoring hydrogen bonding are weak.

(21) Decomposition schemes have been proven to be valuable tools for an understanding of the chemical bond and reactivity; for recent examples, see: (a) Deubel, D. V.; Frenking, G. *J. Am. Chem. Soc.* **1999**, *121*, 2021. (b) Macdonald, C. L. B.; Cowley, A. H. *J. Am. Chem. Soc.* **1999**, *121*, 12113. (c) Fonseca Guerra, C.; Bickelhaupt, F. M.; Snijders, J. G.; Baerends, E. J. *J. Am. Chem. Soc.* **2000**, *122*, 4117. (d) Diefenbach, A.; Bickelhaupt, F. M.; Frenking, G. *J. Am. Chem. Soc.* **2000**, *122*, 6449. (e) Deubel, D. V.; Sundermeyer, J.; Frenking, G. *J. Am. Chem. Soc.* **2000**, *122*, 10101. (f) Uddin, J.; Frenking, G. *J. Am. Chem. Soc.* **2001**, *123*, 1683. (g) Deubel, D. V.; Schlecht, S.; Frenking, G. *J. Am. Chem. Soc.* **2001**, *123*, 10085. (h) Cedeño, D. L.; Weitz, E. *J. Am. Chem. Soc.* **2001**, *123*, 12857. (i) Bickelhaupt, F. M.; DeKock, R. L.; Baerends, E. J. *J. Am. Chem. Soc.* **2002**, *124*, 1500.

(22) Calculated geometrical parameter of MeSNa: C−S 1.849 Å; S−Na 2.562 Å; C−S−Na 108.0 Å.

(23) There are various fragment orbitals which contribute to σ back-donation and π donation, respectively.

(24) Estimation of the Coulomb interaction between Pt and O in the guanine complex **12s** using the Hirshfeld scheme (Hirshfeld, E. L. *Theor. Chim. Acta* **1977**, *44*, 129) gives a stabilizing interaction of −8.0 kcal/mol (with q(Pt) = 0.289 e, q(O) = −0.276 e, and Pt−O = 3.25 Å).

(25) ΔE is not shown in Figure 6.

(26) Sullivan, S. T.; Ciccarese, A.; Fanizzi, F. P.; Marzilli, L. G. *J. Am. Chem. Soc.* **2001**, *123*, 9345.

(27) (a) Sullivan, S. T.; Ciccarese, A.; Fanizzi, F. P.; Marzilli, L. G. *Inorg. Chem.* **2000**, *39*, 836. (b) Sullivan, S. T.; Ciccarese, A.; Fanizzi, F. P.; Marzilli, L. G. *Inorg. Chem.* **2001**, *40*, 455.

Table 2. Energy Decomposition of the Pt−L Bond in the C_s-Symmetric Complexes $[Pt(NH_3)_3L]^{2+}$ (**1s**, **3s**, **5s**, **7s**−**12s**)[a]

	1s, H_2O	**3s**, NH_3	**5s**, H_2S	**7s**, Me_2S	**8s**, MeSNa	**9s**, MeIm	**10s**, MePur	**11s**, MeA	**12s**, MeG
ΔE_{str}(L)	0.1	0.1	0.1	1.1	4.9	1.4	2.6	3.1	4.1
$\Delta E_{str}(\{Pt(NH_3)_3\}^{2+})$	1.5	2.9	4.6	6.0	4.7	2.8	2.8	2.0	2.5
ΔE_{str}	1.6	3.0	4.7	7.1	9.6	4.2	5.4	5.1	6.6
ΔE_{Pauli}	53.6	98.2	100.5	107.8	121.0	118.0	110.1	114.3	113.0
ΔE_{elst}	−58.5	−109.1	−86.8	−101.3	−144.3	−137.5	−117.1	−118.1	−139.3
$\Delta E_{orb}(a')$	−38.2	−58.9	−70.7	−81.9	−104.7	−71.6	−70.8	−74.6	−74.0
$\Delta E_{orb}(a'')$	−3.5	−4.9	−7.6	−10.6	−10.8	−15.7	−17.6	−17.6	−20.0
ΔE_{orb}	−41.7	−63.8	−78.0	−92.5	−115.5	−87.3	−88.4	−92.1	−94.0
ΔE_{int}	−46.6	−74.7	−64.6	−86.0	−138.7	−106.8	−95.4	−95.9	−120.3
ΔE_{Cs}	−45.0	−71.7	−59.9	−78.9	−129.1	−102.6	−90.0	−90.8	−113.7
ΔE_{CsC1}	−4.4	−0.1	−2.0	−4.2	0.0	−0.9	0.0	−3.3	−4.2
ΔE	−49.4	−71.8	−61.9	−83.1	−129.1	−103.5	−90.0	−94.1	−117.9

[a] ΔE corresponds to the C_1-symmetric complexes **1**, **3**, **5**, **7**−**12**, which were optimized without symmetry constraints. All energies are in kcal/mol. These data are visualized in Figure 6.

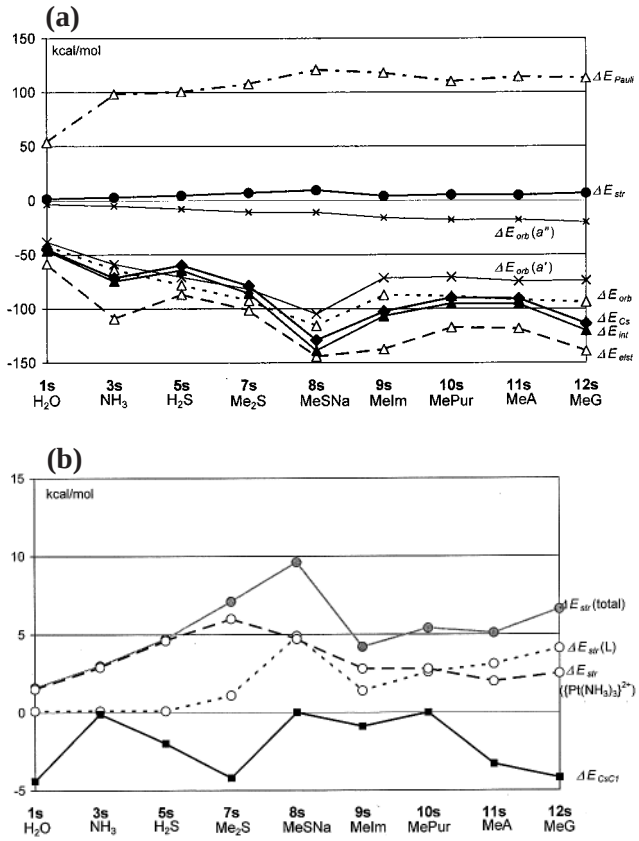


Figure 6. Display of the results from the energy-decomposition analysis.

The anticancer activity of platinum complexes is now attributed to the size of the carrier ligands rather than to hydrogen bonding. The very small size of the NH group, not its hydrogen-bonding ability, is responsible for the good activity exhibited by Pt compounds with amine carrier ligands with multiple NH groups.[26]

N versus S Binding to Pt(II) in Light of the HSAB Principle

In this section, we answer the question of whether the HSAB textbook principle[17] and the preference of the soft platinum(II) center for hard nitrogen ligands over soft sulfur ligands can be reconciled. We focus the discussion on four aspects.

(i) Charge Dependence of the Chemical Hardness. A parabolic energy function E of the number N of system electrons,

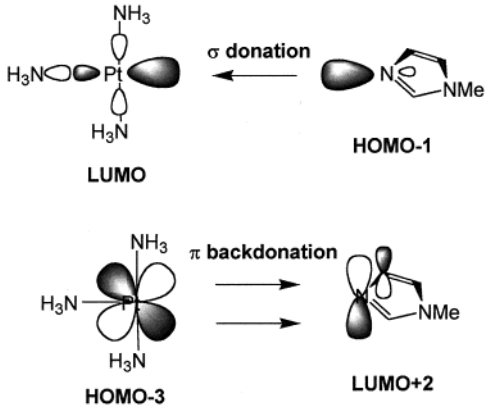


Figure 7. Predominant orbital interactions of σ donation from 1-methylimidazole to $\{Pt(NH_3)_3\}^{2+}$ and of π back-donation, respectively. The σ interactions correspond to the a' irreducible representation, and the π interactions correspond to a''.

leading to a charge-independent hardness $\eta = (\partial^2 E/\partial N^2)$, might be a rough approximation. We have also calculated the Pt−L energies in the neutral complexes *cis*-$[Pt(NH_3)Cl_2L]$; the results are presented in Table 3. Although the difference between the ΔE values with L = NH_3 and H_2S becomes smaller in neutral complexes (3.5 kcal/mol) than in the dicationic cisplatin derivatives (9.9 kcal/mol), the calculated results for neutral complexes corroborate the trend of a Pt(II) preference for N-ligand binding.

(ii) Symbiosis. It was suggested[28] that the hardness of the complex fragment $[ML'_n]$ with hard ligands L′ is increased by additional ligands L′, while soft ligands L″ make the complex fragment $[ML''_n]$ with the same metal M softer. While $\{Pt(NH_3)_3\}^{2+}$ prefers the coordination of an additional ammine ligand, one might expect that $\{Pt(H_2S)_3\}^{2+}$ favors the coordination of dihydrogensulfide. However, the calculations contradict this idea: $\{Pt(H_2S)_3\}^{2+}$ shows an even larger preference for an additional NH_3 ligand; the calculated energy difference between ammonia and dihydrogensulfide coordination is 10.4 kcal/mol (Table 3).

(iii) Environmental Effects. It was found that, in the gas phase, the soft Ag^+ cation binds more strongly to NH_3 than to PH_3.[29] However, the relative energies of the Ag−pnictogene bond are reverse in aqueous solution.[17c] We have calculated

(28) (a) Jorgensen, C. K. *Inorg. Chem.* **1964**, *3*, 1201. (b) Jonas, V.; Frenking, G.; Reetz, M. T. *J. Am. Chem. Soc.* **1994**, *116*, 8741.
(29) Chattaray, P. K.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1994**, *116*, 1067.

Table 3. Competition of O, N, and S Ligands for Coordination with $\{Pt(NH_3)_3\}^{2+}$ in Light of the HSAB Principle (Calculated Reaction Energies of Model Reactions (in kcal/mol))

concept[a]	model reaction	L = H_2O	NH_3	H_2S	H_2S relative to NH_3
	$\{Pt(NH_3)_3\}^{2+} + L \rightarrow [Pt(NH_3)_3L]^{2+}$	−49.4	−71.8	−61.9	9.9
(i) charge dependence	$\{Pt(NH_3)Cl_2\} + L \rightarrow [Pt(NH_3)Cl_2L]$	−23.8	−36.8	−33.3	3.5
(ii) symbiosis	$\{Pt(H_2S)_3\}^{2+} + L \rightarrow [Pt(H_2S)_3L]^{2+}$	−42.6	−65.5	−55.1	10.4
(iii) environment	$\{Pt(NH_3)_3\}^{2+} + L \rightarrow [Pt(NH_3)_3L]^{2+}$, in H_2O[b]	−7.0	−26.7	−19.0	7.7
(iv) competition	$[Pt(NH_3)_3(H_2O)]^{2+} + LH^+ \rightarrow [Pt(NH_3)_3L]^{2+} + H_3O^+$[c]	0.0	+19.0	−6.4	−25.4

[a] See text for explanation. [b] Reaction energy calculated using a polarizable continuum with $\epsilon = 78.4$. [c] Calculated gas-phase proton affinities ($L + H^+ \rightarrow LH^+$): L = H_2O −168.7 kcal/mol; NH_3 −210.1 kcal/mol; H_2S −174.8 kcal/mol.

the stabilization energies for the coordination of H_2O, NH_3, and H_2S to $\{Pt(NH_3)_3\}^{2+}$ both in the gas phase and in a polarizable continuum with a dielectric constant ϵ of 78.4 for water.[30,31] The calculations show that the relative energy difference with L = NH_3 and H_2S is, at 7.7 kcal/mol, almost as large as that in the gas phase (see Table 3); environmental effects do not help us understand the preference for ammonia over dihydrogensulfide. Further investigations of the complexes **0**−**12** in condensed matter are reported and discussed in the next section.

(iv) Competition of Platinum(II) with Very Strong and Hard Acids. To study the influence of the presence of very strong and hard acids such as H^+ on the chemoselectivity of platinum binding to biomolecules, we have calculated the energy of the model reaction $[Pt(NH_3)_3(H_2O)]^{2+} + LH^+ \rightarrow [Pt(NH_3)_3L]^{2+} + H_3O^+$ with L = NH_3 and H_2S (Table 3). The computations show that the proton affinity[32] of ammonia is much larger than the proton affinity of dihydrogensulfide, indicating that, in a stoichiometric system, only the S donors are left for coordination with the heavy-metal cation.

Environmental Effects

Environmental effects on the relative stability of the complexes have been estimated using the conductor-like screening model (COSMO).[30,33] Experimental competition studies were carried out in aqueous solution; water molecules are also required to maintain the structure of DNA.[34] Hydrated biological molecules have a considerably smaller dielectric constant ϵ than does water ($\epsilon = 78.4$).[35] To investigate the influence of a polarizable environment on the stability of the platinum complexes systematically, we have calculated the energies of **1**−**12** at $\epsilon = 1$ (gas phase), 3, 9, and 78.4 (water). The gas-phase geometries have been used since the structures of **0**, **1**, and **9** calculated at $\epsilon = 1$ and 78.4 are similar and the energy deviations due to the geometrical changes are small (Table 4).

Table 4. Calculated Bond Distances (X−Y, in Å), Bond Angles (X−Y−Z, in deg), and Pt−L Bond Energies (ΔE, in kcal/mol) of the Complexes $[Pt(NH_3)_3L]^{2+}$ with L = □[a] (**0**), H_2O (**1**), and MeIm (**9**) in Vacuum ($\epsilon = 1$) and in a Polarizable Continuum with a Dielectric Constant ϵ of 78.4

	ϵ	**0**, L = □[a]	**1**, H_2O	**9**, MeIm
Pt−Nα	1	2.092	2.085	2.086
	78.4	2.062	2.062	2.070
Pt−Nβ	1	2.022	2.054	2.113
	78.4	1.990	2.031	2.065
Pt−Nχ	1	2.089	2.096	2.087
	78.4	2.053	2.070	2.070
Pt−L	1		2.115	2.033
	78.4		2.109	2.038
Nα−Pt−L	1	86.6[b]	84.4	88.3
	78.4	88.0[b]	87.2	90.3
L−Pt−Nχ	1	86.6[b]	92.8	88.4
	78.4	88.0[b]	91.7	90.4
ΔE	78.4//1[c]	0.0	−7.0	−21.7
	78.4	0.0	−5.7	−19.7

[a] □ = free coordination site. [b] Estimated using Nα−Pt−Nχ, Nα−Pt−Nβ, and Nβ−Pt−Nχ. [c] Energy calculated using the continuum model and gas-phase geometries.

The theoretically predicted reaction energies ΔE_{le} for ligand exchange, $[Pt(NH_3)_3(H_2O)]^{2+} + L \rightarrow [Pt(NH_3)_3L]^{2+} + H_2O$, at $\epsilon = 1$, 3, 9, and 78.4 are presented in Table 5 and Figure 8. The energy of the aqua complex $[Pt(NH_3)_3(H_2O)]^{2+}$ (**1**) has been chosen as a reference, since hydrolyzed cisplatin derivatives are active compounds.[4,9ai,36] The results can be summarized as follows: (i) The ligand-exchange energy ΔE_{le} for each ligand L seems to converge with increasing ϵ. The convergence occurs at higher ϵ values in the case of large ligands L because of the ability of large ligands to partially stabilize the positive charge. (ii) The influence of the dielectric constant ϵ on the relative energy of the complexes with NH_3 (**3**) and H_2S (**5**) is very small, confirming the preference of Pt(II) for nitrogen ligands both intrinsically and in condensed matter. (iii) Methyl substituents in the complexes of MeOH (**2**), $MeNH_2$ (**4**), MeSH (**6**), and M_2S (**7**) stabilize the complexes in the gas phase in comparison with **1**, **3**, and **5**. In a polarizable continuum, **2**, **4**, **6**, and **7** are as stable as or less stable than the parent complexes **1**, **3**, and **5**, respectively. (iv) The ion pair MeSNa forms the strongest bond to platinum(II) at each ϵ value. Note that the existence of platinated, deprotonated thiols in vivo is likely.[42] (v) The

(30) (a) Klamt, A.; Schürmann, G. *J. Chem. Soc., Perkin Trans. 2* **1993**, 799. (b) Klamt, A.; Jonas, V. *J. Chem. Phys.* **1996**, *105*, 9972. (c) Gilbert, T. M.; Hristov, I.; Ziegler, T. *Organometallics* **2001**, *20*, 1183. (d) Cooper, J., personal communication.

(31) In Pearson's recent book (ref 17c), solvation is a very important aspect in the discussion of the HSAB principle. Attempts were made to describe solvation effects both accurately and efficiently in the computations, including the consideration of microscopic models. Geometry optimization of the $[Pt(NH_3)_3L]^{2+}$ complexes with two additional aqua ligands in the axial position was performed. These calculations, however, resulted in a movement of the two aqua ligands from the first axial coordination sphere to the second equatorial coordination sphere to form hydrogen bonds with the ammine ligands of the first equatorial coordination sphere. Geometry optimizations of the $[Pt(NH_3)_3L]^{2+}$ model complexes with two highly polarizable iodo counterions in the axial positions yielded structures, some of which contain the I^- ligands in the first equatorial coordination sphere, since the neutral ligands were displaced. The polarizable continuum model which is employed is certainly an approximation, but the comparison of the calculated results to the results of experimental competition studies indicated a good agreement of experiment and computation (see below).

(32) See also: Taft, R. W.; Wolf, J. F.; Beauchamp, J. T.; Scorrano, G.; Arnett, E. M. *J. Am. Chem. Soc.* **1978**, *100*, 1240.

(33) For reviews of continuum solvation models, see: (a) Tomasi, J.; Persico, M. *Chem. Rev.* **1994**, *94*, 2027. (b) Cramer, C. J.; Truhlar, D. G. *Chem. Rev.* **1999**, *99*, 2161.

(34) (a) Nandi, N.; Bhattacharyya, K.; Bagchi, B. *Chem. Rev.* **2000**, *100*, 2013. (b) For a recent computational study on the hydration of DNA base pairs, see: Dakshanamurthy, S.; Welsh, W. J. *Biochemistry* **2001**, *40*, 189.

(35) Dudev, T.; Lim, C. *J. Am. Chem. Soc.* **2000**, *122*, 11146 and refs therein.

(36) (a) Legendre, F.; Bas, V.; Kozelka, J.; Chottard, J. C. *Chem.-Eur. J.* **2000**, *6*, 2002. (b) Davies, M.; Berners-Price, S. J.; Hambley, T. W. *Inorg. Chem.* **2000**, *39*, 5603.

Table 5. Calculated Reaction Energies, ΔE_{le}, for Ligand Exchange, $[Pt(NH_3)_3(H_2O)]^{2+} + L \rightarrow [Pt(NH_3)_3L]^{2+} + H_2O$, in Vacuum ($\epsilon = 1$) and in a Polarizable Continuum with $\epsilon = 3$, 9, and 78.4[a]

ϵ	**0**, L = □[b]	**1**, H_2O	**2**, CH_3OH	**3**, NH_3	**4**, CH_3NH_2	**5**, H_2S	**6**, MeSH	**7**, Me_2S	**8**, MeSNa	**9**, MeIm	**10**, MePur	**11**, MeA	**12**, MeG
1	49.4	0.0	−7.8	−22.4	−28.2	−12.5	−24.4	−33.7	−79.7	−54.1	−40.6	−44.7	−68.5
3	22.2	0.0	0.2	−20.5	−20.1	−12.0	−15.8	−18.6	−52.5	−26.9	−17.7	−15.5	−31.4
9	11.9	0.0	2.5	−19.9	−17.9	−12.2	−13.7	−14.6	−40.9	−18.3	−12.1	−7.7	−19.3
78.4[c]	7.0	0.0	3.3	−19.7	−17.1	−12.0	−13.0	−13.0	−35.5	−14.7	−10.1	−4.8	−14.0

[a] Energies were calculated using gas-phase geometries. These data are visualized in Figure 8. [b] □ = free coordination site. [c] In aqueous solution (ϵ = 78.4), the C_s-symmetric structure **1s** is less stable than **1** by 1.3 kcal/mol, **12s** is less stable than **12** by 3.0 kcal/mol, and **11s** is more stable than **11** by 4.4 kcal/mol.

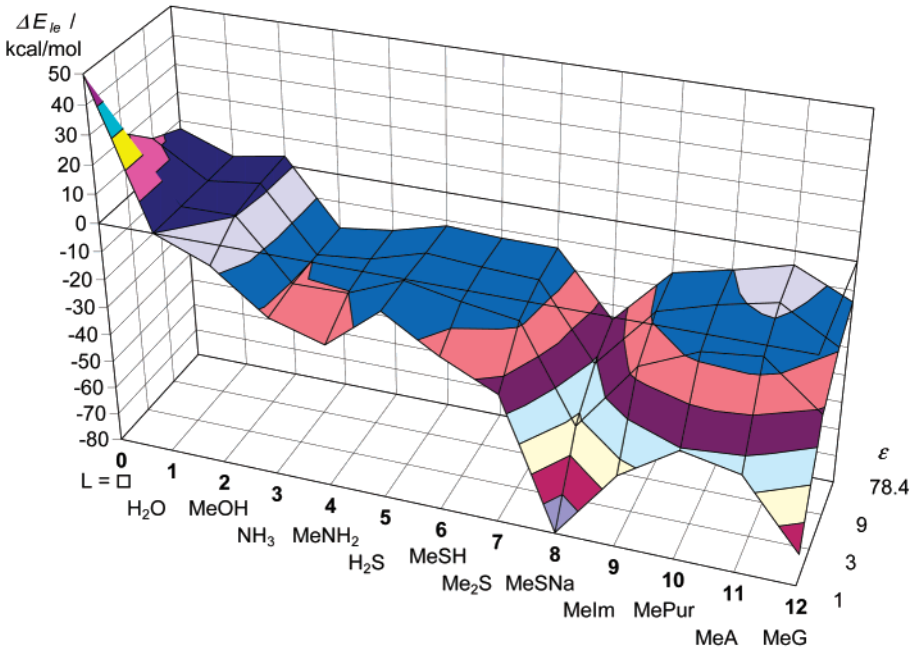


Figure 8. Calculated reaction energies, ΔE_{le}, for ligand exchange, $[Pt(NH_3)_3(H_2O)]^{2+} + L \rightarrow [Pt(NH_3)_3L]^{2+} + H_2O$, in a vacuum ($\epsilon = 1$) and in a polarizable continuum with $\epsilon = 3$, 9, and 78.4.

complexes of MeA (**11**) and MeG (**12**) benefit less from a polarizable continuum than does the purine adduct (**10**), since intramolecular electrostatic interactions are weakened by a polarizable continuum. (vi) At $\epsilon = 78.4$, the dielectric constant of water, 9-methylguanine remains the only purine derivative which forms a complex that is more stable than the adducts of the neutral sulfur ligands (**6** and **7**). (vii) A very strong affinity of platinum(II) to histidine side chains, modeled by 1-methylimidazole, has been found. The displacement of the metal in zinc-containing proteins by platinum was observed[7f] and is a potential origin of the toxicity of Pt-based anticancer drugs. (viii) The remarkable strength of the Pt−L bond predicted for the complexes of simple amine ligands (**4**) in aqueous solution is less important in vivo due to a large proton affinity of the amine moieties.

Finally, we compare the theoretically predicted stability of the complexes $\{Pt(NH_3)_3\}^{2+}$ to results from competition studies. There is a considerable research activity of the Reedijk, Sadler, and Sheldrick laboratories and others;[6,7] we only discuss two pioneering studies on the platination of *S*-adenosyl-L-homocysteine (SAH) and *S*-guanosyl-L-homocysteine (SGH, see Figure 9) in light of the calculated thermodynamic stabilities of the Pt−L bond. Complexation of $\{Pt(dien)\}^{2+}$ with the thioether moiety of SAH occurs rapidly at pH < 7 (I). Fast isomerization to the complex with the RNH_2 site of the amino acid was detected at pH > 7 (II).[6a] Coordination or migration of $\{Pt(dien)\}^{2+}$ to the adenine site was not observed (III).[6a] The complex of $\{Pt(dien)\}^{2+}$ with the thioether moiety of SGH is also formed fast at low pH (IV), but the Pt(dien) moiety slowly

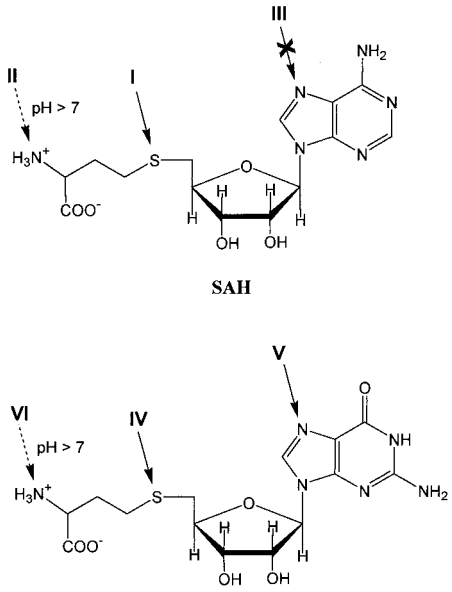


Figure 9. *S*-Adenosyl-L-homocysteine (SAH) and *S*-guanosyl-L-homocysteine (SGH) employed in intramolecular competition studies for multifunctional targets of platinum(II) complexes.

moves to the guanine−N7 site (V).[6b] At higher pH values, complexation of the amino moiety becomes competitive (VI). These results nicely reflect the trend in the calculated thermodynamic stability of $[Pt(dien)L]^{2+}$ at $\epsilon = 78.4$ (Table 5, Figure 8): $MeNH_2$ < MeG < Me_2S < MeA. Migration of $\{Pt(dien)\}^{2+}$ from methionine side chains to histidine side chains of oligopeptides was recently observed,[6g] which is also in agreement with the predicted Pt−L energies at $\epsilon = 78.4$. Furthermore, Volckova et al.[7h] recently reported that the reaction of cisplatin with DNA at physiological pH in the presence of cysteine and glutathione mainly gives the platinated sulfur sites, indicating a strong Pt−S bond to the probably deprotonated thiols. Future computational work will address the question of why the coordination of S ligands is kinetically preferred over the platination of DNA. This challenge also involves the consideration of larger model systems to be investigated with quantum-mechanical-molecular-mechanical (QMMM) hybrid methods.

Conclusions

Density functional theory (DFT) calculations have been carried out to investigate the competition of the purine bases, functionalities of peptide side chains, and protecting agents for the coordination sites of cisplatin derivatives. Simple model complexes, $[Pt(NH_3)_3L]^{2+}$, with 12 oxygen-, nitrogen-, and sulfur-containing ligands L of biological relevance have been used. The calculated geometries as well as Pt−L bond energies of the complexes in the gas phase and in a polarizable environment are reported and analyzed. The results can be summarized as follows:

(i) The calculations demonstrate an intrinsic preference of the platinum(II) center for simple N ligands such as NH_3 and $MeNH_2$ over S ligands such as H_2S and MeSH. Model reactions have been designed to discuss this remarkable result in light of modern interpretations of the HSAB principle. It is shown that neither symbiosis effects, nor environmental effects, nor the charge dependence of the chemical hardness explain the affinity of the metal to nitrogen ligands. Strong and very hard acids show a larger preference for NH_3 than for H_2S ligands, and, in a stoichiometric system, the competing hard acids leave only the sulfur ligand for coordination of the platinum center.

(ii) The origin of the intrinsic stability of the Pt−L bonds has been studied by the analysis of the complexes using the concept of orbital-symmetry-based energy decomposition. The analysis reveals the presence of different binding modes, indicating that a discussion of N versus S ligands is only warranted if similar ligands are compared. The calculations show a considerable contribution from π orbital interactions to the Pt−L bond energy in the complexes with the N-containing heterocycles, which is caused by both donation from L to the metal and back-donation vice versa. The larger stability of the complex $[Pt(NH_3)_3(MeG)]^{2+}$ (MeG = 9-methylguanine) in comparison with $[Pt(NH_3)_3(MeA)]^{2+}$ (MeA = 9-methyladenine) is attributed to electrostatics rather than to orbital interactions. Surprisingly, the net stabilization due to the formation of the hydrogen bond in $[Pt(NH_3)_3(MeG)]^{2+}$ is, at 4.2 kcal/mol, as small as that in the aqua complex $[Pt(NH_3)_3(H_2O)]^{2+}$, supporting the recent Marzilli[26] hypothesis that the activity of platinum anticancer drugs bearing carrier ligands with several N−H groups arises from the small size of these ligands rather than from their ability to form hydrogen bonds.

(iii) Environmental effects on the stability of the dicationic cisplatin derivatives have been studied systematically using a polarizable continuum model with a dielectric constant ϵ of 1 (vacuum), 3, 9, and 78.4 (water). With increasing ϵ, the S complexes become as stable as or more stable than the complexes of the N-containing heterocycles. At $\epsilon = 78.4$, the dielectric constant of water, only MeG remains competitive with neutral sulfur ligands, while thiolates form the strongest bonds with the metal center. A large affinity of platinum(II) to the imidazole moiety of histidine side chains has also been predicted. The platination of simple amines such as $MeNH_2$ remains considerably more exothermic but is prevented by the N protonation of amines. The calculated stability of the complexes shows a remarkable agreement with the reaction products observed in experimental studies on the competition of biological donor ligands for coordination with the platinum center of $\{Pt(dien)\}^{2+}$ (dien = 1,5-diamino 3-azapentane).

Computational Methods

Geometry optimizations were performed at the gradient-corrected density functional theory (DFT) level using Becke's exchange functional and Perdew's correlation functional (BP86).[12] Relativistic effects were considered by the zeroth-order regular approximation (ZORA).[37] Uncontracted Slater-type orbitals (STOs) were used as basis functions.[38] The valence basis functions at the metal have triple-ζ quality, augmented with a set of p functions. The valence basis set at the sulfur atoms has triple-ζ quality, augmented with a set of d polarization functions and a set of f functions.[39] The valence basis set at the other atoms has triple-ζ quality, augmented with a set of d polarization functions (VTZP). The $(1s)^2$ core electrons of C, N, and O, the $(1s2sp)^{10}$ core electrons of S, and the $(1s2sp3spd4spdf)^{60}$ core electrons of Pt were treated within the frozen-core approximation.[40] For the analysis of the Pt−L bonds, Ziegler and Rauk's energy-decomposition scheme has been employed.[19−21] The conductor-like screening model (COSMO) has been utilized to estimate environmental effects on the stability of the complexes.[30] The calculations were carried out with the ADF program package.[41]

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(37) Van Lenthe, E.; Ehlers, A. E.; Baerends, E. J. *J. Chem. Phys.* **1999**, *110*, 8943 and refs therein.
(38) Snijders, J. G.; Baerends, E. J.; Vernooijs, P. *At. Data Nucl. Data Tables* **1982**, *26*, 483.
(39) Large basis sets are required for obtaining accurate energies of sulfur compounds: (a) Turecek, F. *J. Phys. Chem. A* **1998**, *102*, 4703. (b) Timoshkin, A.; Frenking, G. *J. Chem. Phys.* **2000**, *113*, 8430. (c) Jenks, W. S., personal communication. (d) Deubel, D. V. *J. Org. Chem.* **2001**, *66*, 2686.
(40) Baerends, E. J.; Ellis, D. E.; Ros, P. *Chem. Phys.* **1973**, *2*, 41.
(41) (a) Fonseca Guerra, C.; Snijders, J. G.; Te Velde, G.; Baerends, E. J. *Theor. Chem. Acc.* **1998**, *99*, 391. (b) Bickelhaupt, F. M.; Baerends, E. J. In *Reviews in Computational Chemistry*; Lipkowitz, K. B., Boyd, D. B., Eds.; VCH: New York, 2000; Vol. 15, p 1. (c) Te Velde, G.; Bickelhaupt, F. M.; Baerends, E. J.; Fonseca Guerra, C.; Van Gisbergen, S. J. A.; Snijders, J. G.; Ziegler, T. *J. Comput. Chem.* **2001**, *22*, 931.
(42) For recent computational studies on the protonation state in $ZnCys_4$ sites of proteins, see: (a) Dudev, T.; Lim, C. *J. Phys. Chem. B* **2001**, *105*, 10709. (b) Dudev, T.; Lim, C. *J. Am. Chem. Soc.* **2002**, accepted for publication.