[1] L. Pauling, *J. Am. Chem. Soc.* **1940**, *62*, 2643 – 2657.
[2] Reviews: a) G. Wulff, *Angew. Chem.* **1995**, *107*, 1958 – 1979; G. Wulff, *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1812 – 1832; b) K. J. Shea, *Trends Polym. Sci.* **1998**, *2*, 166 – 173; c) K. Mosbach, O. Ramström, *Bio/Technology* **1996**, *14*, 163 – 170; d) E. N. Vulfson, C. Alexander, M. J. Whitcombe, *Chem. Br.* **1997**, *33*, 23 – 26. For a notable recent report on the use of combinatorial methods in molecular imprinting, see e) T. Takeuchi, D. Fukuma, J. Matsui, *Anal. Chem.* **1999**, *71*, 285 – 290.
[3] G. Vlatakis, L. I. Andersson, R. Müller, K. Mosbach, *Nature* **1993**, *361*, 645 – 647.
[4] O. Ramström, L. Ye, K. Mosbach, *Chem. Biol.* **1996**, *3*, 471 – 477.
[5] M. J. Whitcombe, M. E. Rodriguez, P. Villar, E. N. Vulfson, *J. Am. Chem. Soc.* **1995**, *117*, 7105 – 7111.
[6] Amino acid derivatives and short peptides have been noncovalently imprinted in a number of studies that have produced polymers capable of optical resolution. See for example a) B. Sellergren, M. Lepistö, K. Mosbach, *J. Am. Chem. Soc.* **1988**, *110*, 5853 – 5860; b) I. A. Nicholls, L. I. Andersson, K. Mosbach, B. Ekberg, *Trends Biotechnol.* **1995**, *13*, 47 – 51; c) C. Yu, K. Mosbach, *J. Org. Chem.* **1997**, *62*, 4057 – 4064; d) S. Vidyasankar, M. Ru, F. H. Arnold, *J. Chromatogr. A* **1997**, *775*, 51 – 63; e) J. M. Lin, T. Nakagama, K. Uchiyama, T. Hobo, *J. Pharm. Biomed. Anal.* **1997**, *15*, 1351 – 1358; f) O. Ramström, I. A. Nicholls, K. Mosbach, *Tetrahedron: Asymmetry.* **1994**, *5*, 649 – 656; g) M. Kempe, K. Mosbach, *Tetrahedron Lett.* **1995**, *36*, 3563 – 3566; h) L. I. Andersson, R. Müller, G. Vlatakis, K. Mosbach, *Proc. Natl. Acad. Sci. USA* **1995**, *92*, 4788 – 4792.
[7] M. Lübke, M. J. Whitcombe, E. N. Vulfson, *J. Am. Chem. Soc.* **1998**, *120*, 13342 – 13348.
[8] Covalent imprinting with polymerizable carboxylic esters (without spacers) has been successfully carried out before, see B. Sellergren, L. Andersson, *J. Org. Chem.* **1990**, *55*, 3381 – 3383.
[9] This monomer has previously been used in combination with methacrylic acid to imprint amino acid derivatives, see O. Ramström, L. I. Andersson, K. Mosbach, *J. Org. Chem.* **1993**, *58*, 7562 – 7564.
[10] Infrared and ^{1}H NMR studies on a model compound, *N*-(4-hexadecylphenyl)-2-methacryloyloxybenzamide, confirmed the presence of an intramolecular hydrogen bond between the amide N proton and the adjacent oxygen atom.
[11] X. C. Liu, K. Mosbach, *Macromol. Rapid Commun.* **1998**, *19*, 671 – 674.
[12] Selectivity between aspartic and glutamic acid derivatives has previously been reported for imprinted polymers based on methacrylic acid, see L. I. Andersson, K. Mosbach, *J. Chromatogr. Sci.* **1990**, *516*, 313 – 322.
[13] G. H. Chen, Z. B. Guan, C. T. Chen, L. T. Fu, V Sundaresan, F. H. Arnold, *Nat. Biotechnol.* **1997**, *15*, 354 – 357.

A New Platinum Anticancer Drug Forms a Highly Stereoselective Adduct with Duplex DNA**

Yu Chen, John A. Parkinson, Zijian Guo, Tom Brown, and Peter J. Sadler*

Much attention is currently focused on the design of new generations of platinum anticancer complexes that circumvent cisplatin resistance. Such resistance often involves the recognition of platinated DNA adducts by proteins and enzymes in the excision – repair systems in cells.[1] It is therefore vital to understand how ligand design influences the nature of platinated DNA lesions. A complex with high activity against cisplatin-resistant cell lines is the 2-picoline (2-Pic, 2-methylpyridine) complex *cis*-[$PtCl_2(NH_3)$(2-Pic)] (**1**, ZD0473), a new anticancer Pt^{II} drug currently in phase I clinical trials.[2, 3] The steric effect of 2-picoline plays an important role in determining the rates of hydrolysis and substitution reactions with the nucleotide guanosine-5′-monophosphate (5′-GMP).[4, 5] As a result of slow rotation about the Pt–N(2-Pic) bond (0.62 s^{-1}, 296 K), together with the non-C_2-symmetrical structure of complex **1**, four isomers of the bis(GMP) adduct are possible, and these are formed in equal amounts.[5] We show here, in dramatic contrast, that reactions of **1** with the 14mer DNA duplex **2** give predominantly a single stereoisomer, whereas relatively little stereoselectivity is observed for reactions with the deoxydinucleotide d(GpG) or the 14-mer single strand **2a**. The structural basis for this unusually high stereoselectivity has been revealed by NMR studies.

5′d($A_1T_2A_3C_4A_5T_6G_7^*G_8^*T_9A_{10}C_{11}A_{12}T_{13}A_{14}$) **2a**

3′d($T_{28}A_{27}T_{26}G_{25}T_{24}A_{23}C_{22}C_{21}A_{20}T_{19}G_{18}T_{17}A_{16}T_{15}$) **2b**

2a + **2b** = **2**

Reactions of complex **1** with both d(GpG) and 14-mer single strand **2a** at a 1:1 molar ratio (1 mM, pH 6.0, 9 mM phosphate, 100 mM $NaClO_4$, H_2O/D_2O 90/10, 298 K) were followed by 1D ^{1}H and 2D [^{1}H,^{15}N] HSQC NMR spectro-

[*] Prof. Dr. P. J. Sadler, Y. Chen, Dr. J. A. Parkinson, Dr. Z. Guo
Department of Chemistry
University of Edinburgh
West Mains Road, Edinburgh EH9 3JJ (UK)
Fax: (+44) 131-650-6452
E-mail: P.J.Sadler@ed.ac.uk
Prof. Dr. T. Brown
Department of Chemistry
University of Southampton
Southampton SO17 1BJ (UK)

[**] This research was supported by the Biotechnology and Biological Sciences Research Council, Engineering and Physical Sciences Research Council (Biomolecular Sciences Programme), and EC COST programme. We are grateful to the Committee of Vice-Chancellors and Principals of the Universities of the United Kingdom for an Overseas Research Student Award and the University of Edinburgh for a Research Studentship to Y. Chen. We acknowledge the Wellcome Trust for the provision of funding for molecular modeling facilities and Johnson Matthey plc for the loan of some platinum.

  1433-7851/99/3813-2060 $ 17.50+.50/0

scopy. In each case the GG chelate gave rise to four cross peaks of similar intensities, which correspond to similar populations of the four possible stereoisomers: 2-picoline orientated towards 5′-G or 3′-G, and slow rotation about the Pt–N(2-Pic) bond.[6] When the temperature was increased, the four $^1H/^{15}N$ cross peaks for the d(G*pG*) adducts began to merge into two, as observed for the bis(GMP) adducts.[5]

The reaction of complex **1** with duplex **2** at a 1:1 molar ratio was studied under the same conditions, and followed in the same way. After one week one major cross peak was observed (Figure 1, $\delta = 4.51/-67.46$), which accounted for 90% of the

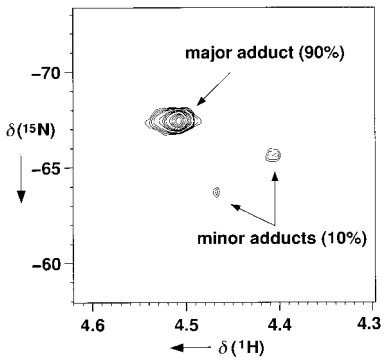


Figure 1. 2D [^1H,^{15}N] HSQC NMR spectrum recorded after one week of reaction of *cis*-[$PtCl_2(^{15}NH_3)$(2-Pic)] (**1**, 1 mol equiv) with the 14-mer DNA duplex **2** (298 K, 100 mM $NaClO_4$, pH 6.0, 9 mM phosphate buffer, H_2O/D_2O 90/10). The integral percentages of the major peak and the two minor peaks are indicated.

total quantity of platinated adducts. Peaks for the H6 ($\delta =$ 8.88) and 2-methyl ($\delta = 3.15$) protons of the 2-picoline ligand of unreacted **1** were replaced by two new signals at $\delta = 9.20$ and 3.19, respectively. A feature of the new 2-picoline signals was their broadness relative to free **1**, as a result of the 2-picoline complex taking on the T_2 relaxation characteristics of a macromolecule by irreversible binding to DNA. New NMR resonances were also observed outside the usual windows expected for both aromatic and methyl protons of DNA. These signals enabled further assignments to be made. We explored the use of NMR methods to determine the structure around the platination site of the major adduct even though the NMR spectra were complicated by the presence of peaks for the minor adducts and free duplex **2**. A ^1H 2D NOESY NMR spectrum (mixing time 200 ms) was acquired for the same sample and compared to that of the cisplatin GG bischelated adduct of the same DNA duplex.[7] The key ^1H NMR assignments derived from these data are listed in Table 1. They are based on the following observations: a clear strong NOE between G7 H8 and G8 H8 with chemical shifts similar to those observed for the cisplatin–DNA adduct of DNA duplex (Figure 2 A),[7, 8] an NOE between 2-picoline H6 and G7 H8, a cross peak between a resonance in the usual H2′/H2″ region and a resonance at $\delta = 0.42$ assignable to T6 H2′ (which is significantly shifted to low frequency relative to that for DNA platinated by cisplatin, $\delta = 1.37$ for duplex **2**,[7] and $\delta = 1.40$ for a reported 12-mer duplex[8]), and a strong cross peak between 2-picoline CH_3 and T6 CH_3, which also showed NOEs to T6 H1′and T6 H2′. Confirmation of the 2-picoline

Table 1. Assignments of key ^1H resonances for the G*G* chelate of duplex **2** with complex **1**.

Assignment (2-picoline)	δ	Assignment (DNA)	δ
H6	9.20	T6 CH_3	1.16
H5	7.67	T6 H1′	5.82
H4	8.18	T6 H2′	0.43
H3	7.59	T6 H2″	1.91
2-CH_3	3.19	T6 H3′	4.69
		T6 H4′	4.00
		G7 H8	8.55
		G8 H8	8.18

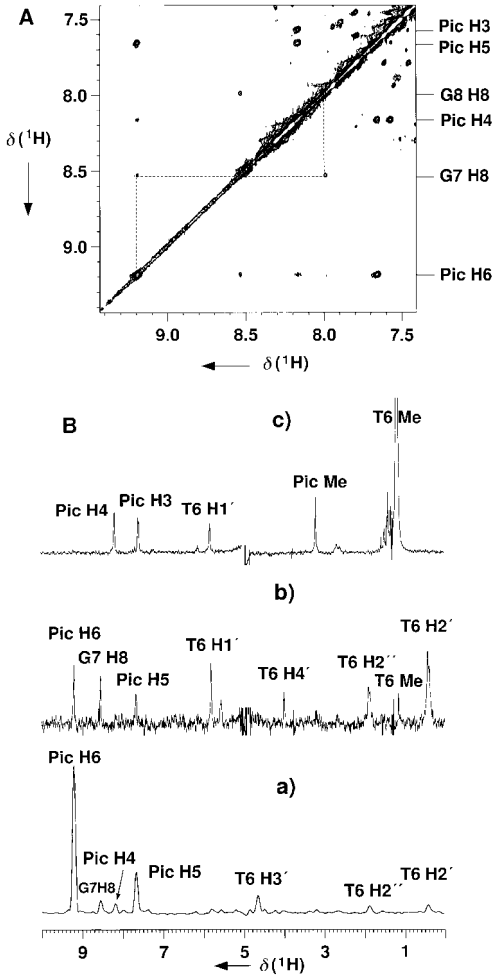


Figure 2. A) Expansion of the aromatic region of the 200 ms 2D NOESY NMR spectrum for the same sample as Figure 1 in 99.9% D_2O. Assignments are shown on the right-hand side (Pic refers to the 2-methylpyridine ligand), and the dashed line shows the connectivity from Pic-H6 to G7 H8 and G7 H8 to G8 H8; B) Slices through the 2D NOESY spectrum at the chemical shifts of a) 2-picoline H6, b) T6 H2′, and c) T6 CH_3, showing NOE connectivities to other protons. Detailed peak assignments and NOE information are listed in Tables 1 and 2, respectively.

ring proton assignments was obtained from a ^1H 2D DQFCOSY NMR spectrum. The assignments of resonances for T6 were further confirmed by the NOE observed between T6 H2′ and G7 H8. Figure 2 B shows slices taken through the NOESY data at the chemical shifts of T6 CH_3, T6 H2′, and 2-picoline H6. Key assignments of NOEs around the platination site are listed in Table 2.

  1433-7851/99/3813-2061 $ 17.50+.50/0

Table 2. Key NOE signals observed between 2-picoline and DNA protons after platination of DNA duplex **2** with the platinum anticancer drug **1**. The corresponding distances in the four models are listed for comparison. Distances over 5 Å are beyond the limit for NOEs, and are labeled (–).

Observed NOE	Distances in models [Å]			
1···**2**	**3a**	**3b**	**3c**	**3d**
H6···G7 H8	4.45	3.47	5.70(–)	5.15(–)
H6···T6 H3′	4.88	4.53	7.21(–)	7.06(–)
H6···T6 H2″	4.98	4.50	7.08(–)	7.02(–)
H6···T6 H2′	3.33	3.52	5.57(–)	5.88(–)
H5···T6 H2′	3.78	3.85	7.86(–)	8.09(–)
CH_3···T6 CH_3	8.22(–)	4.03	9.07(–)	5.31(–)
H3···T6 CH_3	7.26(–)	2.73	9.66(–)	7.35(–)
H4···T6 CH_3	5.42(–)	4.70	9.02(–)	9.15(–)

Four molecular models of the GG adduct of duplex **2** were built by docking $\{Pt(NH_3)(2\text{-Pic})\}^{2+}$ onto the $G_7^*G_8^*$ site of the 14-mer DNA duplex **2**. The structure of the latter was based on that of the cisplatin adduct.[7] The models differed as follows: 2-picoline *trans* to G8 (3′-G) with the 2-methyl group orientated either towards the phosphate backbone (Methyl-Out**, 3a**) or towards the centre of the major groove (Methyl-In, **3b**); 2-picoline *trans* to 5′-G also with either Methyl-Out (**3c**) or Methyl-In (**3d**) orientations (See Scheme 1). Distance restraints were applied to each case, based on the data shown in Table 2, and the models minimized in the region of the bischelate site in order to satisfy the data. Of the four models only that with 2-picoline *trans* to 3′-G with the Methyl-In orientation (**3b**) satisfied all of the observed NOE constraints, as shown in Figure 3.

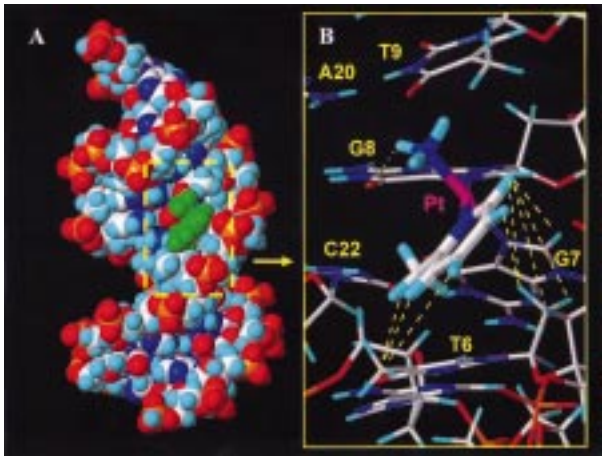


Figure 3. A) Space-filling model of *cis*-[Pt(NH_3)(2-Pic)]-d(ATACATG*G*TACATA)·d(TATGTACCATGTAT), with *cis*-$\{Pt(NH_3)(2\text{-Pic})\}^{2+}$ shown in green. The perfect fit and alignment of the 2-picoline ligand along the major groove can be seen. B) Close-up view of the Pt binding site showing NOE connectivities (yellow dashed lines, listed in Table 2) between 2-picoline and DNA. Hydrogen bonding between Pt-NH_3 and O6 of G8 is shown as a yellow dotted line. Color code: C: white, H: cyan, N: blue, O: red, P: orange, Pt: purple.

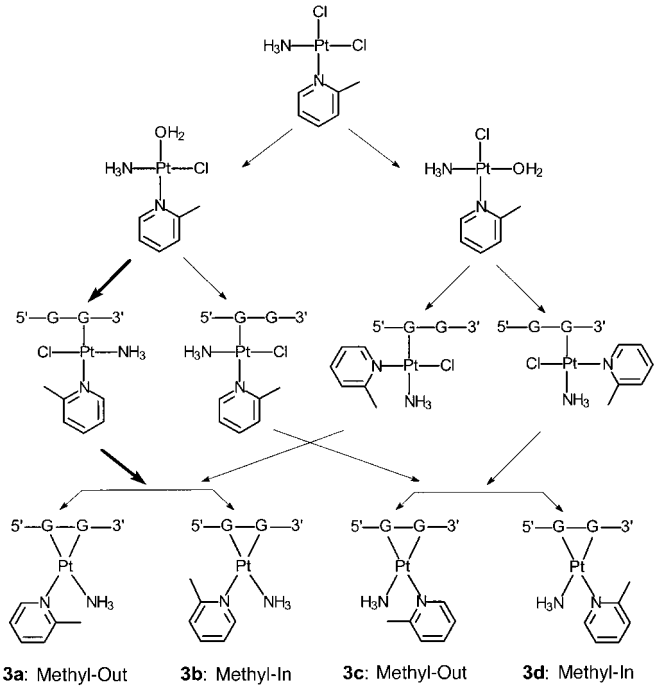
The first notable feature of model **3b** is that the picoline ring fits perfectly into the major groove of the DNA duplex and lies along the phosphate backbone, as shown in Figure 3 A. Models **3c** and **3d**, in which the 2-picoline ligand is *trans* to 5′-G with Methyl-Out or Methyl-In orientations, have the 2-picoline ring in an almost perpendicular orientation with respect to the planes of the nearby nucleotide bases. This steric clash causes models **3c** and **3d** to be far less stable than those with 2-picoline *trans* to 3′-G. The other notable feature is the orientation of the 2-picoline ring which lies almost perpendicular to the Pt square plane (angle 100°), as in the crystal structure of **1** (103°).[4] Model **3b** satisfies several other features of the NMR data. As shown in Table 1 the T6 H2′ resonance at $\delta = 0.44$ is significantly shifted to low frequency from its normal position for a G*G* DNA duplex/cisplatin adduct (usually near $\delta = 1.39$). It can be seen in Figure 3 B that T6 H2′ for molecule **3b** lies directly beneath, and within 3 Å of, the center of the 2-picoline ring. This is consistent with strong aromatic ring current shielding effects.[9, 10] The ^1H chemical shift of the NH_3 signal of the platinated duplex is shifted to high frequency by $\delta = 0.4$ relative to that for **1** itself. This is consistent with the presence of hydrogen bonding between the NH_3 of $\{Pt(NH_3)(2\text{-Pic})\}^{2+}$ and O6 of DNA residue G8 in model **3b**. Additional stabilization of complex **3b** may arise from van der Waals contact between the 2-methyl group of 2-picoline and the T6 methyl group of DNA (C···C: 3.78 Å).[11] This contact is not observed in the Methyl-Out model **3a** (distance between 2-CH_3 and T9 CH_3: 5.13 Å) and appears to be important in distinguishing between the Methyl-In and Methyl-Out models.

In previous reports of the stereoselective formation of platinated GG adducts,[12, 13] the selectivity has been low and with the opposite orientation (NH_3 *cis* to 5′-G) compared to that observed here. In the case of *cis*-[$PtCl_2(NH_3)(C_6H_{11}NH_2)$], a metabolite of the orally active drug JM216, the most abundant platinated G*G* stereoisomer (isomer ratio 2:1) has the cyclohexylamine ligand directed towards the 3′G of calf thymus DNA.[14] This preference was attributed partly to Pt–NH_3 H-bonding with the 5′-phosphate. The same ratio of orientational isomers (2:1) has been observed for an 11-mer DNA duplex platinated at G*G* with *cis*-$\{Pt(NH_3)(4\text{-aminoTEMPO})\}^{2+}$ (TEMPO = 2,2,6,6-tetramethylpiperidine-*N*-oxide (radical)).[15]

Preliminary kinetic studies of the reaction of complex **1** with duplex **2** show that the monoaqua species with 2-picoline *trans* to water reacts faster with DNA, and therefore monofunctional adducts with G*N*7 *trans* to 2-picoline are formed in preference to those with NH_3 *trans* to G*N*7 (Scheme 1). This is probably a result of unfavorable steric interactions when 2-picoline is *cis* to G*N*7. This contrasts with the formation of monofunctional adducts of *cis*- and *trans*-[$PtCl(NH_3)_2(4\text{-MePy})$]$^+$ where the methyl substituent is further away from the coordination plane,[16] and emphasizes further the important role played by the 2-methyl group of **1** that is close to the Pt ion. Monofunctional 3′-G-platinated adducts of DNA duplexes usually form faster and ring-close faster than 5′-G monofunctional adducts.[17] If this is also the case for adducts of **1**, then this, together with the preference for substitution *trans* to 2-picoline, would explain why the bifunctional adduct with 2-picoline *cis* to 5′G is the preferred product.

In conclusion, a number of factors appear to drive the high stereoselectivity in reactions of the anticancer drug **1** with DNA duplex **2**. These include: unfavorable steric interactions between the 2-picoline ring and the nearby nucleotide bases in models **3c** and **3d**, favorable hydrogen bonding between the

  1433-7851/99/3813-2062 $ 17.50+.50/0



Scheme 1. Pathways for reactions of anticancer complex **1** with DNA duplex **2** (only G7 and G8 are shown). Charges on complexes are not shown. A possible preferred route to the major GG adduct with 2-picoline *cis* to 5′-G is indicated by bold arrows.

NH_3 ligand and O6 of G8 in model **3b**, and van der Waals interactions between the 2-picoline CH_3 group and the CH_3 group of nearby T6, which is absent in model **3a**. Both thermodynamic and kinetic factors appear to favor the formation of complex **3b**. The high stability of **3b** may be important in determining the lack of cross-resistance between **1** and cisplatin. Such a lesion may be recognized differently from cisplatin–DNA adducts by the excision-repair systems in cells.[18, 19]

Experimental Section

2-Picoline was purchased from Aldrich. The sodium salts of HPLC-purified 14-mer oligonucleotides were prepared by Oswel (Southampton, UK). *cis*-$[PtCl_2(^{15}NH_3)(2\text{-Pic})]$ (**1**) was prepared from *cis*-$[PtCl_2(^{15}NH_3)_2]$ by a similar procedure to that described for natural abundance mixed-ligand ammine/amine Pt^{II} complexes.[20]

The DNA 14-mer duplex **2** was annealed by slow cooling from 343 K. The reaction of **1** with **2** was conducted at a 1:1 molar ratio (1 mM) in H_2O/D_2O 90/10 (0.5 mL). Samples contained 0.1M $NaClO_4$ to maintain a constant ionic strength. Phosphate buffer (9 mM) was used in the reactions to maintain the pH at 6.0. The sample was freeze-dried twice from 99.9% D_2O and finally dissolved in 99.9% D_2O for experiments in D_2O.

NMR spectra were acquired, as previously described,[4, 5] on both Bruker DMX500 and Varian ^{Unity}INOVA600 NMR spectrometers operating at ^1H resonance frequencies of 500.13 and 599.842 MHz, respectively. 2D ^1H NOESY data sets were acquired for both the H_2O/D_2O 90/10 sample and the 99.9% D_2O sample with a 200 ms mixing time at 278 K. 2D DQFCOSY data were acquired only on the 99.9% D_2O sample.

Measurements of pH were made using a Corning 145 pH meter equipped with an Aldrich micro combination electrode calibrated with Aldrich buffer solutions of pH 4, 7, and 10.

Molecular modeling was carried out using Sybyl version 6.3 (Tripos Inc.). DNA duplex structures were based on energy-minimized models of a cisplatin–DNA duplex calculated from NMR data.[7] The X-ray crystal structure coordinates of **1**[4] were used to construct the fragment $\{Pt(NH_3)(2\text{-Pic})\}^{2+}$ for docking onto DNA. Distances between G*N*7 and Pt were based on the crystal coordinates of the 12-mer DNA duplex/cisplatin adduct.[21] Four different models that reflected the possible geometry of the final DNA adduct were built. Inter-proton distance constraints were built into each model based on an assessment of the distances calculated from the NOE data. Distance bounds were set for strong, medium, and weak NOEs in the ranges 2.5–4.5, 3.0–5.0, and 4.0–5.0 Å, respectively, with force constants of 20 kcal mol^{-1} Å^{-2} each. A total of eight identifiable NOE distance constraints between the 2-picoline ring and the DNA duplex were incorporated into the models. Substructures of each model ($T_6G_7^*G_8^*T_9 + \{Pt(NH_3)(2\text{-Pic})\}^{2+}$) were subjected to 200 steps conjugate gradient energy minimization to allow each model to satisfy the distance constraints.

Received: February 18, 1999 [Z13053IE]
German version: *Angew. Chem.* **1999**, *111*, 2192–2196

Keywords: antitumor agents · bioinorganic chemistry · DNA recognition · platinum · stereoselectivity

[1] R. P. Perez, *Eur. J. Cancer* **1998**, *34*, 1535–1542.
[2] F. I. Raynaud, F. E. Boxall, P. M. Goddard, M. Valenti, M. Jones, B. A. Murrer, M. Abrams, L. R. Kelland, *Clin. Cancer Res.* **1997**, *3*, 2063–2074.
[3] J. Holford, S. Y. Sharp, B. A. Murrer, M. Abrams, L. R. Kelland, *Br. J. Cancer* **1998**, *77*, 366–373.
[4] Y. Chen, Z. Guo, S. J. Parsons, P. J. Sadler, *Chem. Eur. J.* **1998**, *4*, 672–676.
[5] Y. Chen, Z. Guo, J. A. Parkinson, P. J. Sadler, *J. Chem. Soc. Dalton Trans.* **1998**, 3577–3585.
[6] For d(G*pG*), $\delta(^1H/^{15}N) = 4.61/-65.68$, $4.57/-65.73$, $4.48/-65.63$, $4.46/-65.31$ (relative intensities: 2:2:3:3). For **2a**, $\delta(^1H/^{15}N) = 4.84/-65.12$, $4.82/-65.03$, $4.69/-65.12$, $4.65/-65.25$ (partially overlapped with water, relative intensities: approximately 2:2:3:3).
[7] J. A. Parkinson, Y. Chen, Z. Guo, S. J. Berners-Price, T. Brown, P. J. Sadler, unpublished results. The cisplatin G*G* chelate of duplex **2** has essentially the same structural characteristics as the platinated 12-mer DNA duplex d(CCTCTG*G*TCTCC)·(GGAGACCAGAGG) reported by Gelasco and Lippard.[8]
[8] A. Gelasco, S. J. Lippard, *Biochemistry* **1998**, *37*, 9230–9239.
[9] C. Giessner-Prettre, B. Pullman, *Biochem. Biophys. Res. Commun.* **1976**, *70*, 578–581.
[10] J. A. Parkinson, S. E. Ebrahimi, J. H. McKie, K. T. Douglas, *Biochemistry* **1994**, *33*, 8442–8452.
[11] A. H. Krotz, L. Y. Kuo, T. P. Shields, J. K. Barton, *J. Am. Chem. Soc.* **1993**, *115*, 3877–3882.
[12] T. W. Hambley, *Coord. Chem. Rev.* **1997**, *166*, 181–223.
[13] M. J. Bloemink, R. J. Heetebrij, K. Inagaki, Y. Kidani, J. Reedijk, *Inorg. Chem.* **1992**, *31*, 4656–4661.
[14] J. F. Hartwig, S. J. Lippard, *J. Am. Chem. Soc.* **1992**, *114*, 5646–5654.
[15] S. U. Dunham, S. U. Dunham, C. J. Turner, S. J. Lippard, *J. Am. Chem. Soc.* **1998**, *120*, 5395–5406.
[16] C. Bauer, T. Peleg-Shulman, D. Gibson, A. H.-J Wang, *Eur. J. Biochem.* **1998**, *256*, 253–260.
[17] F. Reeder, Z. Guo, P. del S. Murdoch, A. Corazza, T. W. Hambley, S. J. Berners-Price, J.-C. Chottard, P. J. Sadler, *Eur. J. Biochem.* **1997**, *249*, 370–382.
[18] T. Matsumoto, K. Endoh, K. Akamatsu, K. Kamisango, H. Mitsui, K. Koizumi, K. Morikawa, M. Koizumi, T. Matsuno, *Br. J. Cancer* **1991**, *64*, 41–46.
[19] E. Cvitkovic, *Br. J. Cancer* **1998**, *77*, 8–11.
[20] S. J. Barton, K. J. Barnham, A. Habtemariam, R. E. Sue, P. J. Sadler, *Inorg. Chim. Acta* **1998**, *273*, 8–13.
[21] P. M. Takahara, C. A. Frederick, S. J. Lippard, *J. Am. Chem. Soc.* **1996**, *118*, 12309–12321.

  1433-7851/99/3813-2063 $ 17.50+.50/0