A Structural Basis for Nucleic Base–Metallointercalator Interactions: Crystal Structure of [Pt(2,2′-bipyridine)(ethylenediamine)]·AMP·10H_2O (AMP = Adenosine 5′-Monophosphate)

HIDEKI MASUDA
Faculty of Pharmaceutical Sciences, Kyoto University, Shimoadachicho, Yoshida, Sakyo-ku, Kyoto 606, Japan
and OSAMU YAMAUCHI*
Faculty of Pharmaceutical Sciences, Kanazawa University, 13-1 Takara-machi, Kanazawa 920, Japan

(Received January 8, 1987)

Aromatic ring stacking plays a major role in the intercalative binding to DNA by drugs and chemicals with planar aromatic rings and is therefore of prime importance for their antitumor or carcinogenic activities [1–3]. Platinum(II) complexes with aromatic di- and triamines in the coordination plane, such as $[Pt(terpy)Cl]^+$ and $[Pt(bpy)(en)]^{2+}$**, have been known to intercalate into DNA by aromatic ring stacking with the base moiety [1, 4, 5]. Several X-ray studies of the complexes of Pt(II) with DNA [5b, 6, 7] and nucleotides such as AMP [8], 3′-CMP [9], and double helical $d(CpG)_2$ [10] have revealed the intercalative interactions and in the latter cases [8–10] the molecular geometries of the components. Various studies have reported developing small molecular probes for site- or sequence-specific and stereospecific binding with DNA [11]. Our previous spectroscopic study on the interactions in dilute aqueous solution between an intercalator $[Pt(bpy)(en)]^{2+}$ and various nucleoside 5′-monophosphates (AMP, GMP, CMP, and UMP) as constituents of nucleic acids has demonstrated that $[Pt(bpy)(en)]^{2+}$ effectively binds with the nucleotides through ring stacking of coordinated bpy with the nucleotide bases and the electrostatic interaction between the Pt(II) center and the ribose phosphate moiety [12]:

$$[Pt(bpy)(en)]^{2+} + NMP^{2-} \rightleftharpoons [Pt(bpy)(en)]^{2+}\cdots NMP^{2-}$$

(NMP = nucleoside 5′-monophosphate)

The interactions have been evidenced by the upfield shifts of the base proton signals due to the ring current effect of bpy and an induced circular dichroism (CD) peak at 300–350 nm due to the asymmetric carbons of ribose.

For detailed comparison of the modes of the intercalator–nucleotide interactions in dilute aqueous solution and in the solid state, we now report the synthesis and the crystal structure of a new intercalative complex $[Pt(bpy)(en)]\cdot AMP\cdot 10H_2O$ (**1**) having piles of alternating bpy and unpaired adenine rings stacked with each other.

Experimental

Complex **1** was prepared as pale yellow needles from equimolar amounts of $[Pt(bpy)(en)]Cl_2$ and Na_2AMP in aqueous ethanol. Crystals suitable for an X-ray diffraction study were grown from an aqueous ethanolic solution of **1** at room temperature. Crystal data: $PtC_{22}H_{48}N_9O_{17}P$, $M_r = 936.74$, monoclinic, space group $P2_1$, $a = 10.402(2)$, $b = 23.031(4)$, $c = 7.491(3)$ Å, $\beta = 95.07(1)°$, $U = 1787.6$ Å^3, $D_c = 1.741$ g cm^{-3}, $Z = 2$, graphite monochromatized Cu Kα radiation, μ(Cu Kα) = 85.67 cm^{-1}. Intensity data were collected with a Rigaku AFC-5 automated diffractometer (ω–2θ scan, $\theta_{max} = 120°$). The structure was solved by the heavy atom method and was refined by least-squares techniques using the program KPPXRAY [13], the final R-value being 5.8% for 2629 reflections for which $F_o \geq 3\sigma(F_o)$†.

Results and Discussion

Figure 1 shows the molecular structure of **1**, where $[Pt(bpy)(en)]^{2+}$ and AMP^{2-} are stacked with each other between the adenine ring and one of the pyridine rings of bpy with the separation of 3.5 Å. The Pt(II) complex in **1** retains its planar coordination structure. The crystal structure (Fig. 2) exhibits a layer structure with the Pt(II) complex molecules intercalated between the adenine rings with essentially the same face-to-face separation. The adenine ring effectively stacks with $[Pt(bpy)(en)]^{2+}$ without base-pairing, which is in contrast with the modes of stacking observed earlier [8–10]. The 6-amino group of AMP located above Pt(II) (3.6 Å) is not coordinated to Pt(II) but hydrogen-bonded to the phosphate oxygen atom of a neighboring AMP molecule with the N···O distance of 2.90 Å. This may stabilize the interaction between the intercalator and the un-

*Author to whom correspondence should be addressed.

**Abbreviations used in the text: AMP, adenosine 5′-monophosphate; GMP, guanosine 5′-monophosphate; CMP, cytidine 5′-monophosphate; UMP, uridine 5′-monophosphate; 3′-CMP, cytidine 3′-monophosphate; $d(CpG)_2$, double helical deoxycytidylyl-(3′-5′)-deoxyguanosine; bpy, 2,2′-bipyridine; en, ethylenediamine; terpy, 2,2′,2″-terpyridine; phen, 1,10-phenanthroline.

†See also 'Supplementary Material'.

0020-1693/87/$3.50
© Elsevier Sequoia/Printed in Switzerland

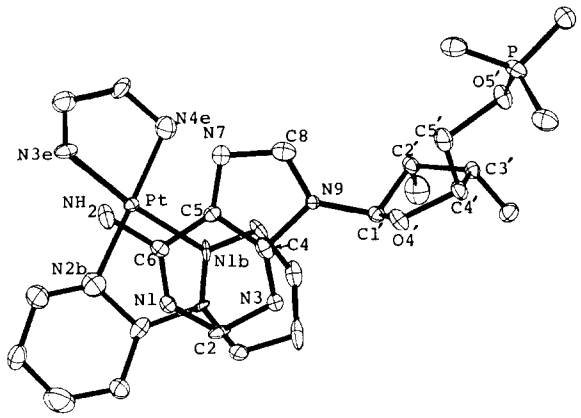

Fig. 1. Structure of the $[Pt(bpy)(en)]^{2+}$–AMP^{2-} complex showing the atom numbering scheme. The atoms are shown as 30% thermal ellipsoids. Selected bond distances: Pt–N1b, 2.083(14); Pt–N2b, 2.084(25); Pt–N3e, 2.011(16); Pt–N4e, 2.033(23); N1–C2, 1.300(25) Å. Bond angles: N1b–Pt–N2b, 83.1(10); N3e–Pt–N4e, 74.1(9); N2b–Pt–N4e, 178.2(9); N1b–Pt–N3e, 172.1(11); C2–N1–C6, 125.8(18)°. Torsion angles: O4′–C1′–N9–C4 (χ), −100.9(18); O5′–C5′–C4′–C3′ (γ), −69.7(18); C4′–O4′–C1′–C2′ (ν_0), −17.2(15)°.

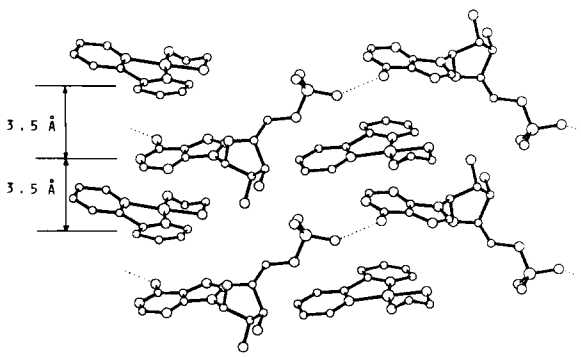

Fig. 2. Crystal structure showing alternating bpy-adenine stacking (–B–I–B–I–) with the same face-to-face separation of 3.5 Å and hydrogen bonds (···).

paired base. The AMP molecule assumes the *anti* conformation with $\chi = -100.9°$, and its ribose phosphate moiety has the usual C2′-*endo* ring pucker ($\nu_0 = -17.2°$) and the *trans*–*gauche* C4′–C5′ conformation ($\gamma = -69.7°$)*.

The AMP–bpy interaction in the solid state involves the six-membered pyrimidine ring of the adenine nucleus (Fig. 1), while the phosphate group extends away from the Pt(II) center to be engaged in the above mentioned hydrogen bonding. In this connection, the intramolecular bpy-adenine stacking involving the imidazole moiety has been reported for a dimeric ternary Cu(II) complex $[Cu(AMP)(bpy)(H_2O)]_2^{2+}$ [15]. A broader overlap between bpy and the adenine ring in the present complex has been indicated by the ^1H NMR and CD spectra [12], and the NMR spectrum of **1** dissolved in D_2O (15 mM) in fact exhibited the ring current effect of bpy causing the upfield shifts ($\Delta\delta$, ppm) of the H2 (0.32), H8 (0.16), and H1′ (0.19) signals which are in good agreement with the values observed for an equimolar mixture (20 mM) of $[Pt(bpy)(en)]Cl_2$ and Na_2AMP in D_2O [12]. The difference between the interaction modes in solution and in the solid state may be ascribed to the requirements for crystal growth and packing. The structure in the solid state may explain the stacking mode for adenosine, which showed smaller $\Delta\delta$ values and weaker CD activity probably because of the absence of the Pt(II)–phosphate interaction [12]. It is inferred from Fig. 1 that a slight movement of the AMP molecule on the coordination plane and rotation around the C4′–C5′ bond would produce a situation that explains the observed NMR and CD spectral properties.

Interestingly the crystal structure (Fig. 2) shows a unique sequence of the alternating unpaired base (B) and intercalator (I), –B–I–B–I–, unlike that expected for DNA–intercalator interactions from the nearest neighbor exclusion model [4, 16] and observed for Pt(II) intercalators [3, 4–7, 9], indicating that the alternating B–I stacking can take place in the absence of such steric requirements as seen in DNA. The –I–I–BP–I–I–BP– and –BP–BP–I–BP–BP–I– stacking modes (BP = base pair) in 2:2 [Pt(terpy)Cl]·AMP [8] and the [Pt(phen)(en)]–3′-CMP complex [9], respectively, may be due to the base-pairing, which is observed for these cases but is absent in **1**.

Supplementary Material

Tables of atomic coordinates, anisotropic thermal parameters, bond distances and angles, torsion angles, and observed and calculated structure factors can be obtained from the authors on request.

Acknowledgements

We are grateful to Professor Katsunosuke Machida of Kyoto University for helpful discussions and to Dr. Yoshitaka Itatani of Kanazawa University for the elemental analysis and the NMR spectra.

References

1 M. J. Waring, *Annu. Rev. Biochem., 50,* 159 (1981).
2 H. M. Berman and P. R. Young, *Annu. Rev. Biophys. Bioeng., 10,* 87 (1981).
3 J. K. Barton and S. J. Lippard, in T. G. Spiro (ed.), 'Nucleic Acid–Metal Ion Interactions', Wiley-Interscience, New York, 1980, p. 31.

*For definition of tortion angles and atom numbering, see for example ref. 14.

4 S. J. Lippard, *Acc. Chem. Res., 11,* 211 (1978).
5 (a) K. W. Jennette, S. J. Lippard, G. A. Vassiliades and W. R. Bauer, *Proc. Natl. Acad. Sci. U.S.A., 71,* 3839 (1974); (b) S. J. Lippard, P. J. Bond, K. C. Wu and W. R. Bauer, *Science (Washington, D.C.), 194,* 726 (1976).
6 P. J. Bond, R. Langridge, K. W. Jennette and S. J. Lippard, *Proc. Natl. Acad. Sci. U.S.A., 72,* 4825 (1975).
7 S. Arnott, P. J. Bond and R. Chandrasekaran, *Nature (London), 287,* 561 (1980).
8 Y.-S. Wong and S. J. Lippard, *J. Chem. Soc., Chem. Commun.,* 824 (1977).
9 S. Vijay-Kumar, T. D. Sakore and H. M. Sobell, *Nucleic Acids Res., 12,* 3649 (1984).
10 A. H. J. Wang, J. Nathans, G. van der Marel, J. H. van Boom and A. Rich, *Nature (London), 276,* 471 (1978).
11 (a) P. B. Dervan, *Science (Washington, D.C.), 232,* 464 (1986); (b) J. K. Barton, *Science (Washington, D.C.), 233,* 727 (1986).
12 O. Yamauchi, A. Odani, R. Shimata and Y. Kosaka, *Inorg. Chem., 25,* 3337 (1986).
13 T. Taga, T. Higashi and H. Iizuka, 'KPPXRAY', Kyoto University, 1985.
14 W. Saenger, 'Principles of Nucleic Acid Structure', Springer-Verlag, New York, 1984.
15 K. Aoki, *J. Am. Chem. Soc., 100,* 7106 (1978).
16 D. M. Crothers, *Biopolymers, 6,* 575 (1968).