New insight into DNA damage by cisplatin at the atomic scale

Raji Heyrovska

Institute of Biophysics, Academy of Sciences of the Czech Republic, 135 Kralovopolska, 612 65 Brno, Czech Republic. Email: rheyrovs@hotmail.com

Cisplatin is cis-diamminedichloroplatinum (II) of chemical formula, $Pt(NH_3)Cl_2$, abbreviated as cis-DDP and known commercially as platinol. It is used widely as an anticancer drug for various types of cancer, ever since its discovery two centuries ago and has become a target of extensive researches[1-5]. Transplatin, trans-DDP on the other hand, is found to be less or ineffective to treat cancers. Cisplatin is known to interact mainly with the N(7) nitrogen of guanine in nucleic acids, after a water molecule takes away one of the chlorines by hydrolysis. This initiates the damage of nucleic acids and eventually leads to apoptosis[1]. However the way how this happens and why transplatin is less effective is not completely clear. Here the author brings some new insights, using the precise structures of these molecules at the atomic level, how cisplatin can interact with the nitrogen of guanine and adenine and rupture the hydrogen bonding in the Watson Crick base pairs and damage the structure of DNA. It is hoped that the results presented here will contribute to a better atomistic insight into the structure, bonding and feasibility of the biochemical reactions involving these compounds and their derivates[4] for the alleviation of cancer.

Cisplatin, $Pt(NH_3)Cl_2$, is nearly a square planar inorganic coordination compound. The crystal structure[6] of cisplatin, shows that the Pt-Cl and Pt-N bondlengths are 2.33(0.01) Å and 2.01(0.04) Å respectively. Theoretical estimates[7] give 2.34 Å and 2.09 Å, respectively for Pt-Cl and Pt-N bond lengths, which are close to the above[6]

experimental values. Here it is pointed out that these bond lengths, in fact, are sums of the covalent radii of the adjacent atoms, a general rule found valid for many inorganic, organic and biological compounds[8-10]. Thus, the bond lengths, d(Pt-Cl) = 2.34 Å and d(Pt-N) = 2.09 Å, as sums of the covalent radii, R_{cov}(Pt) = 1.39 Å, R_{cov}(Cl) = 0.95 Å and $R_{cov}(N_{sb.})$ = 0.70 Å, which are halves of the respective bond lengths[11,12], d(Pt-Pt), d(Cl-Cl) and $d(N\text{-}N)_{sb.}$. The covalent radii of the atoms in $Pt(NH_3)Cl_2$ drawn to scale are given in Fig. 1a and the atomic structures of cis-DDP and trans-DDP are shown in Figs. 1b and 1c respectively.

The action of cisplatin as an anticancer agent is attributed to its binding mainly with the N(7) of guanine[1-5] which is one of the two purines forming the Watson Crick base pairs. In Fig. 2 are given the covalent radii of the atoms which account for all the bond lengths in nucleic acids[8,9], which are used in Fig. 3 for the atomic structures along with all the bondings in adenine (A), thymine (T), cytosine (C) and guanine (G) constituting the Watson Crick base pairs[8,9]. The binding of cisplatin to the nitrogen $N_{d.b.}$(7) of guanine is facilitated by the hydrolysis[1-5] of the chlorine bound to platinum as shown in the cytotoxic pathway in[3]. The Cl probably first forms a hydrogen bond[13] with a water molecule prior to detachment from Pt. The atomic structure of the resulting guanine-$PtCl(NH_3)_2$ complex is shown in Fig. 4.

While the first chlorine binds to guanine, the second chlorine of cis-DDP can also removed similarly by another water molecule and the guanine-$Pt(NH_3)_2$ complex binds to a second available nitrogen of a nearby base pair. Although cisplatin is known to interact mainly with the $N_{d.b.}$(7) of guanine, other reactive nitrogens in the Watson -Crick base pairs like $N_{d.b.}$(3) of adenine are also vulnerable (see Fig. 3). The disposition of these nitrogens of guanine and adenine in DNA is shown in Fig. 5a in the molecular structure at the atomic scale of DNA as given in[8,9]. The lengths

of the hydrogen bonds connecting A with T and C with G in the Watson-Crick base pairs are interpreted in[13]. Since the $N_{d.b.}(3)$ nitrogen of adenine (A) is closest to the $N_{d.b.}(7)$ of guanine (G) for bond formation with Pt at a distance of about 2 Å and is sterically favorably diposed at an angle close to ~90^0 vacated by the two Cl atoms of cis-DDP, the [= $Pt(NH_3)_2$] complex bonds with the $N_{d.b.}(7)$ of guanine and $N_{d.b.}(3)$ of adenine as shown in Fig. 5b. It can be seen on comparing Fig. 5b with Fig. 5a of the intact DNA, that in the former, the hydrogen bond of the Watson-Crick base pair ruptures and causes damage to the structure of DNA. Also, if the Pt forms covalent bonds with the $N_{d.b.}(7)$ of guanine and $N_{d.b.}(3)$ of adenine, the $N_{d.b.}$ will acquire the single bond radius, $N_{s.b.}$ which is larger (see Fig. 2). The data[14] on Pt-N(7)(guanine) bond lengths are around 2.51 to 2.16 Å at 20 and 61 % occupancy respectively, which shows that they decrease from a longer distance of coordination bond length to probably a single bond length, $d(Pt\text{-}N_{s.b.})$ = 2.09 Å at higher occupancy. In the latter case, the bonding of the $N_{s.b.}(7)$ with the adjacent atoms in guanine and similarly of $N_{s.b.}(3)$ in adenine will also change causing further strains in the structures of the two purines. Thus cisplatin causes extensive structural damage to DNA.

In transplatin (see Fig 1c), the two chlorines are 180^0 apart and hence cannot bind to N(7) and N(3) of guanine and adenine like cis-DDP. This could be a reason why trans-DDP is not as effective an anticancer agent as cisplatin.

To summarize, presented here for the first time are structures drawn to scale at the atomic level of cis-DDP and trans-DDP and of the binding of cisplatin to guanine and adenine of the Watson-Crick base pairs in DNA and the subsequent damage of the structure in DNA.

References

1. Jamieson, E.R. & Lippard, S.J. Structure, Recognition, and Processing of Cisplatin-DNA Adducts. *Chem. Rev.* **99,** 2467-2498 (1999).

2. Trzascka, S. Cisplatin. *Chem. & Eng. News.* **83,** 3 (2005).

3. Alderden, R.A., Hall, M.D. & Hambley, T.W. The discovery and development of cisplatin. *J. Chem. Edu.* **83,** 728-734 (2006).

4. Suchankova, T., Kubicek, K., Kasparkova, J., Brabec, V. & Kozelka, J. Platinum–DNA interstrand crosslinks: Molecular determinants of bending and unwinding of the double helix. *J. Inorg. Biochem*. (2011), doi:10.1016/j.jinorgbio.2011.09.025; *Available online 21 September 2011.*

5. Lee, N-K., Park, J-S., Johner, A., Obukhov, S., Hyon, J-Y., Lee, K.J., & Hong, S.C. Elasticity of cisplatin-bound DNA reveals the degree of cisplatin binding. *PRL* **101**, 248101 (2008).

6. Milburn, G.H.W. & Truter, M.R. The crystal structures of cis- and trans-dichlorodiammineplatinum(II) *J. Chem. Soc. (A)*, 1609-1616 (1966).

7. Fu, C-F. & Tian, S.X., Molecular dynamics study of solvation differences between cis- and transplatin molecules in water. *J. Chem. Phys.* **132,** 1745071-7 (2010).

8. Heyrovska, R. Atomic Structures of the Molecular Components in DNA and RNA based on Bond Lengths as Sums of Atomic Radii. http://arxiv.org/abs/0708.1271v4

9. Heyrovska, R. Structures of the molecular components in DNA and RNA with bond lengths interpreted as sums of atomic covalent radii. *The Open Structural Biology Journal.* **2,** 1-7 (2008).

10. Heyrovska, R. & Narayan, S. Atomic structures of molecules based on additivity of atomic and/or ionic radii. http://precedings.nature.com/documents/3292/version/1 (2009).

11. Pauling, L. *The Nature of the Chemical Bond*. Cornell Univ Press, NY, 1960

12. http://www.webelements.com/

13. Heyrovska, R. Dependence of the length of the hydrogen bond on the covalent and cationic radii of hydrogen, and additivity of bonding distances. *Chem. Phys. Lett.* **432,** 348 - 351 (2006).

14. Takahara, P.M., Frederick, C.A. & Lippard, S.J. *J. Am. Chem. Soc.* **118,** 12309-12321 (1996).

Acknowledgements The author thanks the Institute of Biophysics, Academy of Sciences of the Czech Republic for financial support.

Competing finacial interests: None

Figure legends:

Figure 1a-c Structures of cis- and transplatins. a) Atomic covalent radii, R_{cov} of Cl (greenish yellow), Pt (white), nitrogen (blue) and H (green); subscript s.b.: single bond) radii. b) and c) Atomic structures of cis- and transplatins respectively. All bond lengths are sums of R_{cov} of adjacent atoms. In b): cisplatin (area of the rectangle represented by the dotted lines: 5.65 x 5.8 Å = 32.8 $Å^2$ = 0.328 nm^2) and in c): transplatin (area of the square represented by the dotted lines: 5.8 x 5.8 Å = 33.6 $Å^2$ = 0.336 nm^2).

Figure 2 Covalent radii R_{cov} of the atoms in DNA. Subscripts, s.b.: single bond, g.b.: graphitic bond, d.b.: double bond.

Figure 3 Atomic structures of the purines and pyrimidines of the Watson-Crick base pairs in DNA. Uracil (U) replaces Thymine (T) in RNA. All bond lengths are sums

of the covalent radii of the adjacent atoms (given in Fig. 2). Base pairing occurs when hydrogen bonds connect T with A, and C with G along the broken lines. See[8,9].

Figure 4 Guanine-cisplatin complex. One Cl of CDDP is aquated and removed by water enabling Pt to bind with the N(7) of guanine.

Figure 5a,b Atomic structure of DNA a) before and b) after damage by cis-platin. All bond lengths are sums of the radii of the adjacent atoms given in Fig. 2. See[8,9].

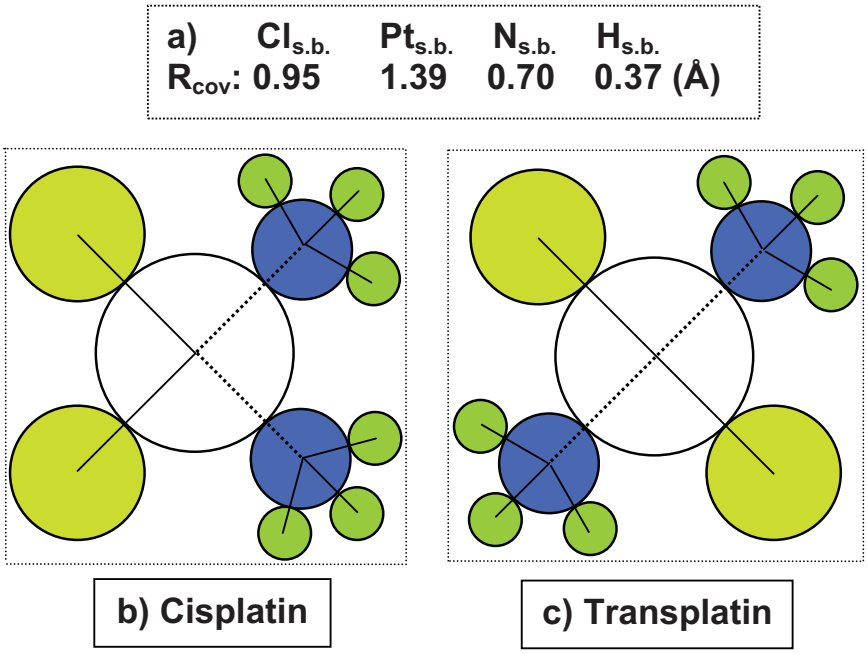

Fig. 1a-c

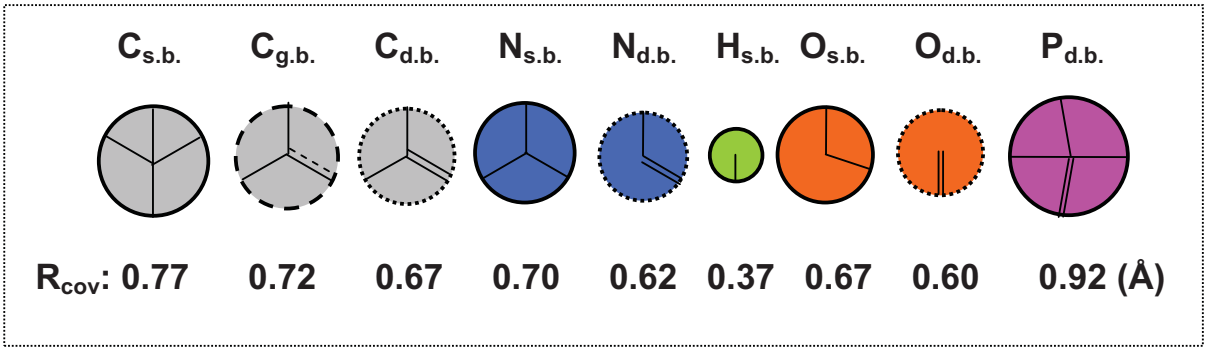

Fig. 2

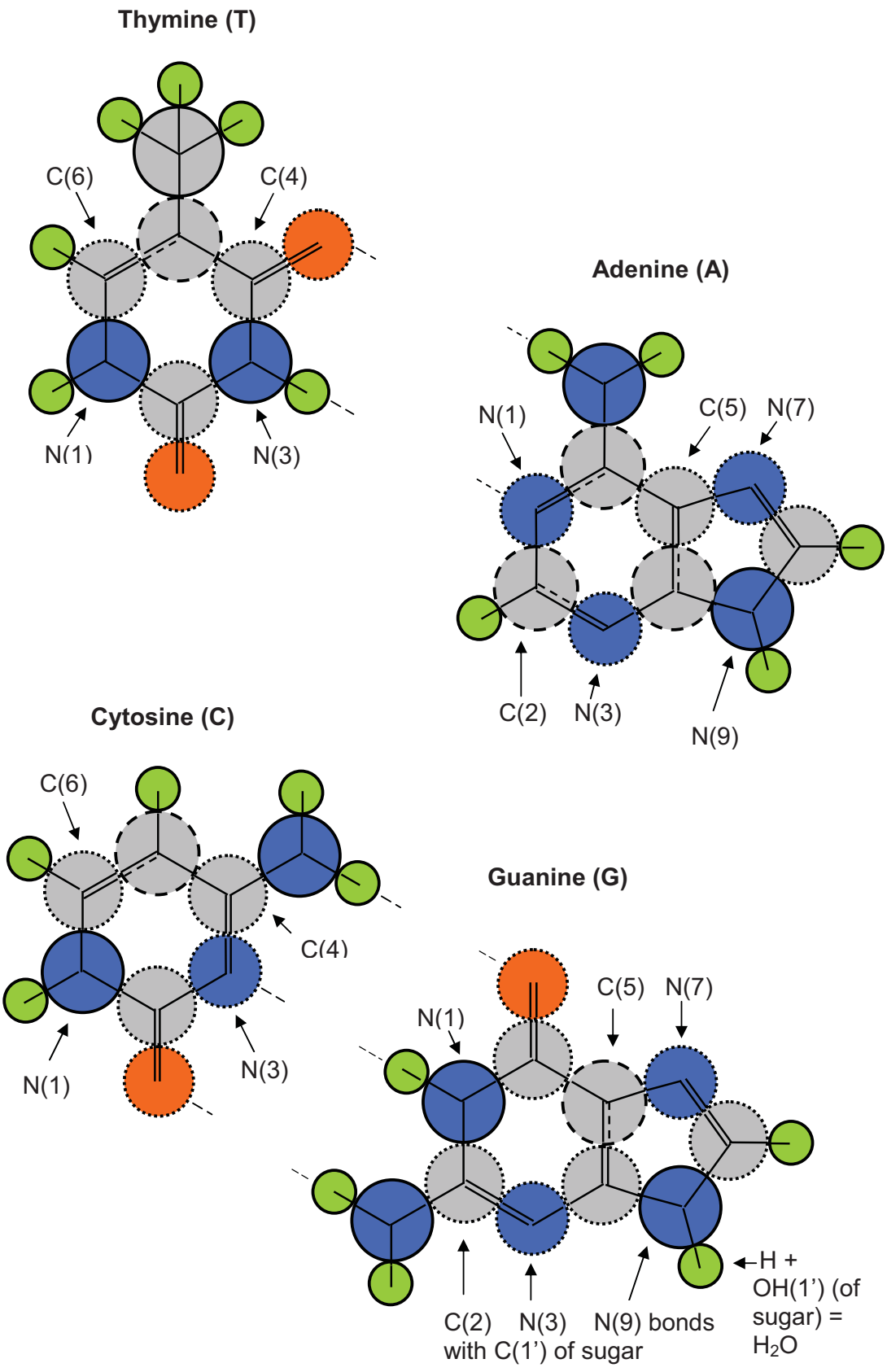

Fig. 3

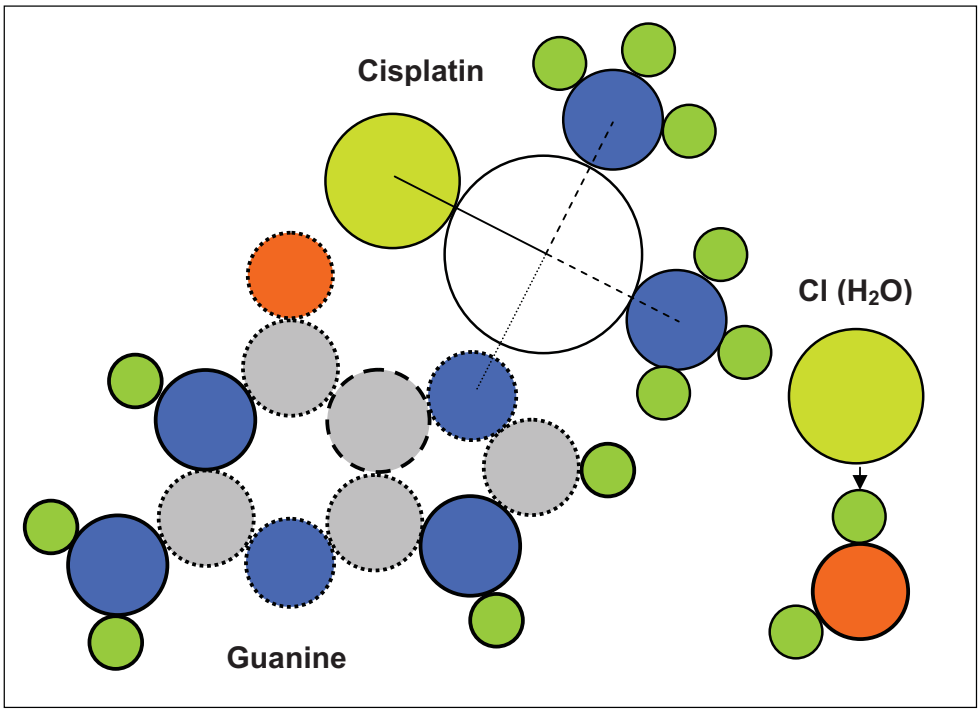

Fig. 4

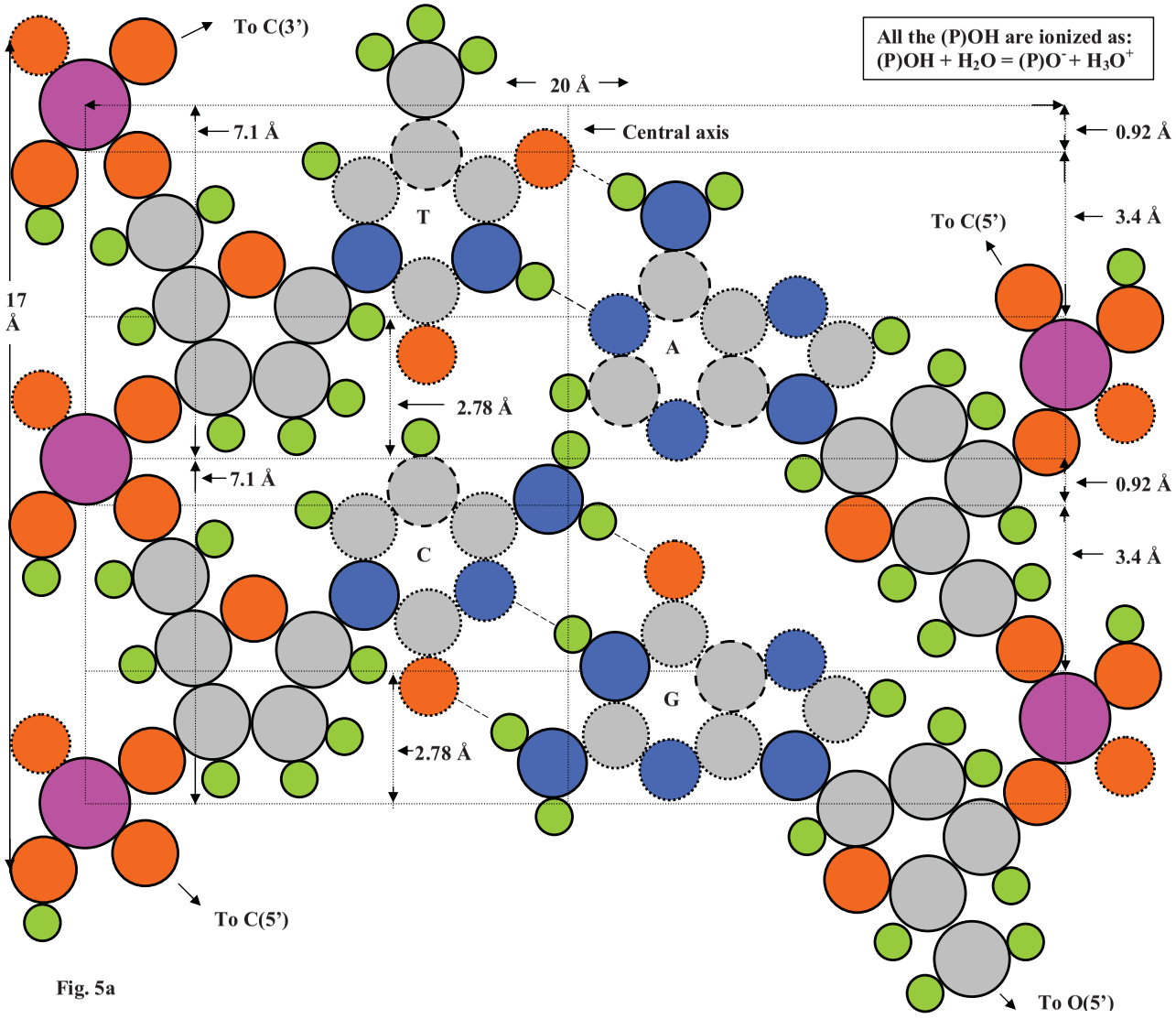
To C(3')
20 Å
All the (P)OH are ionized as:
(P)OH + H2O = (P)O- + H3O+
7.1 Å
Central axis
0.92 Å
T
To C(5')
3.4 Å
17 Å
A
2.78 Å
7.1 Å
0.92 Å
C
3.4 Å
G
2.78 Å
To C(5')
To O(5')

Fig. 5a

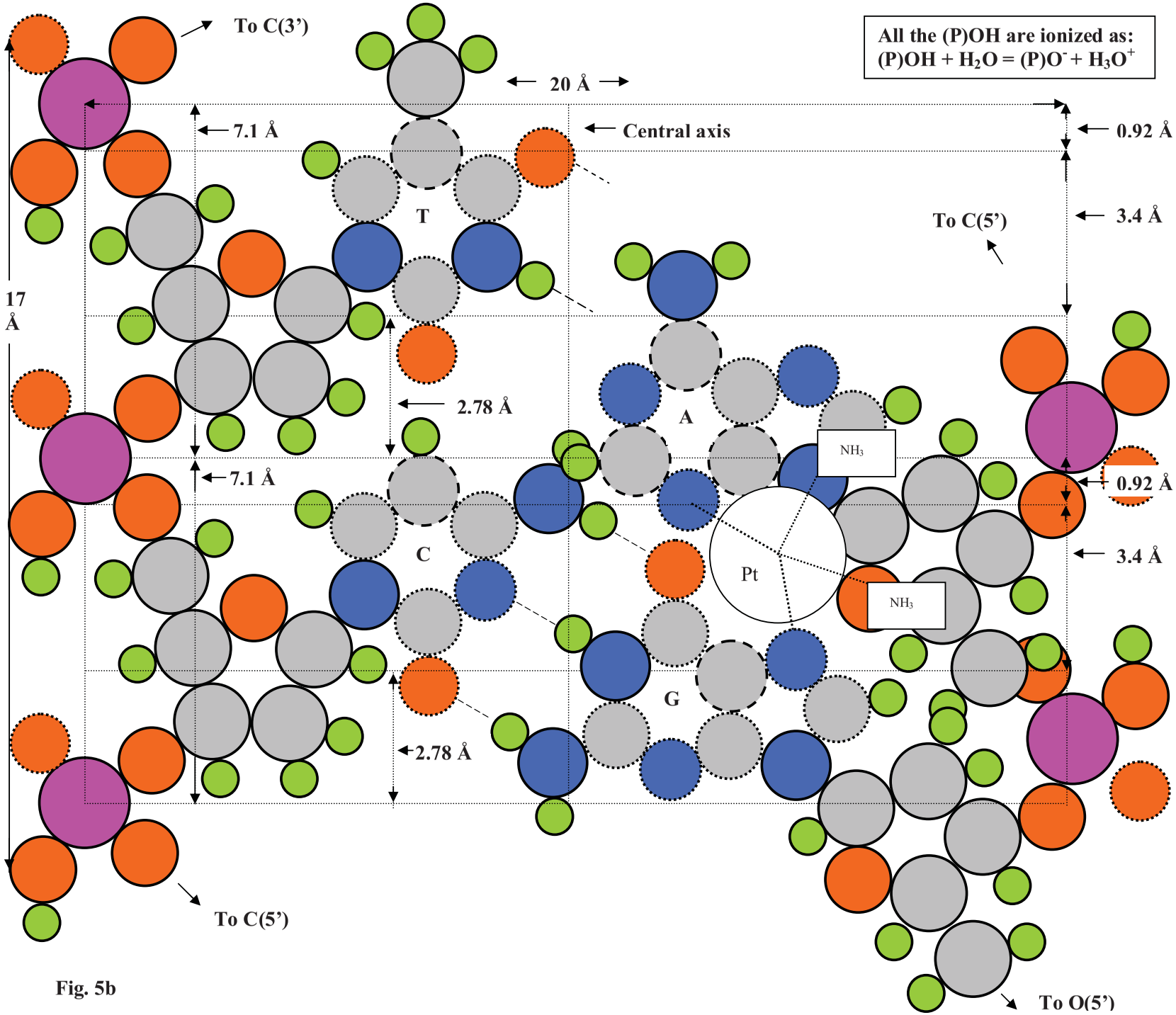
To C(3')
20 Å
All the (P)OH are ionized as:
(P)OH + H2O = (P)O- + H3O+
7.1 Å
Central axis
0.92 Å
T
To C(5')
3.4 Å
17 Å
2.78 Å
A
NH3
7.1 Å
0.92 Å
C
Pt
3.4 Å
NH3
G
2.78 Å
To C(5')
To O(5')

Fig. 5b