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pH   Ⅱ   NTP   NTP   5′-   5′-
ArL   Pt ArL   NTP $^{n-}$ ArL = Phen   Bpy   Trp $n = 2$ 3
$I = 0.1$ mol/L KNO$_3$ 25℃ . $\Delta \log K_{Pt}$
                    π-   π-
                        Ⅱ
        O641.4   A

The Increasing Stability of Ternary Platinum Ⅱ Complexes
by Intramolecular Aromatic-Ring Staking Interaction

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Abstract   The stability constants of the ternary mixed-ligand complexes of Pt ArL NTP $^{n-}$ $n = 2$ or 3   have been determined by potentiometric pH titration in aqueous solution $I = 0.1$ mol/L KNO$_3$ 25℃   where NTP refers to adenosine 5′-triphosphate ATP and uridine 5′-triphosphate UTP   ArL refers to 1 10-phenanthroline Phen   2 2′-bipyridyl Bpy   and L-tryptophane Trp . The stability difference between the ternary complexes and the binary complexes has been compared and discussed. The increased stability in the ternary mixed-ligand complexes can be attributed to the cooperative effect of $\pi_A - \pi_B$ and the intramolecular ligand-ligand aromatic-ring stacking interaction. The extent of the intramolecular aromatic-ring stacking interaction in the ternary platinum Ⅱ complexes has been calculated   which is in accord with the size of the aromatic rings forming the stack.
Key words   Ternary mixed-ligand complex Platinum Nucleotide Aromatic-ring stacking

1   Introduction

The intramolecular aromatic-ring ligand-ligand stacking interaction in the ternary mixed-ligand complexes is now well known for its obvious influence on the stability of complexes   which has received consid-

erable attention in recent years [1-3]. Different from that of common chemical bonds such as the ionic bond the covalent bond and the hydrogen bond the intramolecular aromatic-ring stacking interaction is a special form of ligand-ligand interaction which depends on the stacking of the non-coordinated aromatic rings in complexes [4]. Subsequently it is also quite different from the hydrophobic interaction between alkanecarboxylate ligands [5]. Since the first stacking interaction in the ternary mixed-ligand complex of copper Ⅱ reported by Sigel in 1974 in view of its important biological roles in the living system [6] many bioinorganic chemists have been attracted to the study on it and one review has been given out [7]. So far the study in this field has been extended to a large number of ligands such as nucleotides xanthosines amino acids a series of aromatic carboxylic acids and so on [8-10]. Though ternary Cu Ⅱ complexes have received much attention in this field relatively little work has been done involving ions of other transition metals. In fact similar stacking also exists in the ternary mixed-ligand complexes composed of other metal ions [8] and yet despite its relevance to the antitumor activity of drugs no studies of the platinum Ⅱ complexes containing nucleotides have been reported. Obviously it is quite certain that it will be more important to study the aromatic-ring stacking interaction in the platinum Ⅱ complexes for further evidence so we studied the ternary platinum Ⅱ complexes involving nucleotides NTP NTP = adenosine 5′-triphosphate and uridine 5′-triphosphate and heterocyclic-ring base ArL ArL = 1 10-phenanthroline Phen 2 2′-bipyridyl Bpy and L-tryptophane Trp as the second ligands. The stability constants of the binary and ternary complexes have been determined and the stability difference between them was compared and discussed. The percentages of the stacked isomers in the ternary mixed-ligand Pt ArL NTP $^{n-}$ complexes were calculated.

2　Experimental

The disodium salt of adenosine 5′-triphosphate Na$_2$H$_2$ATP· 3H$_2$O and trisodium salt of uridine 5′-triphosphate Na$_3$HUTP· 2H$_2$O were purchased from Sigma Chemical Co. of the USA. HNO$_3$ KNO$_3$ K$_2$PtCl$_4$ Phen Bpy and Trp were all of A. R. or G. R. grade reagents. The concentrations of the solution of ArL were measured by accurate weighing. Carborate-free sodium hydroxide as the standard solution was measured with potassium hydrogen phthalate. The concentration of the stock solution of Pt Ⅱ was determined with EDTA. The stock solution of the NTP was always freshly prepared and the exact concentration of NTP solution was analyzed by potentiometric pH titration with the standard solution of sodium hydroxide. Double-distilled water was used for preparing solutions. The pH titrations were carried out with a ZD-2A automatic potentiometric meter made in Shanghai Dazhong factory of analytical instrument with the accuracy of ± 0. 01pH. The pH meter accompanied with glass electrodes was calibrated with standard buffer solutions of pH = 4. 00 6. 86 and 9. 18 before and after each titration. Both the determination of pH and the calibration were carried out in the double-layer titrating cell at a constant temperature 25 ± 0. 1 ℃ under an atmosphere of purified N$_2$. The ionic strength of the solutions was adjusted to 0. 1 mol/L with KNO$_3$. The dissociation constants $K_{H_2NTP}^H$ and K_{HNTP}^H of the acid NTPs the stability constants $K_{Pt\ NTP}^{Pt}$ of the binary complexes and $K_{Pt\ ArL\ NTP}^{Pt\ ArL}$ of the ternary mixed-ligand complexes were determined according to the literature method [11]. The concentrations of NTP Pt^{2+} and HNO$_3$ were 0. 4 0. 3 and 1. 0 mmol/L respectively the ratio of concentration of Pt^{2+} : NTP was 2 : 1 in the binary complexes Pt NTP $^{2-}$ and Pt^{2+} : ArL : NTP = 1 : 2 : 1 ArL = Phen and Bpy or 1 : 1 : 1 ArL = Trp in the ternary complexes. The solution of Pt^{2+} was mixed with that of NTP only before the beginning of titrating in order that the dephosphorylation of NTP which is metal-ion promoted was kept to a minimum. All the experiments were carried out as described in detail recently [12]. For all systems at least three independent pairs of titration curves were recorded and the results averaged.

3　Results and discussion

The molecular structures of ligands adenosine 5′-triphosphate ATP and uridine 5′-triphosphate

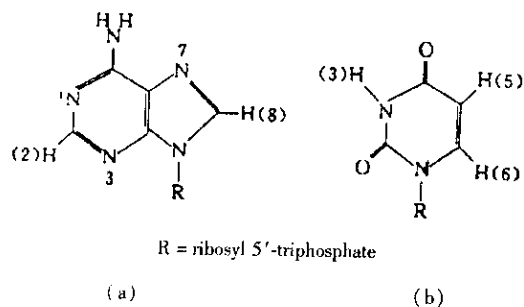UTP are shown in Fig. 1. Both of them can form stable binary and ternary complexes with divalent metal ions.

R = ribosyl 5′-triphosphate

(a)　　　　　　　　　　(b)

Fig. 1　Molecular structures of nucleotide
ATP^{4-} a and UTP^{4-} b

The dissociation constants of acids and the stability constants of complexes were measured and calculated in the way as in references 11 13 . The negative logarithms of dissociation constants $pK_{H_2NTP}^H$ and pK_{HNTP}^H the stability constants of binary Pt NTP $^{2-}$ and the ternary Pt ArL NTP $^{n-}$ complexes and the values of $\Delta\log K_{Pt}$ are presented in Table 1 ionic charge committed .

Table 1　The negative logarithms of dissociation constants of NTP and the stability constants of binary complexes Pt NTP $^{2-}$ and the ternary complexes Pt ArL NTP $^{n-}$ in aqueous solution $I = 0.1$ mol/L KNO$_3$ 25℃

NTP	$pK_{H_2NTP}^H$	pK_{HNTP}^H	$\log K_{Pt\ NTP}^{Pt}$	ArL	$\log K_{Pt\ ArL\ NTP}^{Pt\ ArL}$	$\Delta\Delta\log K_{Pt}$
ATP	4.05	6.40	5.82	Phen	6.14	+0.32
				Bpy	5.85	+0.03
				Trp	5.24	−0.58
UTP	2.04	6.38	5.46	Phen	5.67	+0.21
				Bpy	5.58	+0.12
				Trp	5.12	−0.34

Usually one way to quantify the stability of the ternary mixed-ligand complexes of this kind here is through

$$\Delta\log K_M = \log K_{MAB}^{MA} - \log K_{MB}^M$$

where $\Delta\log K_M$ is the comparison of the coordination tendency of ligand B to free M and to M A which indicates the position of this equilibrium

M A + M B ⇌ M A B + M
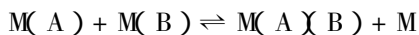
In general $\Delta\log K_M$ is a negative value since there are more coordination sites in the binary complexes than in the ternary complexes and it is the reason for $K_{MA}^M > K_{MA_2}^{MA}$ as a general rule. The statistic value for the coordination of the two different bidentate ligands to a square planar coordination sphere is $\Delta\log K_{st} = -0.6$ [14] . It is obvious that many of the these values of Pt ArL NTP $^{n-}$ in Table 1 are larger than expected on statistical grounds even on the coordination of complexes with Trp. The increasing stability is partly explained by the π_A-π_B cooperative effect [12] of transferring π-electron on oxygen atom of NTP to empty π orbital of electron-accepting ArL when both ligands ArL and NTP were coordinated to metal Pt^{2+}. Another reason for the increasing stability of the ternary complexes is the aromatic-ring stacking interaction caused by the possible overlapping of noncoordrdinated aromatic residues of ligand ArL and NTP. As it can be seen in Fig. 2 in the ternary mixed-ligand Pt Phen ATP $^{2-}$ complexes the phenanthroline rings of ligand phenanthroline were situated above the purine ring of ligand ATP and thus an additional stability resulted from charge-transferring interactions between the aromatic parts of ligands within the ternary complex.
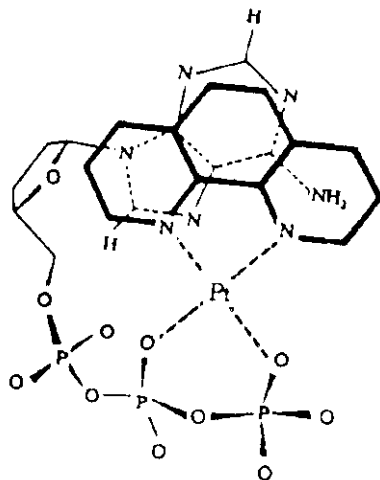

Fig. 2　The simplified structure of stacked isomer
of Pt Phen ATP $^{2-}$

However $\Delta\log K_{Pt}$ of the Pt Trp NTP $^{3-}$ is rather smaller than that of the other complexes containing ligands Phen and Bpy see Table 1 . It is not surprising when we take into account the following

three different aspects 1 a decreasing π_A-π_B coop-erative effect due to the coordination of one amino N at-om and one carboxyl O atom in Trp to metal Pt^{2+} whereas double N atoms in Phen and Bpy as π elec-tron-accepting heteroaromatic N bases coordinated to a transition metal ion favor the coordination of O donors e. g. NTP 2 The size of aromatic-ring in Trp is smaller than those in Phen and Bpy which result in the decreasing of the aromatic-ring stacking interaction 3 Another important factor is that Trp is a minus-charged ligand whereas Phen and Bpy are both of neu-trality. It is also well known that the charge-neutrali-zing interaction between ligand and metal ions has an essential effect on the increasing stability of comple-xes [14] .

The quantity of the stacked isomer in the ternary mixed-ligand complex could be measured by calculat-ing its percentage in the total of the complexes. It seems reasonable that in the solution of the ternary complexes studied here there are these equilibriums as follows charge omitted

$$Pt \ ArL \ + NTP \rightleftharpoons$$
$$Pt \ ArL \ \ NTP \ _{op} + Pt \ ArL \ \ NTP \ _{st \ tot}$$
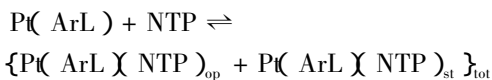
$$K^{Pt \ ArL}_{Pt \ ArL \ NTP} = K_{exp}$$
$$= \frac{Pt \ ArL \ \ NTP \ _{op} + Pt \ ArL \ \ NTP \ _{st}}{Pt \ ArL \ \ NTP} \qquad 1$$

$$Pt \ ArL \ \ NTP \ _{op} \rightleftharpoons Pt \ ArL \ \ NTP \ _{st}$$

$$K_I = \frac{Pt \ ArL \ \ NTP \ _{st}}{Pt \ ArL \ \ NTP \ _{op}} \qquad 2$$

Where K_{exp} is the equilibrium constant corresponding to Eq. 1 determined by experiments the footnote" op" or" st" stands for the species of open or stacked iso-mers in the ternary complexes respectively the footnote " tot" is the sum of the isomers above. K_I is the equi-librium constant of Eq. 2 which shows the forming tendency of stacked isomer. Eq. 1 can be expressed as Eq. 3 if there is no stacking happening

$$Pt \ ArL \ + NTP \rightleftharpoons Pt \ ArL \ \ NTP \ _{op}$$

$$K_{op} = \frac{Pt \ ArL \ \ NTP \ _{op}}{Pt \ ArL \ \ NTP} \qquad 3$$

Then K_I and st% can be calculated by Eq. 4 and Eq. 5

$$K_I = \frac{K_{exp}}{K_{op}} - 1$$

$$= \frac{10^{\Delta log K_{exp}}}{10^{\Delta log K_{op}}} - 1$$
$$= 10^{\Delta\Delta log K} - 1 \qquad 4$$

$$st\% = \frac{Pt \ ArL \ \ NTP \ _{st}}{Pt \ ArL \ \ NTP \ _{tot}}$$
$$= \frac{K_I}{K_I + 1} \qquad 5$$

Though the absolute value of the dimensionless constant K_I can not be directly determined by experi-ment so far we can assume that in the solution of the Pt/ArL/UTP systems no stacked isomers were seen in the ternary Pt ArL UTP $^{n-}$ complexes. Therefore the percentages of the stacked Pt ArL ATP $_{st}^{n-}$ iso-mers assembled in Table 2 were all relative values. However it has influence neither on the existence of the aromatic-ring stacking interactions in the ternary mixed-ligand complexes of Pt ArL NTP $^{n-}$ nor the correspondence with the order of the stacking degree.

Table 2   The values of K_I and st% of the ternary
Pt ArL ATP $_{st}^{n-}$ complexes

ArL	$Log K_{op}$	$Log K_{exp}$	$\Delta\Delta log K$	K_I	st%
Phen	5. 67	6. 14	0. 47	1. 95	66
Bpy	5. 58	5. 85	0. 27	0. 86	46
Trp	5. 12	5. 24	0. 12	0. 32	24

It can be seen from Table 2 that the extent of the stacked isomers of the ternary Pt ArL ATP $^{n-}$ com-plexes increases in the order

$$Pt \ Trp \ \ ATP \ ^{3-} < Pt \ Bpy \ \ ATP \ ^{2-}$$
$$< Pt \ Phen \ \ ATP \ ^{2-}$$
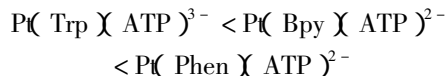
which is in accordance with the order of the aromatic-ring size of ligand ArL forming stacks

Trp indole ring < Bpy bipyridyl ring
< Phen phenanthroline ring
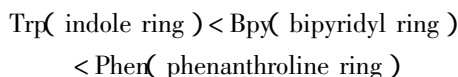
It comes to the conclusion that in the ternary complexes the larger the size of aromatic-ring of ligands forming stacking the more notable the intramolecular aromatic-ring stacking interaction and the higher the stability of the mixed-ligand complexes see Table 1 . The sim-plified structure of the suitable stacking between the Phen ring and purine ring of ATP in the Pt Phen ATP $^{2-}$ is shown in Fig. 2. Furthermore the aromat-

ic-ring stacking interaction is in essence a kind of electron ring-current effect. Changes of resonance signals of protons on aromatic-ring before and after the stacking can be detected by means of ^{1}H NMR study. So the aromatic-ring stacking interaction in the ternary complexes might be further expounded more powerfully. We will report the result.

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