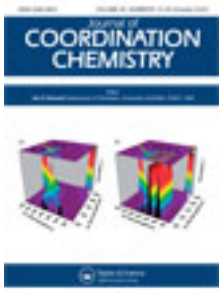

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L-Arginine and zinc ion effect on recognition and hydrolysis rate of adenosine 5′-triphosphate

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L-Arginine and zinc ion effect on recognition and hydrolysis rate of adenosine 5′-triphosphate

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Zn^{2+} can interact with adenosine 5′-triphosphate (ATP) by electrostatic and coordination interactions, and the interaction sites between Zn^{2+} and ATP vary at different pH in the ATP–Zn^{2+} binary system. Non-covalent interactions exist between the carboxyl of arginine (Arg) and Zn^{2+}, which led to competition between ATP and Arg to interact with Zn^{2+} in the ATP–Zn^{2+}–Arg ternary system. Kinetics studies show that the hydrolysis rate constant of ATP in the ATP–Zn^{2+} binary system was $2.44 \times 10^{-2}\,min^{-1}$, about 11-fold faster than that ($2.27 \times 10^{-3}\,min^{-1}$) in the ATP–$Zn^{2+}$–Arg ternary system. This may be attributed to coordination interactions between the carboxyl of Arg and Zn^{2+} and the decreased activity of zinc ion toward the phosphate groups *via* nucleophilic attack. A mechanism that the hydrolysis occurred through an addition–elimination mechanism is proposed.

Keywords: ATP; Zinc ion; L-Arginine; Recognition; Catalytic hydrolysis

1. Introduction

Adenosine 5′-triphosphate (ATP) is called "energy currency" in the biosystem because it can provide energy for activities of living cells by breaking its triphosphate chain [1–3]. It is well-known that ATP hydrolysis is catalyzed by both ATPase and a divalent metal ion, which provides a binding site for ATP or serves as a cofactor that catalyzes the phosphoryl transfer process [4–9]. Thus, interactions and properties of ATP-metal ion complexes in solution have received considerable research interest [10, 11]. Most of this research focused on the fundamental issue of whether metal ions stabilize the transition state of the solution reaction (the most energetically efficient way of catalyzing a reaction) or a significant different transition state (which may be more sensitive to catalysis) [12, 13]. However, the roles of ATPase and metal ions in the cleavage mechanism of ATP at the molecular level remain unknown because the biological system is complicated. Therefore, the non-enzymatic catalyzed ATP

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hydrolysis reaction, which is referred to as a mimic ATPase, has attracted attention of chemists and biologists. Natural polyamine, synthetic systems, and their metal complexes have been developed to elucidate the interaction and catalytic hydrolysis mechanism of ATP [9, 14–18]. ATP hydrolysis is catalyzed not only by polyamines and metal ions, but also by other ligands, such as amino acids.

Amino acid is the basic component of protein and some amino acids play critical roles in binding and catalysis of ATP hydrolysis. For example, Arg238 has been found in the crystal structure of the ATP pocket in myosin, which plays a key role in ATP hydrolysis [19, 20]. The activity of myosin decreases when Arg238 is mutated to another amino acid in the ATP pocket [21, 22]. Meanwhile, β-Arg246 is also important in recognizing and catalyzing hydrolysis of ATP in the F_0F_1-ATP synthase [23] because mutagenesis of β-Arg246 to histidine has deleterious effects on the catalysis of ATP hydrolysis [24]. Therefore, Arg residues are critical to synthetic and hydrolytic processes of ATP in myosin and F_0F_1-ATPase. However, there are a few reports on the role of Arg and metal ions in ATP hydrolysis at the molecular level. Arg is generally in a zwitterionic form with a positive charge distributed equally over three nitrogen atoms in the guanidinium group. Thus, Arg is protonated in a wide range of pH values and serves as a biological recognition site through directed hydrogen-bonding or electrostatic interactions with negatively charged groups, especially phosphate [25, 26]. Thus, this article focuses on interactions among Zn^{2+}, ATP, and Arg and proposes that the mechanism of ATP hydrolysis catalyzed by Zn^{2+}–Arg proceeds through an "addition–elimination" mechanism.

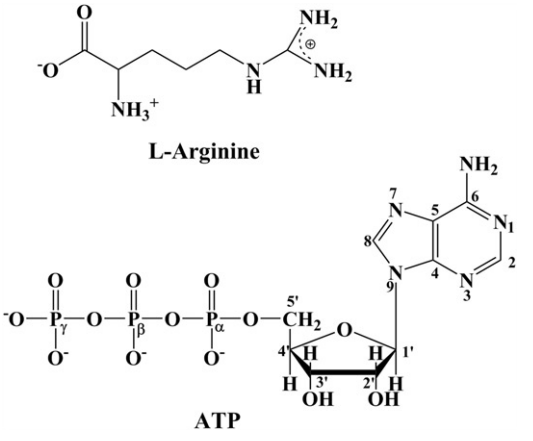
2. Experimental

2.1. *Materials*

ATP disodium salt (99%), adenosine 5′-diphosphate (ADP, 99%), adenosine 5′-monophosphate (AMP, 99.7%), and L-arginine (99%) were purchased from Acros Organics (USA). $ZnCl_2$ was purchased from Tianjin Chemical Reagent Institute (China). Deuterium oxide (D_2O, 99.9%) was obtained from the Cambridge Isotope Laboratories Inc. All these chemicals were used without purification. The structures of ATP and L-arginine are shown in scheme 1.

2.2. *Potentiometric pH titrations*

A solution of ATP, Zn^{2+}, and/or Arg was titrated with an NaOH solution at $25 \pm 0.1^{\circ}C$ under an argon atmosphere. A constant ionic strength was maintained with 0.1 mol L^{-1} $NaNO_3$ and a total volume of 25 mL was used in each titration. The pH measurements were carried out with a WDDY-2008 microcomputer automatic potentiometric titrator with a glass-calomel electrode assembly. The accuracy of the electrode was checked using standard buffer solutions with pH values of 4.00 and 9.18. The calculations were carried out by SCMAR program [27] (Newton–Gauss nonlinear least-squares) on an IBM compatible computer.



Scheme 1. The structures of ATP and L-arginine.

2.3. *Fluorescent measurements*

Fluorescence spectra were recorded on an F-7000 spectrofluorophotometer (Hitachi, Japan) by using 5/5 nm slit widths, an excitation wavelength of 281 nm, and emission from 300 to 550 nm; 3.0 mL of solution containing an appropriate concentration of ATP was titrated by successive additions of Zn^{2+} or Arg.

2.4. *IR and NMR measurements*

IR spectra were measured with a Nicolet Nexus 670 FT-IR spectrometer (America) with ZnSe windows at pH 7.0. The ^{1}H and ^{31}P NMR spectra were recorded on an Inova 400 MHz spectrometer. ^{31}P NMR chemical shifts were referenced to 85% phosphoric acid. The pH of the solution was adjusted to the desired pH by using 0.1 mol L^{-1} NaOH or HCl.

2.5. *Kinetics*

Kinetic studies were performed at 60°C by following the time-dependent change in the integrals from the resolved ^{31}P NMR signals for T_α, T_β, and T_γ of ATP, D_α and D_β for ADP, M for AMP, the peak OP for the inorganic phosphate, and PN for the intermediate species.

For NMR measurements, the solution (0.5 mL 10% D_2O) containing ATP with and without Zn^{2+} and/or Arg was placed in a 5 mm NMR tube and all the concentrations of ATP, Arg, and Zn^{2+} were 0.03 mol L^{-1}.

3. Results and discussion

3.1. *Potentiometric pH titrations*

Overall stability constants of the reaction of the molecular complex formation in the ATP/Arg/Zn^{2+} binary and ternary systems are shown in table 1 and the species

Table 1. Overall stability constants ($\log\beta$) for complexes of ATP with Zn^{2+} and/or Arg.

Species	$\log\beta$	Species	$\log\beta$
ATPH	6.58	ZnATP	5.18
$ATPH_2$	10.45	ZnATPH	9.95
ArgH	11.62	ZnArgATPH	29.96
$ArgH_2$	20.02	$ZnArgATPH_2$	37.15
$ArgH_3$	23.83	$ZnArgATPH_3$	41.13

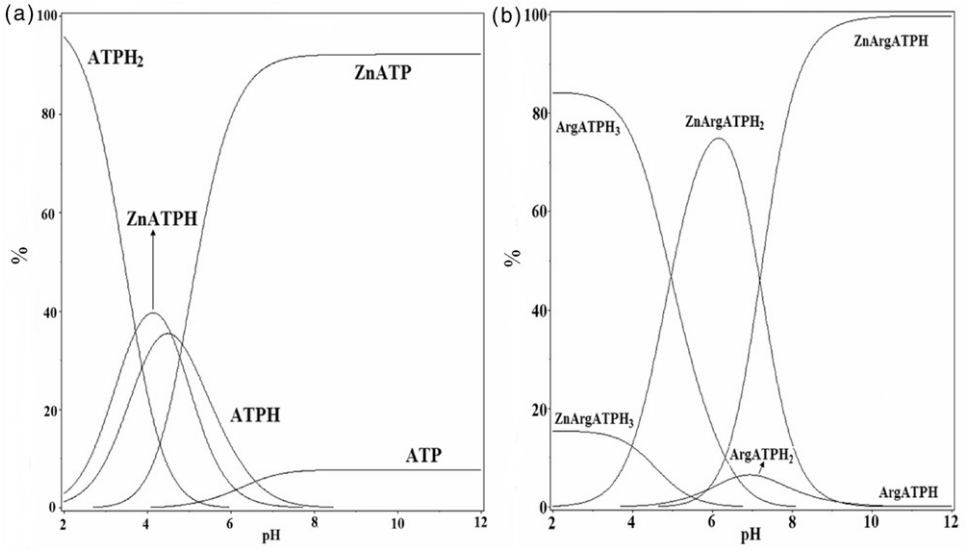


Figure 1. Species percentage distribution diagrams for the binary and ternary systems: (a) the ATP–Zn^{2+} binary system; and (b) the ATP–Zn^{2+}–Arg system.

distribution diagrams of the complexes are shown in figure 1. The stability constants of ATP and ATP–Zn^{2+} complexes in this article are consistent with those provided in other references [28–30]. Figure 1(a) shows that the ZnATPH complex was formed in the pH range of 2–6 and the distribution peaked at pH 4.0. With increasing pH, the N-1 site of ATP was deprotonated and Zn^{2+} interacted with the N-7 site of ATP since ATP took an *anti* conformation [31]. Thus, ZnATP began to form at pH 3.0 with a maximum distribution at pH 8.0. The ternary species distribution curves in the ATP–Arg–Zn^{2+} system are shown in figure 1(b). Complexes including the protonated $ZnArgATPH_3$, $ZnArgATPH_2$, and ZnArgATPH are found in the ternary system. The $ZnArgATPH_3$ species was observed to form at $pH < 2.0$, while the other two complexes, $ZnArgATPH_2$ and ZnArgATPH, formed stepwise as the pH increased, and their concentrations peaked at pH 6.0 and 11.0, respectively. $ZnArgATPH_2$ is the major compound at pH from 5 to 7, which is the ideal pH range for bioactivities.

Table 2. Characteristic IR bands (cm^{-1}) of the spectra of the complexes in the different ATP–Zn^{2+}–Arg systems and free ATP.

Compound	N–H	C–N(N-7)	$\nu_{as}PO(\alpha$ and $\beta)$	P–O–C	$\nu_{s}PO(\gamma)$
ATP	1650	1497	1254	1049	969
ATP–Zn^{2+}	1660	1511	1208	1074	956
ATP–Zn^{2+}–Arg	1666	1509	1220	1077	955

3.2. *IR spectra*

The IR spectra of ATP and its complexes discussed in this article are shown in figure S1 of the "Supplementary material." Table 2 shows the wavenumbers and positions of ATP and its complexes [32, 33]. Small shifts in the bands at 4000–1700 cm^{-1} may be due to rearrangement of the strong hydrogen-bonding network of free ATP upon complexation [34]. The absorption around 1497 cm^{-1}, assigned to the purine ring vibration of ATP, showed a shift of about 14 cm^{-1} for its complexes, suggesting a possible N-7 binding site [34]. The band at 969 cm^{-1}, which was assigned to the symmetric stretching vibration of the γ-phosphate in free ATP [33–35], shifted to 956 cm^{-1} and its intensity was greatly reduced upon complexation. The intense band at 1254 cm^{-1}, which was attributed to the asymmetric stretching band of the α- and β-phosphate groups of free ATP [33, 35], shifted to 1208–1220 cm^{-1}. This indicated that oxygen of α-, β-, and γ-phosphates of ATP participated in coordination for all compounds. Thus, the interaction sites of ATP involved in the interactions with Zn^{2+} and/or Arg were the N-7 site, α-, β-, and γ-P of ATP, which were confirmed by fluorescence and NMR experiments.

3.3. *Fluorescence*

ATP emits a strong fluorescence band at 384 nm when the excitation wavelength is 281 nm. Compared with that of ATP, ADP showed less fluorescence intensity and AMP displays a very weak signal (figure S2 of the "Supplementary material"). That was because the number of phosphates in the molecules shifts the light emission and modifies its intensity [36]. Quenched spectra can give some information about the molecular environment in the vicinity of the chromophore molecule [36–38].

Fluorescence emission spectra of ATP with and without Zn^{2+} in aqueous solutions at pH 3.0 are shown in figure 2. The fluorescence intensity of ATP at 384 nm decreased gradually as the concentration of Zn^{2+} increased in the solution. As to the cause of the weakening of the fluorescence intensity of ATP after the addition of Zn^{2+}, we ruled out chemical quenching, color quenching, and dilution quenching because Zn^{2+} does not absorb in the spectral range (300–550 nm), and the volume and concentration of ATP were kept constant. The most likely explanation is that zinc binds oxygen of phosphate of ATP to form a ZnATP complex and modified the fluorescence intensity of ATP. In figure S3 of the "Supplementary material," the fluorescence intensity of ADP also gradually decreased with addition of Zn^{2+}, which indicated that Zn^{2+} also interacted with the oxygen of phosphate groups of ADP. While the reduced scale of fluorescence intensity in the ADP–Zn^{2+} system was less than that in the ATP–Zn^{2+} system, the fluorescence intensity of AMP was almost constant with addition of Zn^{2+} into the AMP

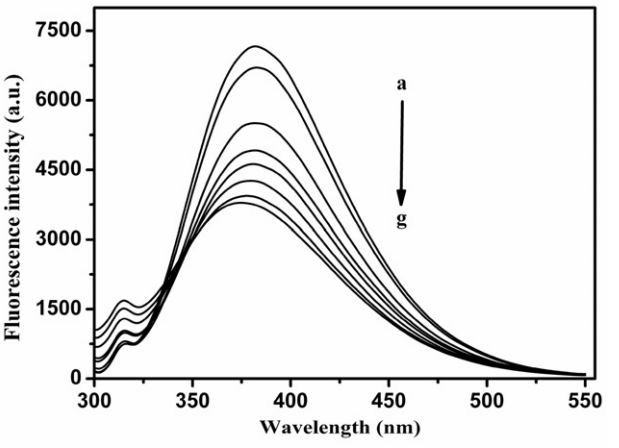


Figure 2. Changes in fluorescence spectra of ATP with gradual addition of Zn^{2+} in an aqueous solution at pH = 3.0, a–g: [ATP] = 1.0×10^{-4} mol L^{-1}, [Zn^{2+}] = 0–1.6×10^{-3} mol L^{-1}; excitation wavelength: 281 nm.

solution, indicating that zinc ion interacted mainly with β- and γ-P while the interactions between the α-P of ATP and Zn^{2+} were very weak or even nonexistent, which can be also confirmed by ^{31}P NMR.

Further research on the interactions among ATP, Zn^{2+}, and Arg was carried out by comparing fluorescence intensities of ATP, ADP, and AMP aqueous solutions with addition of Arg into the nucleic acid–Zn^{2+} binary systems (figure S4 of the "Supplementary material"). Fluorescence intensity of ATP and ADP decreased, while the fluorescence intensity of AMP was almost constant when Arg was added into the nucleic acid–Zn^{2+} solution. These findings suggest that Arg can interact with β- and γ-P, while it does not recognize the α-P of ATP [39]. That is because Arg has a positively charged guanidinium chain and a negatively charged carboxyl group, which can form hydrogen-bonding, coordination interaction, and/or electrostatic interactions with the negatively charged phosphates of ATP and Zn^{2+}.

3.4. *NMR experiment*

Figure 3(a) shows that the change in the ^1H chemical shifts of ATP in the absence of Zn^{2+} as a function of pH is in agreement with that reported by Wang *et al.* [40]. In addition, it serves as reference for other spectra. The two peaks at 8.09 and 8.38 ppm are assigned to H-2 and H-8 protons of ATP at pH 7.0, respectively. The chemical shifts of H-2 and H-8 of the adenine ring of ATP changed significantly in the ATP–Zn^{2+} binary system compared to those in the ATP solution (figure 3a). It has been well-recognized that the coordination of a metal ion to a binding site deshields neighboring protons. Therefore the resonance of such protons shifts downfield [41–43] and ATP takes a *syn* conformation at relatively low pH [31]. Thus, Zn^{2+} can interact with the N-1 site of ATP at low pH because the chemical shifts of H-2 were downfield compared to that in the ATP solution. Protons, however, were added to the N-1 site to form the zwitterionic species $^{+}H_2(ATP)^{3-}$, with the N-1 site being positively charged at relatively low pH

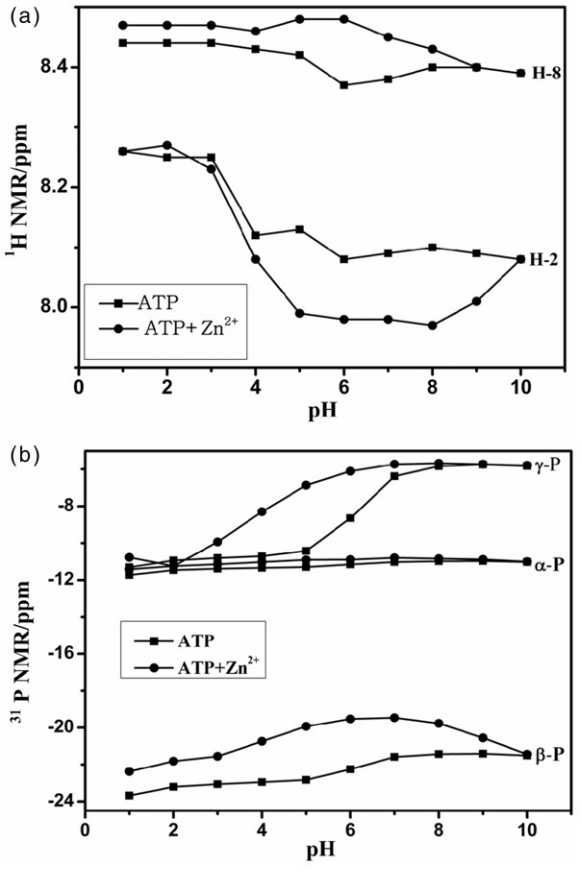


Figure 3. Plot of the chemical shifts of ATP in the absence and presence of Zn^{2+} as a function of pH at 298.15 K: (a) the ^{1}H chemical shifts of H-2 and H-8; and (b) ^{31}P chemical shifts of ATP.

values. Compared to H^+, Zn^{2+} has the advantage of higher charge. Thus, Zn^{2+} can at least partially replace the proton to bind to the N-1 site at low pH [44]. With increasing pH, the chemical shifts of H-2 were upfield in the ATP–Zn^{2+} binary system compared with that in ATP solution. It can be explained by the fact that ATP became an *anti* conformer and the N-1 site was deprotonated, thus, no geometric advantage existed between the N-1 site of ATP and Zn^{2+}. To some extent, the upfield signals of H-2 can be explained by the fact that Zn^{2+} promotes self-association of ATP [41]. In figure 3(a), it is shown that signals of H-8 were downfield in the whole pH range when zinc was added to the ATP solution. This is very likely due to the fact that Zn^{2+} can interact directly with the N-1 site of ATP because the adenine ring is an aromatic system, thus, signals of H-8 moved downfield at low pH. In addition, H-8 interacts directly with N-7 site as there was geometric advantage between the adenine ring of ATP and Zn^{2+} with increasing pH as ATP took an *anti* conformer. Interaction sites of ATP with metal ions involve not only the N-1 and N-7 sites in the adenosine ring, but also the triphosphate groups. From the ^{31}P NMR spectra, all the phosphate groups of ATP can coordinate with Zn^{2+} since the ^{31}P chemical shifts of α-, β-, and γ-P were

downfield compared with those in the ATP solution, although the interaction between Zn^{2+} and α-P was weaker than that among Zn^{2+}, β-P, and γ-P (figure 3b). The results indicate that the main interaction sites of ATP with Zn^{2+} changed at different pH values.

In the ATP–Arg binary system, chemical shifts of H-2 and H-8 were almost the same as those in the ATP solution at relatively low pH values (figure S5 of the "Supplementary material"). The interactions were very weak or nonexistent between ATP and Arg because the N-1 site of ATP was protonated at low pH and Arg was positively charged in a wide range of pH. The signals of H-2 and H-8 were upfield in the ATP–Arg binary system compared to those in the ATP solution with increasing pH (figure S5 of the "Supplementary material"). ATP took an *anti* conformer and the N-1 site was deprotonated at rather high pH. Therefore, ATP had geometric advantage to interact with Arg by hydrogen-bonding and electrostatic interaction [39]. The interaction also existed between Arg and the triphosphate groups of ATP [26, 39] because the triphosphate group of ATP is negatively charged and the guanidinium group of Arg is positively charged, although the interaction was weaker than that in the ATP–Zn^{2+} binary system (figure S6 of the "Supplementary material").

In the ATP–Arg–Zn^{2+} ternary system, the tendency for change of chemical shifts of H-2 and H-8 of ATP was similar to that in the ATP–Zn^{2+} binary system at $pH \leq 6$, while it was different from that in the ATP–Zn^{2+} binary system at $pH > 6$ (figure S5 of the "Supplementary material"). This suggested that the adenine ring of ATP interacted mainly with Zn^{2+} at $pH \leq 6$ since the N-1 site of the adenine ring was protonated and Arg was positively charged. With increasing pH, Zn^{2+} can interact with the N-7 site of ATP because ATP became an *anti* conformation [31], and can also interact with Arg through coordination and electrostatic interaction since Arg has a carboxyl group. Therefore, the chemical shifts of H-2 and H-8 of ATP in the ATP–Arg–Zn^{2+} ternary system were different from those in the ATP–Zn^{2+} binary system at $pH > 6$. The interesting aspect of the ^{31}P chemical shifts for all three phosphorus atoms of ATP in the ternary system is almost the same as that in the binary ATP–Zn^{2+} system (figure S6 of the "Supplementary material"). Such finding indicates that the major coordination interaction of triphosphate of ATP occurred with the metal ion which has a much stronger interaction than that between the triphosphate group of ATP and Arg. The role of Arg was to stabilize the metal ion–ATP complex in the ternary system because the guanidinium group of Arg can interact with the triphosphate groups of ATP through hydrogen-bonding and Arg coordinated to Zn^{2+} *via* its carboxyl group. Coordination interaction, hydrogen-bonding, and electrostatic interaction are the main interactions in the ternary system. All of them may affect the hydrolysis rate of ATP in the ternary system, as discussed in the following section.

3.5. *Catalytic hydrolysis of ATP*

The kinetics of ATP hydrolysis catalyzed by Zn^{2+}–Arg as a function of time were studied at 60°C and pH 7.0 using ^{31}P NMR spectra. The ^{31}P signal of ATP in the different systems at the same hydrolysis times is illustrated in figure 4. The observed rate constant k_{obs}, equation (1), was obtained from the plot of $\ln([ATP]/[ATP]_0)$ as a

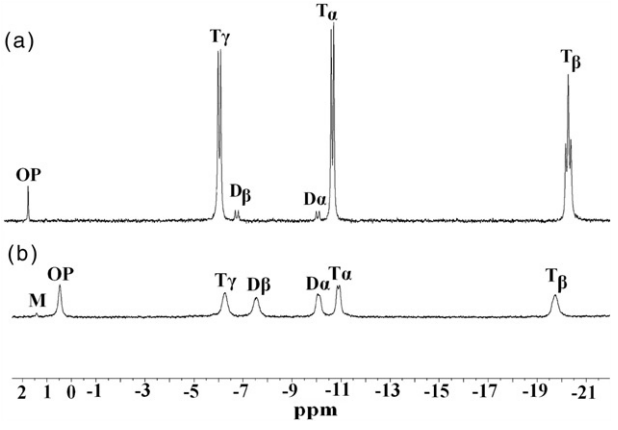


Figure 4. ^{31}P NMR spectra of ATP hydrolysis at the same reaction times in the binary and ternary system at pH = 7.0 and $T = 60^{\circ}$C: (a) $t = 60$ min in the Zn^{2+}–ATP binary system; and (b) $t = 60$ min in the Zn^{2+}–ATP–Arg ternary system.

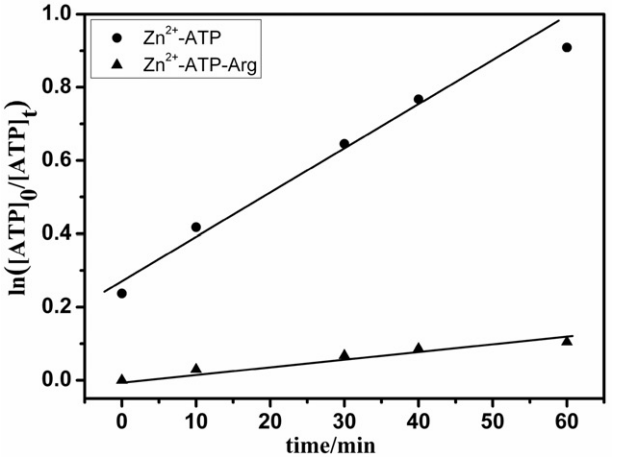
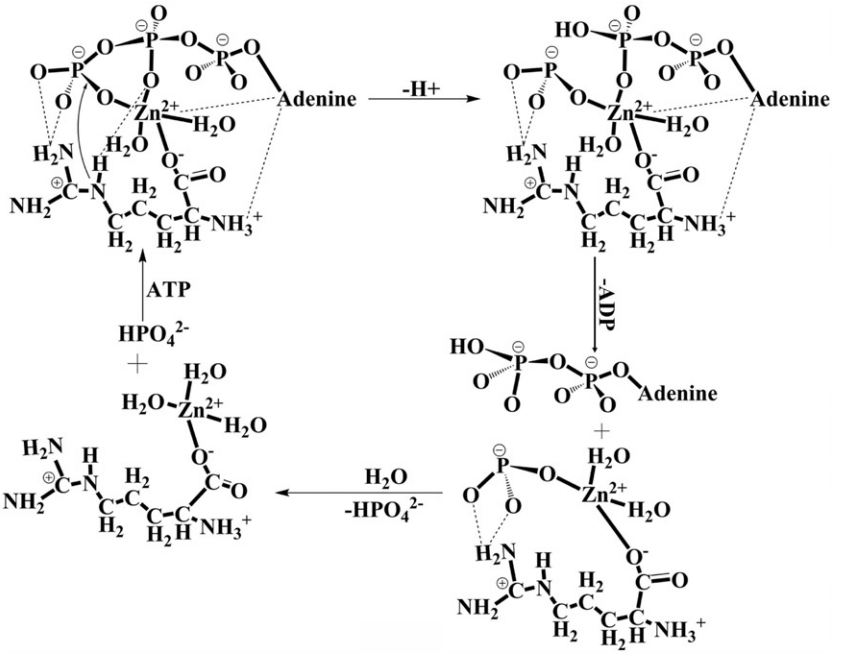


Figure 5. Rate constants for ATP hydrolysis in different systems at pH = 7.0 and $T = 60^{\circ}$C. Zn^{2+}–ATP (●) and Zn^{2+}–ATP–Arg (▲).

function of time, where $[ATP]_0$ and [ATP] are the initial and observed concentrations of ATP, respectively.

$$r = k_{obs}[ATP] = -d[ATP]/dt. \quad (1)$$

From a kinetic study, Zn^{2+} and Zn^{2+}–Arg moderately accelerated ATP hydrolysis with a rate constant of $2.44 \times 10^{-2}\,min^{-1}$ and $2.27 \times 10^{-3}\,min^{-1}$ (figure 5, which is about 12.14- and 1.13-fold as fast as that of ATP ($2.01 \times 10^{-3}\,min^{-1}$)) in ATP solution, respectively. The rate constant of ATP hydrolysis in the ATP–Zn^{2+}–Arg ternary system was slower than that in the ATP–Zn^{2+} binary system, attributed to the fact that Zn^{2+} can coordinate with the oxygen of the carboxyl group of Arg, which leads to decrease in



Scheme 2. Postulated mechanism for ATP hydrolysis catalyzed by Zn^{2+} and Arg.

activity of Zn^{2+} toward the phosphate groups of ATP through nucleophilic attack since the positive charge of Zn^{2+} fluxed to Arg and the electron-withdrawing effect of Zn^{2+} to phosphate decreased. The catalytic effect of the zinc ions on ATP hydrolysis was greater than that of cadmium ions in ATP–metal ion binary system [45], because Zn^{2+} formed stronger bonds with ATP than Cd^{2+}, due to much higher electron density of Zn^{2+} than Cd^{2+}. In the metal ion–amino acid–ATP ternary system, the rate constant of ATP is much slower in the ATP–Arg–Zn^{2+} ternary system than in the ATP–Zn^{2+} binary system, but the rate constant of ATP is faster in the ATP–Cd^{2+}–Glu ternary system than in the ATP–Cd^{2+} binary system [45]. Therefore, the rate of the ATP–metal ion–amino acid ternary systems including acceleration or retardation, compared with that in the metal ion–ATP binary system, depends on the properties of the metal ion.

Catalytic efficiency depends on defined structural requirements of the complex itself, which involves a protonation pattern, electrostatic interaction, hydrogen-bonding, and spatial arrangement of the reacting species at the catalytic site [46]. Therefore, according to an addition–elimination mechanism [47], the proposed mechanism of ATP hydrolysis catalyzed by Arg and Zn^{2+} in the ternary system is presented in scheme 2. Hydrolysis of ATP in the ternary system was divided into three steps: the first was recognition and interactions among ATP, Zn^{2+}, and Arg, discussed in detail in previous sections. The second step involved nucleophilic attack on γ-P of ATP by the unprotonated nitrogen in the guanidinium group of Arg or by a water molecule to form an intermediate and the release of ADP. The phosphoramidate intermediate did not exist after 1 h of hydrolysis in the ATP–Arg–Zn^{2+} ternary system (figure 4), which was found in other

metal ion–ATP–amino acid systems [48]. The existence of the phosphoramidate intermediate depended on several factors, such as pH, time, and the concentration of ATP. Due to the higher affinity of Zn^{2+} to oxygen than nitrogen, the products were ADP and the Zn–Arg–PO_3 complex. The final step of the mechanism involved capture of a water molecule by the negatively charged PO_3^-, loss of HPO_4^{2-} from the Zn–Arg–PO_3 complex, and regeneration of the catalytic Zn-Arg complex. The mechanism of ATP hydrolysis catalyzed by the metal ion–amino acid complexes was different from that of the other biomolecules hydrolysis [49–51], whose catalytic reaction is reversible. The rate constant of ATP decreases in the ATP–Zn^{2+}–Arg ternary system compared with that in the ATP–Zn^{2+} binary system, which can be attributed to coordination competition of the mixed ligands (Arg and ATP) and the Zn^{2+}–Arg complex serves as a catalyst in the hydrolysis process. Whereas, rate enhancements in the ATP–Cd^{2+}–Glu ternary system are due to water coordinated to Cd^{2+} that serves as an acid catalyst in the hydrolysis process. Thus, the metal ion can regulate or control the ATP hydrolysis process in the ATP–metal ion binary system and the ATP–metal ion–amino acid ternary system.

4. Conclusion

Zn^{2+} can partially replace the proton to bind to the N-1 site at low pH and interact directly with the N-7 site of the adenosine ring of ATP with increasing pH by electrostatic and coordination interactions. Zn^{2+} also coordinated with oxygen of all three phosphate groups of ATP in the entire pH range covered by the experiments in this article, although the interactions between Zn^{2+} and α-P were weak in the ATP–Zn^{2+} binary system. Zn^{2+} not only interacted with ATP, but was also engaged in non-covalent interactions with oxygen of the carboxyl group of Arg in the ATP–Arg–Zn^{2+} ternary system. Kinetics studies showed that the rate constant of ATP hydrolysis catalyzed by Zn^{2+} was larger than that by Zn^{2+}–Arg because Zn^{2+} coordinated to oxygen of the carboxyl of Arg. In the metal ion–amino acid–ATP ternary system, the rate constant of ATP is much slower in the ATP–Arg–Zn^{2+} ternary system than that in the ATP–Zn^{2+} binary system, but the rate constant of ATP is faster in the ATP–Cd^{2+}–Glu ternary system than in the ATP–Cd^{2+} binary system. Thus, recognition and catalytic hydrolysis of ATP depend on the properties of the amino acid and also on the character of the metal ions, similar to enzyme catalysis.

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