Kinetics and Mechanism of Angiotensin Phosphorylation by the Transforming Gene Product of Rous Sarcoma Virus*

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We have studied steady state kinetics of phosphorylation of [Val⁶]angiotensin II by pp60⁺⁺, the transforming gene product of Rous sarcoma virus. Results of initial rate studies at varying substrate concentrations indicated that the mechanism was sequential; Michaelis constants for ATP and peptide were 7 μM and 0.24 mM, respectively, and V_max was 1.0 nmol/min/mg. The end product ADP and the ATP analog AMP-PNP were competitive inhibitors at varying ATP concentrations and noncompetitive inhibitors at varying peptide concentrations. A dead-end analog of angiotensin II, [ΔPhe⁴]angiotensin II, was a noncompetitive inhibitor at varying ATP concentrations, but induced substrate inhibition at varying peptide concentrations. The kinetic data allowed us to conclude that the reaction proceeded via an Ordered Bi Bi mechanism with ATP as the first binding substrate. We also presented evidence that, while pp60⁺⁺ contained essential histidine residues in its active site, the mechanism does not involve a phosphoryl enzyme intermediate.

Tyrosyl protein kinase activity has been demonstrated to be integral to the transforming gene products of several different retroviruses, to be associated with cellular receptors for growth factors, and to be present as cytoplasmic components in normal cells (1-6). The introduction of small peptide substrates for tyrosyl protein kinases has facilitated progress in understanding the functions and properties of these enzymes (7-9). These peptides are either fragments of a viral transforming protein or angiotensin analogs. The former group of peptides has amino acid sequences that include the in vivo tyrosine phosphorylation site. The latter group of peptides, however, has as yet no obvious relation to the enzymes in vivo. Nonetheless, their usefulness has been demonstrated in studies of viral protein kinases as well as in identification of novel enzymes in normal rat liver (6, 9).

A great number of reports have dealt with characterization of the tyrosyl protein kinase activity associated with the transforming protein, pp60⁺⁺, of Rous sarcoma virus (10). However, none of these reports have addressed the question of mechanism whereby in vitro phosphorylation proceeds. Here we describe results of kinetic experiments in which we studied the phosphorylation of [Val⁶]angiotensin II by ATP as catalyzed by pp60⁺⁺. With the aid of product and substrate analogs, we have obtained evidence for pathway of the phosphoryl transfer reaction.

EXPERIMENTAL PROCEDURES

Materials—[Val⁶]angiotensin II was synthesized in our laboratory by solid phase method. ADP, AMP-PNP, ATP, kynurenin, and diethyl pyrocarbonate were from Sigma. Angiotensin pentapeptide was obtained from Peninsula Laboratories, Inc. (San Carlos, CA). [NO₂Tyr⁴]Angiotensin II was a gift from Drs. N. Bramson and E. T. Kaiser of The Rockefeller University. [ΔPhe⁴]-[Ain⁶]angiotensin II were generously provided by Drs. T. Balasubramanian and G. R. Marshall of Washington University. [γ-³²P]ATP (5,000 Ci/mmol) was from Amersham Corp. and was diluted with unlabeled ATP to obtain the appropriate specific activity. Preparations of pp60⁺⁺ were purified from RR1022 cells as described previously (9, 11) and had specific activity between 100 and 200 units/mg when assayed with 40 μM ATP (22,000 cpm/pmol) and 2 mM [Val⁶]angiotensin II.

Peptide Phosphorylation Assay—Reaction mixtures (25 μl) containing 10% glycerol, 25 mM MES, pH 6.5, 10 mM MnCl₂, 10 mM 2-mercaptoethanol, 200-400 ng of enzyme, and [γ-³²P]ATP and [Val⁶]angiotensin II at various concentrations. Incubation was at 30 °C for 20 min, followed by 3 min at 90 °C. Peptide phosphorylation was assayed by paper electrophoresis as described previously (9) except that electrophoresis buffer also contained 5 mM EDTA.

Data Processing—The nomenclature of Cleland was used in designation of reactants and kinetic constants (12). All experiments were performed at least three times, and the results presented here are representative of each experiment. Initial rate data were fitted by linear regression analyses to the rate equation described in Scheme 1a for a sequential mechanism. Intercepts and slopes of double reciprocal plots were replotted against 1/[substrate] or [inhibitor] to obtain V_max, Michaelis constants, dissociation constants, and inhibition constants according to relationships described by Cleland (12, 13).

RESULTS

We previously reported the use of angiotensin analogs as in vitro substrates for tyrosyl protein kinases (9). We have now used [Val⁶]angiotensin II in studying the kinetics and mechanism of phosphorylation catalyzed by pp60⁺⁺, the transforming gene product of Rous sarcoma virus. The enzyme was partially purified from Rous sarcoma virus-transformed rat cells; it was free of serine and threonine kinase activity and showed a linear time course of phosphorylation over 30 min (Ref. 9 and data not shown). Rate of phosphorylation of [Val⁶]angiotensin II increased with increasing concentration of peptide up to about 1.5 mM (Fig. 1a, open circles). At concentrations of peptide above 4 mM, the enzyme appeared to become saturated. When a lower concentration of ATP was used in the assay, however, high concentration of peptide did not alter the rate of phosphorylation.

1 The abbreviations used are: AMP-PNP, adenyly-5'-yl imidodiphosphate; AT II, [Val⁶]angiotensin II; Ain, 2-aminoindaned-2-carboxylic acid; NO₂Tyr, nitrotyrosine; ΔPhe, dehydrophenylalanine; MES, 2-(N-morpholino)ethanesulfonic acid.
concentrations of ADP (Fig. 1a, closed circles). The rate of reaction also was linear with respect to ATP concentration up to at least 180 μM (Fig. 1b). Initial rates were determined by varying concentration of one substrate while holding concentration of the other substrate fixed, and results are expressed in double reciprocal plots. When the concentration of ATP was varied, increasing concentration of AT II resulted in a decrease in both the slope and the intercept of the plot (Fig. 2a). The same effect was evident with fixed concentrations of ATP and varying concentrations of peptide (Fig. 2b). In both cases, the lines converge to the left of the ordinate. These patterns are indicative of a sequential mechanism and rule out a Ping Pong Bi Bi pathway, in which case the double reciprocal plots would have been observed with varying peptide concentration.

We examined the effects of one of the end products, ADP, on the reaction rates. At fixed concentration of peptide and varying concentrations of ATP, increasing concentrations of ADP caused a change in the slope, but not the intercept, of the double reciprocal plots (Fig. 3a). At fixed concentrations of peptide, both slope and intercept increased with increasing concentrations of ADP (Fig. 3b). ADP is therefore a linear competitive inhibitor of ATP and a linear noncompetitive inhibitor of peptide. These results are consistent with a sequential mechanism in which ADP and ATP bind the same enzyme form. We have not succeeded in obtaining the other end product, phosphopeptide, in sufficient quantity to perform the same kind of analyses as were done with ADP.

In order to differentiate between a random and ordered pathway, we sought to study the effects of dead-end inhibitors of either substrate. The analog AMP-PNP is a well characterized inhibitor of ATP (14) and was used for this purpose. As shown in Fig. 4, this analog was a competitive inhibitor of ATP and showed noncompetitive inhibition with peptide. These observations allowed us to rule out an Ordered Bi Bi or Theorell-Chance mechanism in which peptide binds first and ATP binds second. In those cases, uncompetitive inhibition would have been observed with varying peptide concentration. Data obtained from initial rate studies were replotted to yield Michaelis and dissociation constants for substrates and inhibition constants for product and analog inhibitors (Table I). K_{m} for ATP, as determined from replot of data in Fig. 2b, was 7.0 μM. However, data in Fig. 1b suggest that the K_{m} for peptide should be considerably higher than 7 μM. The discrepancy may be a result of inhibition by peptide substrate (Fig. 1a and see below). Data in Fig. 2b and Table I were determined at

![Fig. 1](image1.png)

**Fig. 1.** Phosphorylation of [Val']angiotensin II as a function of peptide and ATP concentrations. a, ATP was present at 40 μM (O), and reaction rates were indicated by the left-hand ordinate. Reaction rates were also determined at 1 μM ATP (●) and were indicated by the right-hand ordinate. b, reaction rates were determined at 2 mM peptide. Peptide phosphorylation was assayed as described under "Experimental Procedures.”

![Fig. 2](image2.png)

**Fig. 2.** Double reciprocal plots of initial rates of [Val']angiotensin II phosphorylation at varying concentrations of ATP and peptide. a, concentrations of [Val']angiotensin II were held constant at 40 μM (O), 60 μM (●), 120 μM (Δ), and 220 μM (▲). b, ATP concentrations were held constant at 1 μM (O), 5 μM (●), 10 μM (Δ), and 24 μM (▲).

![Fig. 3](image3.png)

**Fig. 3.** Double reciprocal plots of initial rates of phosphorylation in the presence of ADP. a, [Val']angiotensin II was present at 80 μM, and [ATP] was varied. ADP was present at 0 (O), 16 μM (●), 40 μM (Δ), and 75 μM (▲). b, [ATP] was held constant at 6 μM, and peptide concentration was varied. ADP was present at 0 (O), 16 μM (●), 40 μM (Δ), and 90 μM (▲).

![Fig. 4](image4.png)

**Fig. 4.** Double reciprocal plots of initial rates of phosphorylation in the presence of AMP-PNP. a, [Val']angiotensin II was present at 80 μM, and [ATP] was varied. AMP-PNP was present at 0 (O), 50 μM (●), 100 μM (Δ), and 200 μM (▲). b, [ATP] was held constant at 6 μM, and peptide concentration was varied. AMP-PNP was present at 0 (O), 100 μM (●), 200 μM (Δ), and 300 μM (▲).
Relatively low concentrations of peptide substrate whereas those in Fig. 1b were obtained with 2 mM peptide. Under the latter conditions, some degree of inhibition by peptide may have been taking place, and a higher concentration of ATP was therefore required to reach the half-maximal rate. Also, with peptide as varying substrate, Kd for ADP is severalfold higher than Kc. The latter constant approximates the dissociation constant for enzyme-ADP complex, Kd. The difference between Kc and Kd may be due to the fact that concentration of ATP used in the experiment was close to Kc of ATP. Hence, the apparent Kd in effect close to being twice the value of Kd (Kd being equal to Kc multiplied by (1 + A/Kc)). If this factor is taken into account, Kc would then be comparable to Kd.

We next examined a number of angiotensin analogs for their effects on phosphorylation of AT II. Three of the peptides examined had the tyrosine of AT I1 replaced with a different residue. None of the peptide analogs was phosphorylated by pp60src. 2 Surprisingly, only one of the five peptides, the dehydrophenylalanine analog of AT I1, acted as an inhibitor (Table II). The other peptides had no observable effect on the reaction rate at concentrations up to 5 mM (not shown). When [ΔPhe4]AT I1 was used in initial rate studies, it was found to result in parabolic noncompetitive inhibition with ATP (Fig. 5a). However, a rather complex pattern of double reciprocal plots was obtained when ATP concentration was held constant and peptide concentration was varied (Fig. 5b).

The presence of inhibitor, the reaction rate increased with increasing concentration of peptide up to about 0.16 mM. Beyond that concentration, the reaction rate decreased asymptotically. The noncompetitive inhibition by [ΔPhe4]AT I1 at varying ATP concentrations ruled out a simple Ordered Bi Bi or Theorell-Chance mechanism with ATP as the first binding substrate. Thus, we have to differentiate between a rapid equilibrium Random Bi Bi mechanism or a modified Ordered Bi Bi mechanism in which the free enzyme binds peptide, but the binary complex does not allow subsequent binding by ATP. A schematic representation of the latter kinetic mechanism is shown in Fig. 6a. Such a pathway resembles a rapid equilibrium Random Bi Bi reaction in that the free enzyme binds both substrates. However, a productive sequence would ensue only if ATP binds enzyme first, followed by binding of peptide to the binary complex. Binding of peptide to the free enzyme may result in steric hindrance that precludes ATP from access to the active site. In the model depicted in Fig. 6a, substrate inhibition at high peptide concentration is most likely due to formation of dead-end complex EB, and perhaps also of EB2. At high ATP concentration (40 μM or greater), the enzyme preferentially cycles between E and EA by virtue of mass action, and inhibition by peptide alleviated. Results in Fig. 5b suggest that the presence of [ΔPhe4]AT I1 induced substrate inhibition at concentrations of AT I1 that by itself would not have been sufficient to cause inhibition. A mechanism that would account for the induced substrate inhibition is depicted in Fig. 6b. In such a pathway, the binding of inhibitor results in a conformational change in the enzyme such that a second molecule of peptide substrate or inhibitor will be accommodated. The additional equilibria that have to be considered are

\[
E + I = EI \\
EI + I = EI_2 \\
EI + B = EIB \\
E + I = EA1 \\
EAI + I = EAI_2 \\
EAI + B = EABI_2
\]

where E, A, B, and I are, respectively, free enzyme, ATP, AT II, and [ΔPhe4]AT II and K values are the respective equilibrium constants.

Scheme 1a represents a rate equation for a sequential bi-reactant kinetic mechanism (12). When the above equilibria

### Table I

**Summary of AT I1 phosphorylation kinetic data**

| Inhibitor   | Substrate | Kinetic constants |
|-------------|-----------|-------------------|
|             |           | K\(_d\) | K\(_d\) |
| ATP (AT I1)| ADP       | 7.0 μM | 11.7 μM |
| ATP (AT I1)| AMP-PNP   | 0.24 mM| 0.40 mM |

In the presence of inhibitor, the reaction rate increased with increasing concentration of peptide up to about 0.16 mM. Beyond that concentration, the reaction rate decreased asymptotically. The noncompetitive inhibition by [ΔPhe4]AT I1 at varying ATP concentrations ruled out a simple Ordered Bi Bi or Theorell-Chance mechanism with ATP as the first binding substrate. Thus, we have to differentiate between a rapid equilibrium Random Bi Bi mechanism or a modified Ordered Bi Bi mechanism in which the free enzyme binds peptide, but the binary complex does not allow subsequent binding by ATP. A schematic representation of the latter kinetic mechanism is shown in Fig. 6a. Such a pathway resembles a rapid equilibrium Random Bi Bi reaction in that the free enzyme binds both substrates. However, a productive sequence would ensue only if ATP binds enzyme first, followed by binding of peptide to the binary complex. Binding of peptide to the free enzyme may result in steric hindrance that precludes ATP from access to the active site. In the model depicted in Fig. 6a, substrate inhibition at high peptide concentration is most likely due to formation of dead-end complex EB, and perhaps also of EB2. At high ATP concentration (40 μM or greater), the enzyme preferentially cycles between E and EA by virtue of mass action, and inhibition by peptide alleviated. Results in Fig. 5b suggest that the presence of [ΔPhe4]AT I1 induced substrate inhibition at concentrations of AT I1 that by itself would not have been sufficient to cause inhibition. A mechanism that would account for the induced substrate inhibition is depicted in Fig. 6b. In such a pathway, the binding of inhibitor results in a conformational change in the enzyme such that a second molecule of peptide substrate or inhibitor will be accommodated. The additional equilibria that have to be considered are

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where E, A, B, and I are, respectively, free enzyme, ATP, AT II, and [ΔPhe4]AT II and K values are the respective equilibrium constants.

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### Table II

**Inhibition of angiotensin phosphorylation by peptide analogs**

AT I1 phosphorylation was assayed at 0.8 mM AT II, 6 μM ATP, and 1 mM peptide analog. Structure of Ain is as follows.

| AT II analog | Sequence | V (pmol/min/mg) | Activity (%) |
|--------------|----------|----------------|--------------|
| None         | Tyr-Ile-His-Pro-Phe | 53.7 | 100 |
| AT II pentapeptide | Asp-Arg-Val-Ain-His-Pro-Phe | 52.1 | 97 |
| [Ain1]AT II   | Asp-Arg-Val-His-Pro-Phe | 56.9 | 106 |
| [ΔPhe4]AT II | Asp-Arg-Val-ΔPhe-His-Pro-Phe | 9.06 | 17 |
| [NO2Tyr4]AT II| Asp-Arg-Val-(NO2Tyr)-His-Pro-Phe | 52.7 | 98 |
| Kyotophyrin  | Tyr-Arg  | 56.8 | 106 |

2 Sequence of AT II: Asp-Arg-Val-Yrn-Val-His-Pro-Phe.

3 T. W. Wong and A. R. Goldberg, unpublished observations.
were taken into account in consideration of enzyme conservation, we obtained a rate equation of the form shown in Scheme 1b. In double reciprocal form (Scheme 1c), the equation predicts parabolic noncompetitive inhibition by [ΔPh4]AT II at varying ATP concentrations since the equation is of the form \( y = a(1 + b + c + d) \). At varying concentrations of ATP II, the equation is of the form \( y = a(x + x/b) \) and predicts a hyperbolic concave-pattern for the double reciprocal plot. Furthermore, the equation in Scheme 1c predicts that substrate inhibition requires the presence of I. Thus, it appears that the data obtained could be adequately interpreted by the Ordered Bi Bi mechanism shown in Fig. 6. On the other hand, a Random Bi Bi mechanism would not be compatible with the kinetic data, especially with the inhibition pattern obtained with [ΔPh4]AT II. We replotted the slopes and intercepts of Fig. 5a versus concentrations of peptide inhibitor. By doing that, we obtained parabolic curves for both intercept and slope replots (not shown), which were extrapolated to yield apparent \( K_a \) and \( K_b \) of 0.8 and 0.6 mM, respectively. We did not attempt to obtain sufficient data to calculate the various equilibrium constants for the enzyme-inhibitor complexes.

Results of the kinetic experiments suggest that the \textit{in vitro} phosphorylation of angiotensin II by pp60-src proceeds via a ternary complex intermediate. However, there is as yet no evidence to exclude the possibility that a phosphorylated enzyme form mediates the phosphoryl transfer from ATP to the phenolic moiety of peptide. It is possible that phosphoryl transfer occurs between ATP and enzyme, but ADP does not depart from the active site until after the transfer between phosphoryl enzyme and ATP II has taken place. We examined this possibility by studying the effects of chemical modification on the enzymatic activity. Diethyl pyrocarbonate reacts with imidazole and amino groups and has been used to selectively modify histidine residues of enzyme active sites (15). Before initiating kinase reaction, we preincubated reaction mixtures with various concentrations of diethyl pyrocarbonate. As shown in Fig. 7, the enzymatic activity was inactivated by 50% by 0.08% diethyl pyrocarbonate and was almost abolished at concentration above 0.15%. Preincubation of the reaction mixture in the presence of ATP did not provide any significant protection of the enzyme. These observations suggest that if a phosphoryl enzyme intermediate existed, the modified residues would not likely have been imidazole or amino moieties. This is because in those cases phosphorylation of enzyme should have provided some protection from inactivation by diethyl pyrocarbonate. We cannot rule out the possibility that formation of phosphoryl enzyme intermediate requires the presence of peptide substrate. However, experimental verification of that possibility is not presently feasible. Furthermore, we re-examined the phosphoamino acid content of pp60-src labeled \textit{in vitro} with [γ-32P]ATP. In previous studies, analyses were performed with acid hydrolysates. Under those conditions, phosphoamino acids other than phosphoserine, phosphothreonine, and phosphotyrosine would have been completely destroyed. We therefore performed base hydrolysates on samples of 32P-labeled pp60-src and separated the hydrolysates by two-dimensional thin layer electrophoresis under conditions that allowed separation of phosphoserine, phosphothreonine, phosphotyrosine, 3-phosphohistidine, and phosphoarginine. Again, phosphotyrosine was the only radiolabeled phosphoamino acid observed. Since Snyder et al. (16) observed previously that Rous sarcoma virus mutants lacking the tyrosine phosphorylation site exhibited unabated protein kinase activity, our data prompted us to conclude that...
Pyrocarbonate was added to the reaction mixtures, and incubation was continued for 10 min. Bovine serum albumin was then added to 0.1 mg/ml, and aliquots were removed for assaying kinase activity.

The reaction mechanism probably does not involve a phosphoryl enzyme intermediate.

**DISCUSSION**

By studying steady state kinetics of the phosphorylation of angiotensin II, we have determined the effects of co-substrates, product, and substrate analogs on the initial rate of reaction. The kinetic data allow us to conclude that the kinase reaction follows a sequential pathway. The order of substrate addition was determined by studying effects of AMP-PNP and [ΔPhe]{\textsuperscript{4}}angiotensin II. The substrate inhibition induced by the presence of [ΔPhe]{\textsuperscript{4}}angiotensin II was most helpful in the diagnosis of an Ordered Bi Bi mechanism. In the mechanism proposed, the enzyme binds either ATP or peptide. However, occupation of the active site by AT II precludes subsequent binding by ATP and therefore does not allow for a productive reaction. Thus, the mechanism can be viewed as intermediate between a rapid equilibrium Random Bi Bi and an Ordered Bi Bi mechanism.

The observation that most analogs of AT II did not inhibit peptide phosphorylation suggests that the enzyme exhibits rather stringent selectivity in binding substrate. [NO₂Tyr{\textsuperscript{4}}]AT II was not phosphorylated by the enzyme presumably because the nitro group rendered the molecule too bulky for interaction with the active site. Similarly, other analogs were either too large (as in [Ain{\textsuperscript{4}}]AT II) or too small (as in AT II pentapeptide) to compete with AT II for binding sites. [ΔPhe{\textsuperscript{4}}]AT II differs from the other analogs in that the residue at position 4 has a rigid planar geometry. This unusual feature of the peptide may distort the topology of the enzyme active site such that there will be sufficient room for a second molecule of peptide to bind. Occupation of the enzyme active site by two peptide molecules may account for inhibition at high concentration of peptide substrate. In the presence of [ΔPhe{\textsuperscript{4}}]AT II, the process is facilitated, and inhibition is observed at much lower concentrations of peptide substrate. Substrate inhibition induced by a dead-end analog also was observed previously with yeast hexokinase and thymidylate synthetase (17, 18).

Results of our experiments also suggest that pp60{\textsuperscript{src}} contains essential histidine and/or lysine residues and that the reaction mechanism does not involve a phosphoryl enzyme.

It remains to be determined if phosphorylation of that tyrosine residue of pp60{\textsuperscript{src}} has any functional significance on the enzymatic activity. We have not been able to obtain sufficient quantity of phosphorylated AT II to study the reverse reaction: ADP + phosphopeptide = ATP + peptide. Fukami and Lipmann (19) previously demonstrated a similar reaction involving pp60{\textsuperscript{src}} using anti-pp60{\textsuperscript{src}} IgG as substrate. Our results are almost identical with those obtained by Whitehouse et al. (20) for bovine heart and skeletal muscle cAMP-dependent kinase using kemptide substrate. However, they differ in some aspects from those of Erneux et al. (21), who studied the steady state kinetics of phosphorylation of peptide substrate by epidermal growth factor-receptor kinase. The latter authors concluded that while the mechanism was also Ordered Bi Bi, the order of substrate binding was peptide first, and ATP second. At the moment, it is not clear if the apparent difference in our interpretations reflects any difference in enzymatic specificity.

**Acknowledgments**—We thank Diane Morganthal for excellent technical assistance and Andrea Gifford for typing the manuscript. We also thank our colleagues for generously providing analogs of angiotensin II used in these studies.

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Kinetics and mechanism of angiotensin phosphorylation by the transforming gene product of Rous sarcoma virus.
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J. Biol. Chem. 1984, 259:3127-3131.

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