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Enzymes Activated by Monovalent Cations

Patterns and predictions for these enzyme-catalyzed reactions are explored.

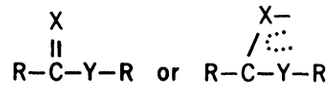
C. H. Suelter

The activation of certain enzyme-catalyzed reactions by monovalent cations is of interest to biologists and chemists, particularly since a potassium activation of the reaction catalyzed by pyruvate kinase was demonstrated (*1*). However, in contrast to the rather specific functions that may be assigned to certain divalent cations, the mode of action of the monovalent cations, K^+ and Na^+—particularly with respect to their ability to penetrate cell membranes, their affinities for active transport, and their potency for activating many enzymes (*2*)—has unfortunately remained obscure.

From an extensive compilation of enzymes requiring K^+, Evans and Sorger (*3*) made the following generalizations. (i) A large number of enzymes catalyzing a wide variety of unrelated reactions are activated by monovalent cations. (ii) Those enzymes activated by K^+ are also usually activated by Rb^+ and NH^{4+} but are activated little by Na^+ and not at all by Li^+. A few enzymes activated by Na^+ are also activated by Li^+, but they are activated much less or not at all by K^+, Rb^+, and NH_4^+. (iii) The molar concentration of K^+, Rb^+, or NH_4^+ required for maximum activity is high, having an activation constant K_A near $0.01M$ in most cases. (iv) The conformation of pyruvate kinase, an enzyme activated by monovalent cations, is affected by such cations. From these generalizations, Evans and Sorger (*3*) suggested that monovalent cations exert a role by maintaining a specific protein conformation necessary for optimum catalytic efficiency. In contrast, Melchior (*4*) and Lowenstein (*5*) proposed a complex of univalent cation and adenosine triphosphate based on results from model systems for a role of monovalent cations in phosphoryl transfer reactions. Yet not all enzymes activated by monovalent cations catalyze phosphoryl transfers.

If the monovalent cations participate in the catalysis, as implied by Melchior and Lowenstein, then the interaction of these cations with the substrate and enzyme forming a ternary complex for the catalytic event is consistent with (i) a conformational change of the protein, (ii) a hyperbolic saturation for cation activation as is normally observed (*6*), and (iii) a characteristic pattern of the reactions catalyzed by these enzymes.

In this article I now present my examination of the literature on these enzymes which culminated in the elaboration of a characteristic pattern for reactions activated by monovalent cations. The intermediates for one of the substrates in monovalent cation activated enzyme catalyzed reactions have the structure



where X is O, N, or C and where Y is O or N. The converse of this statement is not true.

Table 1 is a compilation of the enzymes activated by monovalent cations (*7*). For convenience, the enzymes are divided into two main classes; phosphoryl transfer (class K-P) and elimination reactions (class K-E). Class K-P is also subdivided into three subclasses, A, B, and C.

Reactions Activated by Monovalent Cations

Class K-P. The phosphorylation of the oxygen in the grouping $R - C(=X) - OH$, where X is O, NH, or CH_2, is catalyzed by the enzymes in class K-P. In many cases a phosphorylated compound is not the final product; however, a carboxyl oxygen is transferred to inorganic or pyrophosphate as phosphoryl transfer proceeds (*8*).

Subclass A of class K-P includes reactions in which X is oxygen, for example, carboxyl phosphorylation. In cases where monovalent cation activation has not been reported (*9*), it is possible that monovalent cations, particularly NH^+_4, were present in assay solutions preventing the detection of activation.

Subclass B includes those reactions in

The author is a professor of biochemistry at Michigan State University, East Lansing. A preliminary account of this material was published as Abstract No. 56 of the Biological Chemistry Division of the American Chemical Society, 158th National Meeting, September 1969.

Table 1. Enzymes activated by monovalent cations. Abbreviations are: ATP, adenosine triphosphate; AMP, adenosine monophosphate; ADP, adenosine diphosphate; CoA, coenzyme A; GMP, guanosine monophosphate; IMP, inosine monophosphate; NAD, nicotinamide-adenine dinucleotide; NADP, nicotinamide-adenine dinucleotide phosphate; PEP, phosphoenolpyruvate. Systematic name and number for each enzyme was taken from list introduced by International Commission on Enzymes (*32*).

Enzyme	Biological source
Class K-P. Phosphorylation of $-C(=X)-OH$, *where X is O, NH, or* CH_2	
Subclass A. Phosphorylation of $-C(=O)-OH$	
ATP: Acetate phosphotransferase (E.C. 2.7.2.1)	Rumen microorganism (*33*)
ATP: L-Aspartate 4-phosphotransferase (E.C. 2.7.2.4)	*Bacillus polymyxa* (*34*), *Rhodopseudomonas spheroides* (*35*)
Acetate: CoA ligase (AMP) (E.C. 6.2.1.1)	Rat heart (*35*, *36*), rabbit heart (*37*)
D-Alanine: D-alanine ligase (ADP) (E.C. 6.3.2.4)	*Streptococcus faecalis* (*38*)
γ-L-Glutamyl-L-cysteine: glycine ligase (ADP) (E.C. 6.3.2.3)	Pigeon liver (*39*), *Saccharomyces cerevisiae* (*40*)
Succinate: CoA ligase (ADP) (E.C. 6.2.1.5)	Tobacco leaves (*41*)
L-Glutamate: L-cysteine γ-ligase (ADP) (E.C. 6.3.2.2)	*Phaseolus vulgaris* (seedlings) (*42*), *Triticum vulgare* (wheat germ) (*43*)
D-Pantoate: β-alanine ligase (AMP) (E.C. 6.3.2.1)	*Escherichia coli* (*44*)
Deamido-NAD: L-glutamine amido-ligase (AMP) (E.C. 6.3.5.1)	*S. cerevisiae* (*45*), rat liver (*45*)
Formate: tetrahydrofolate ligase (ADP) (E.C. 6.3.4.3)	Human erythrocytes (*46*), chicken liver (*46*), leukocytes (*47*), *Aerobacter aerogenes* (*48*), spinach leaves (*49*)
ATP: Carbamate phosphotransferase (E.C. 2.7.2.2)	*E. coli* (*50*), rat liver (*51*)
Propionyl-CoA: CO_2 ligase (ADP) (E.C. 6.4.1.3)	Bovine liver (*52*), pig heart (*53*)
L-Tyrosine: tRNA ligase (AMP) (E.C. 6.1.1.1)	Rat liver (*54*), pancreas (*55*)
L-Leucine: tRNA ligase (AMP) (E.C. 6.1.1.4)	*E. coli* (*56*)
L-Lysine: tRNA ligase (AMP) (E.C. 6.1.1.6)	*E. coli* (*57*)
Subclass B. Phosphorylation of $-C(=CH_2)-OH$	
ATP: Pyruvate phosphotransferase (E.C. 2.7.1.40)	Rabbit muscle (*58*), *Amia colva* (*58*) (enzyme in nine other marine organisms was activated by K^+), *Zea mays* (seed) (*59*), *Cucurbita pepo* (seed) (*60*), rat brain (*61*), yeast (*62*), mouse liver (*63*)
ATP: Oxalacetate decarboxylase (PEP) (*64*)	*Aspergillus niger* (*65*)
ATP: Pyruvate, phosphate phosphotransferase (AMP) (*64*)	*Bacteroides symbiosus* (*66*)
ATP: D-Fructose 1-phosphotransferase (E.C. 2.7.1.3)	Bovine liver (*67*)
ATP: D-Fructose-6-phosphate 1-phosphotransferase (E.C. 2.7.1.11)	Rabbit muscle (*68*), yeast (*69*), sheep brain (*70*), rat brain (*71*), slime mold (*72*)
Subclass C. Phosphorylation of $-N=C(-OH)-$	
5′-Phosphoribosyl-formylglycineamide: L-glutamine amido-ligase (ADP) (E.C. 6.3.5.3)	Pigeon liver (*73*)
Class K-E. Elimination reactions	
Tryptophanase (E.C. 4.2.1.e)	*E. coli* (*74*)
L-Serine hydro-lyase (adding indole) (E.C. 4.2.1.20)	*Bacillus subtilis* (*75*)
L-Serine hydro-lyase (deaminating) (E.C. 4.2.1.13)	Rat liver (*76*), *E. coli* (*77*)
L-Threonine hydro-lyase (deaminating) (E.C. 4.2.1.16)	Sheep liver (*76*), yeast (*78*)
5-Aminolevulinate hydro-lyase (adding 5-aminolevulinate and cyclizing (E.C. 4.2.1.24)	*Rhodopseudomonas spheroides* (*79*)
Propanediol hydro-lyase (E.C. 4.2.1.28)	*A. aerogenes* (*80*)
Ethanolamine ammonia-lyase (*64*)	*Clostridium* (*81*)
Glycerol hydro-lyase (*64*)	*Lactobacillus 208A* (*82*)
L-*threo*-3-Methylaspartate ammonia-lyase (E.C. 4.3.1.2)	*Clostridium tetanomorphum* (*16*)
5-Formiminotetrahydrofolate ammonia-lyase (cyclizing) (E.C. 4.3.1.4)	Rat liver (*83*)
Fructose-1,6-diphosphate D-glyceraldehyde-3-phosphate-lyase (class II) (E.C. 4.1.2.13)	*S. cerevisiae* (*84*), *Euglena gracilis* (*85*), 25 species of bacteria (*86*)
L-Rhamnulose 1-phosphate L-lactaldehydelyase (E.C. 4.2.1b)	*E. coli* (*87*)
S-Adenosylmethionine alkyltransferase (cyclizing) (E.C. 2.5.1.4)	Rabbit liver (*88*), Baker's yeast (*88*)
Aldehyde: NAD(P) oxidoreductase (E.C. 1.2.1.5.)	*S. cerevisiae* (*89*)
D-Glucose-6-phosphate: NAD oxidoreductase (cyclizing) (D-myoinositol) (*64*)	Yeast (*90*)
Glycerol: NAD oxidoreductase (E.C. 1.1.1.6)	*A. aerogenes* (*91*)
Tartrate: NAD oxidoreductase (*64*)	*Pseudomonas putida* (*92*)
L-Threonine: NAD oxidoreductase (decarboxylating) (E.C. 1.1.1.d)	*Staphylococcus aureus* (*93*)
L-Malate: NAD oxidoreductase (decarboxylating) (E.C. 1.1.1.38)	*Lactobacillus arabinosus* (*94*)
D-Malate: NAD(P) oxidoreductase (decarboxylating) (*64*)	*E. coli* (*95*)
L-Homoserine: NAD(P) oxidoreductase (E.C. 1.1.1.3)	*E. coli* (*96*)
IMP: NAD Oxidoreductase (E.C. 1.2.1.14)	*A. aerogenes* (*97*)
5,10-Methylenetetrahydrofolate: NADP oxidoreductase (E.C. 1.5.1.5)	Baker's yeast (*98*)
Unclassified	
ATP: Protein phosphotransferase (E.C. 2.7.1.37)	Brain (*99*)
Orthophosphoric diester phosphohydrolase (E.C. 3.1.4.1)	*E. coli* (*100*)
Carbamyl phosphate (acetyl phosphate): phosphohydrolase (*64*)	Guinea-pig kidney cortex (*101*), guinea-pig brain microsomes (*102*)
ATP: Phosphohydrolase (E.C. 3.6.1.3)	Muscle (*103*), human erythrocyte membranes (*104*)
5,6,7,8-Tetrahydrofolate: NADP oxidoreductase (E.C. 1.5.1.3)	Guinea pig liver (*105*), mouse leukemia cells (*105*), carcinoma cells (*105*)
AMP Aminohydrolase (E.C. 3.5.4.6)	Bovine brain (*106*), rabbit muscle (*107*)
5′-Phosphoribosyl-5-formamido-4-imidazolecarboxamide: tetrahydrofolate 10-formyltransferase (E.C. 2.1.2.3)	Pigeon liver (*108*), chicken liver (*108*)
Acetyl-CoA: orthophosphate acetyltransferase (E.C. 2.3.1.8)	*Clostridium kluyveri* (*109*)
Nucleosidetriphosphate: RNA nucleotidyltransferase (E.C. 2.7.7.6)	*Bacillus stearothermophilus* (*110*)
Peptidase (ribosomal)	*E. coli* (*111*)
Amino acid active transport system	Chicken myocardium (*11*)
Amino acid polymerase (ribosomal)	*E. coli* (*112*)
Adenyl cyclase	Brain (*12*)
Starch synthetase (particulate)	*Zea mays* (seeds) (*113*), *Pisum sativum* (seeds), *Phaseolus vulgaris* (seeds), *Triticum aestivum* (seeds), *Glycine max.* (seeds), *Solanum tuberosum* (tubers)
ATP : GMP Phosphotransferase (E.C. 2.7.4.8)	*E. coli* (*114*)

which X is carbon. Pyruvate kinase obviously should be included here. Enzymes catalyzing the phosphorylation of fructose at the 1 position are included if the configuration of the substrate undergoing phosphorylation is envisaged in the linear form with the carbonyl oxygen in the enol configuration or in the furanose ring configuration (*10–12*).

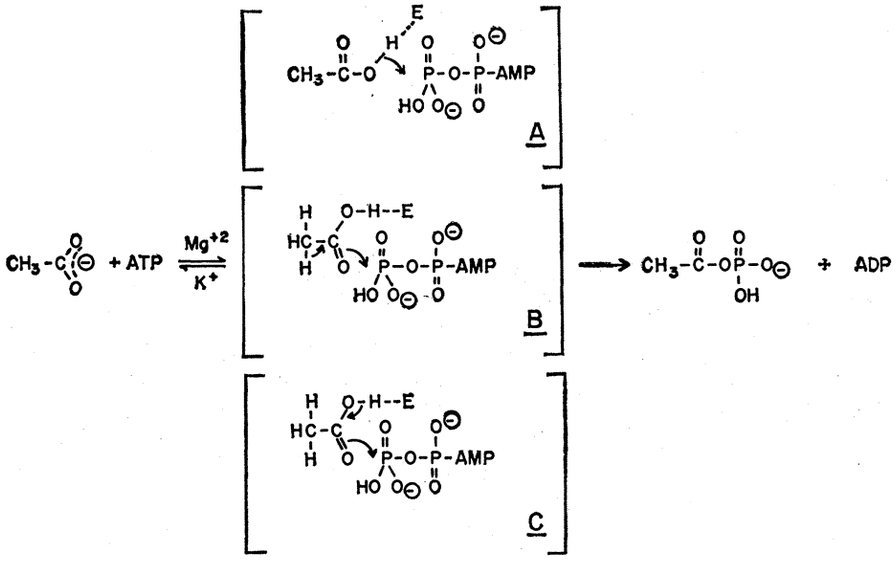


Fig. 1. Three schematic representations of mechanisms for reaction catalyzed by acetokinase. The E denotes an enzyme functional group.

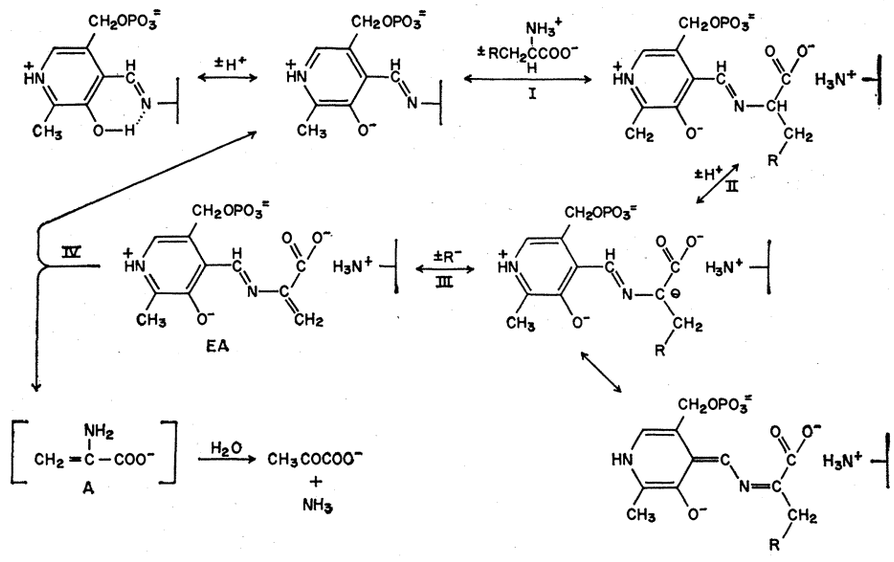
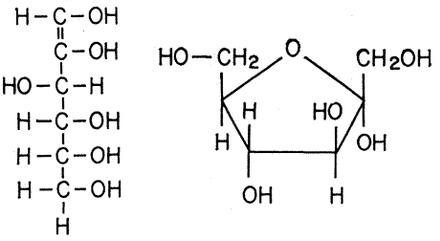


Fig. 2. Schematic representation of mechanism for the reaction catalyzed by tryptophanase (*14*).

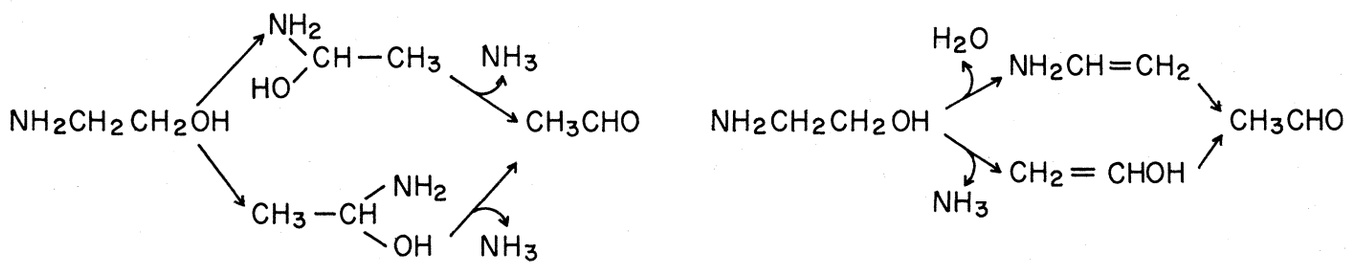


Subclass C is that group of enzymes catalyzing the phosphorylation of R—C(=N—R)—OH, the configuration of the group in *N*-formyl glycinamide ribonucleotide undergoing transient phosphorylation in the synthesis of *N*-formylglycinamidine ribonucleotide.

The phosphorylation of a carboxyl group (subclass A) may be portrayed in a number of schemes as shown with acetokinase (Fig. 1). Mechanism B, distinguishable from mechanism A and C with respect to the projected hydrogen exchange at the α carbon, is similar to the exchange of hydrogens observed at the β carbon of pyruvate catalyzed by pyruvate kinase in the absence of net reaction (*13*).

Class K-E. This class, representing a group of elimination reactions not involving phosphoryl transfer, has not been divided into subclasses because each reaction involves either —C=C(—OH)— or —C=C(—NH_2)— in the transition between reactants and products. Many of the enzymes in this class also require cofactors, such as pyridoxal phosphate, cobalamines, nicotinamide-adenine dinucleotide (NAD), or divalent metals.

The mechanism of the first reaction listed in class K-E, catalyzed by the pyridoxal enzyme tryptophanase, has previously been proposed as noted in Fig. 2 (*14*). Monovalent cation might be expected to interact with the enzyme bound α-aminoacrylate (EA), because this is a key reaction in the pyridoxal-dependent elimination reactions (*14*). Analogous structures can be written for threonine dehydrase, serine dehydrase, and tryptophan synthetase. δ-Aminolevulinic dehydratase is not a pyridoxal-containing enzyme; yet the mechanism



Figs. 3 (left) and 4 (right). Alternate mechanisms suggested for ethanolamine deaminase catalysis (*15*).

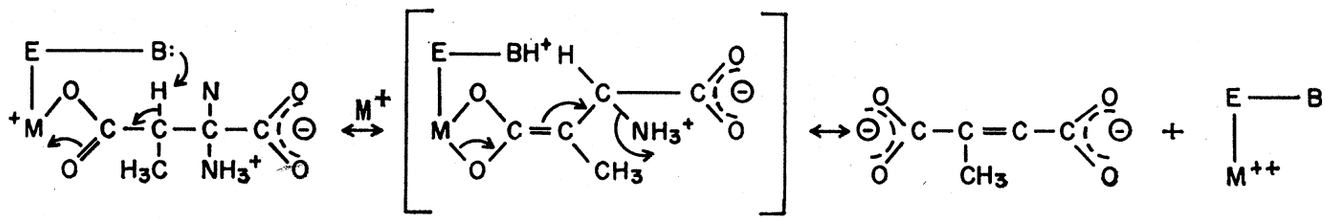


Fig. 5. Schematic for reaction catalyzed by β-methylaspartase (*16*).

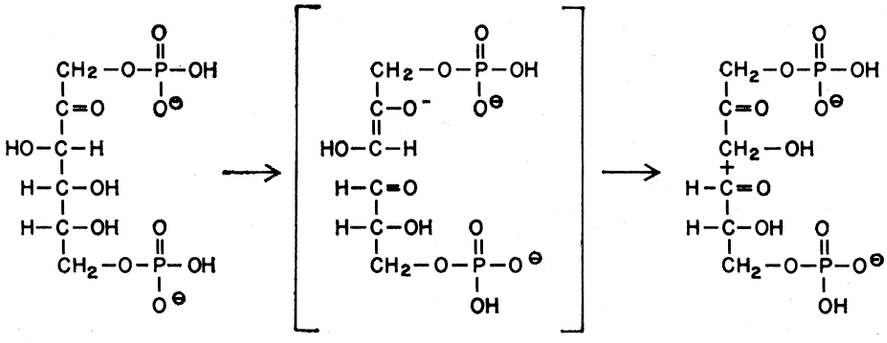


Fig. 6. Aldolytic cleavage of fructose-1,6-diphosphate depicting carbanion intermediate of dihydroxy acetone phosphate.

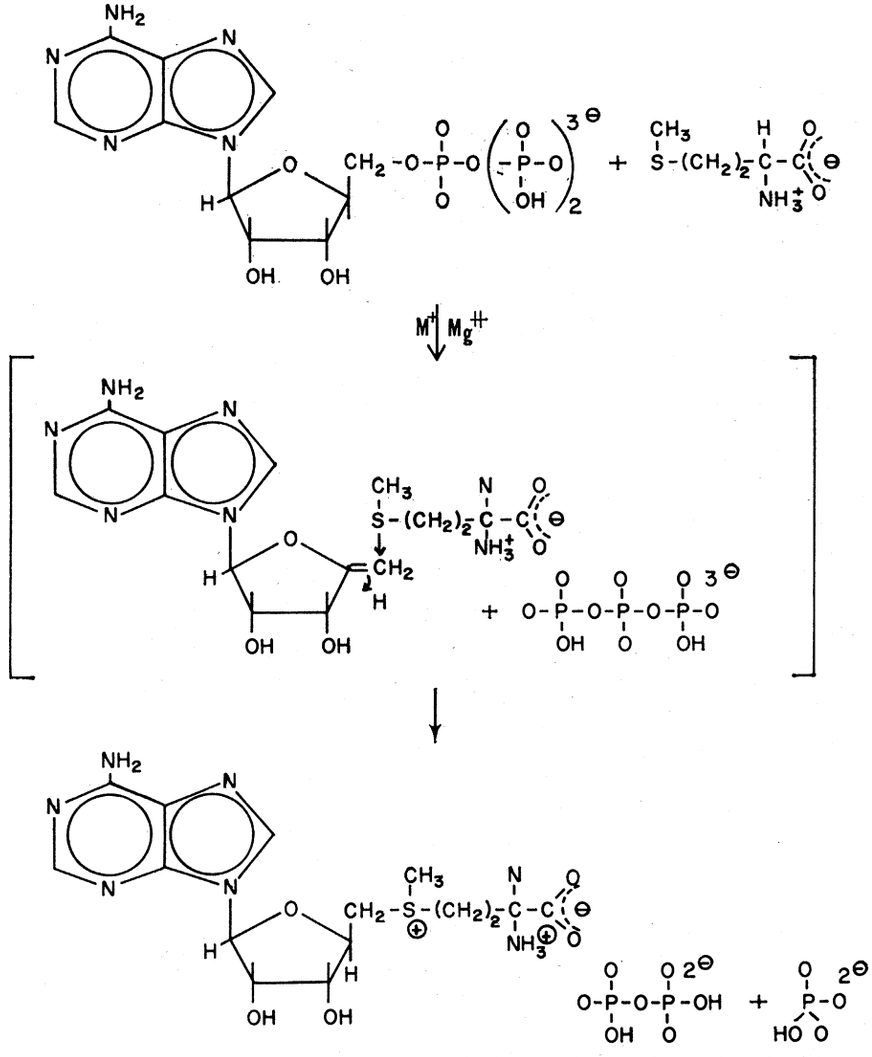


Fig. 7. Reaction catalyzed by *S*-adenosylmethionine synthetase depicted with a hypothetical intermediate.

can proceed with the same enol-keto intermediates.

Of the two alternate mechanisms (Figs. 3 and 4) previously suggested by Babior and Li (*15*) for ethanolamine deaminase and applicable to glycerol dehydrase and 1,2-propanediol dehydrase, the mechanism depicted by Fig. 4 is consistent with the pattern of monovalent cation–activated systems.

The mechanism for β-methylaspartase (Fig. 5) previously shown by Bright (*16*) portrays an intermediate with an enol-keto tautomer.

Fructose-1,6-diphosphate aldolase (class II aldolase) catalyzes the aldolytic cleavage of fructose-1,6-phosphate by a mechanism somewhat analogous to the class I aldolase (*17*) except the formation of the carbanion intermediate of dihydroxy acetone phosphate (Fig. 6) with the enol-keto tautomer is enhanced by potassium in the class II enzymes (*18*) and by the Schiff base in the class I systems (*19*).

The mechanism of *S*-adenosylmethionine synthetase is envisaged in Fig. 7 with an enol-keto tautomer in the hypothetical intermediate.

The mechanism of glucose-6-phosphate D-myoinositol-1-phosphate cyclase (Fig. 8) is supported by the deuterium exchange observed at carbon-6 of glucose-6-phosphate (*20*). Tartrate dehydrogenase catalyzes the reaction in Fig. 9. The final product with the enol-keto tautomer is depicted as dihydroxy fumarate since this is the thermodynamically more stable form in solution (*21*). Mechanisms for L-threonine dehydrogenase and malic enzyme (*22*) depicted in Fig. 10 contain the enol-keto configuration in the intermediate.

A proposed but admittedly tentative mechanism of the reaction catalyzed by glycerol dehydrogenase is shown in Fig. 11. The intermediate resembles that already suggested for class II fructose-1,6-diphosphate aldolase, tartrate dehydrogenase, and is consistent with the mechanism of glucose-6-phosphate D-myoinositol-1-phosphate cyclase catalysis (*20*) in that a proton exchange is predicted at carbon-1.

While the reaction catalyzed by 5,10-

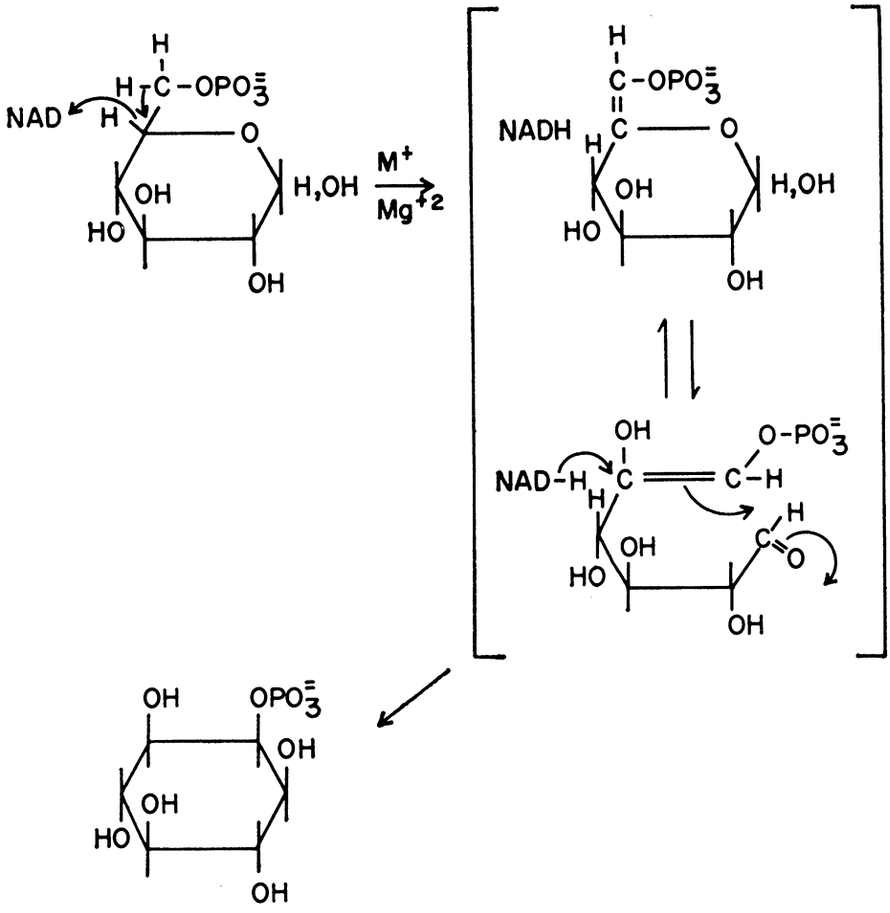


Fig. 8. Representation of reaction catalyzed by glucose 6-phosphate D-myoinositol 1-phosphate cyclase.

methylenetetrahydrofolic dehydrogenase yielding 5,10-methenyltetrahydrofolate (Fig. 12) with the enol-keto tautomer in the product is consistent with the scheme, the mechanisms of reactions catalyzed by acetaldehyde dehydrogenase, inosine-5'-phosphate dehydrogenase, and homoserine dehydrogenase are not as clear; it does not seem necessary to predict mechanisms at this stage.

Finally, several enzymes remain in an unclassified group because of insufficient data. These include ribosome-catalyzed peptidyl transfer (amino acid polymerization), several K^+-activated phosphatases and phosphodiesterases, phosvitin kinase, and adenosine monophosphate (AMP) deaminase. Some of these, for instance those involving phosphate cleavage or ester formation, might be placed in one subclass of class K-P. Others such as AMP deaminase might be considered in a class K-E or yet a third class.

Patterns of Monovalent Cation Activation

The enol-keto configuration of a portion of one substrate of a reaction activated by a monovalent cation is consistent for those reactions in which data are available. In cases where data are not available, reasonable mechanisms consistent with the pattern are presented.

In practical terms the pattern suggests that (i) phosphorylation of a carboxyl group or enolate anion, (ii) eliminations leading to the enol-keto tautomer, and (iii) other reactions in which the enol-keto tautomer is an intermediate or potential intermediate are candidates for monovalent cation activation. Monovalent cation activation is also conserved in an evolutionary sense (Table 1). For example, pyruvate kinase isolated from many organisms spanning the evolutionary scale still retains the activation requirement. In certain cases, for example, fructose-1,6-diphosphate aldolase, an alternate mechanism has evolved. Perhaps as already implied by Rutter (*17*), alternative mechanisms for other enzyme reactions activated by monovalent cations may have evolved and thus the evolutionary conservation for monovalent cation activation noted above will appear to have been lost. In any case, the observed conservation is consistent with a unique role for monovalent cations in the catalysis.

Role of Monovalent Cation

While it is not my intention to define a precise role of monovalent cations in enzyme catalysis, certain data related to other aspects of the activation are pertinent. Compounds which bind monovalent cations also contain a potential

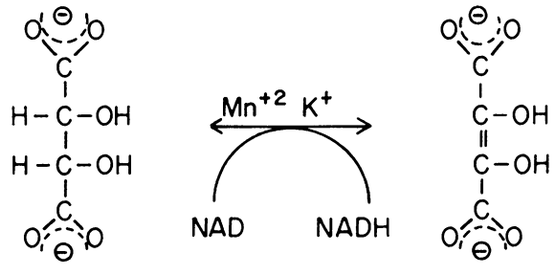
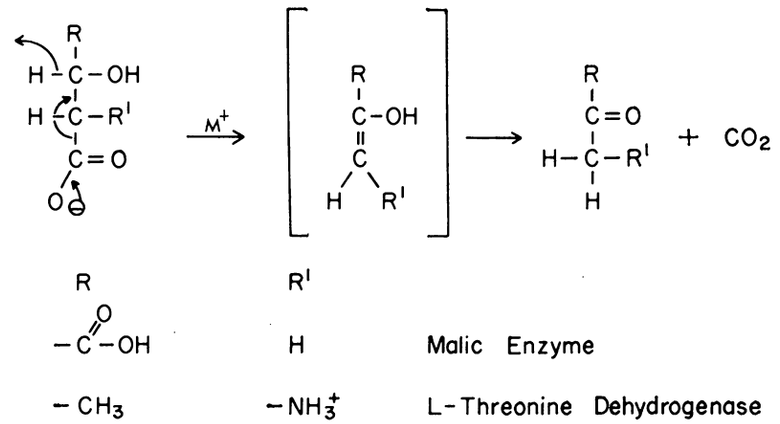


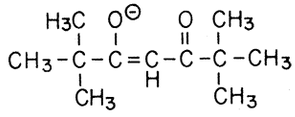
Fig. 9 (above). Reaction catalyzed by tartrate dehydrogenase.



R	R'	
$-C(=O)-OH$	H	Malic Enzyme
$-CH_3$	$-NH_3^+$	L-Threonine Dehydrogenase

Fig. 10 (right). Generalized mechanism for reactions catalyzed by malic enzyme and threonine dehydrogenase (*22*).

enol-keto tautomer. Guter and Hammond (*23*) reported complexation of Li^+ by the dipivaloylmethane anion.



Dipivaloylmethane anion

The x-ray crystallographic structure of the K^+ complex with nonactin, a macrotetrolide antibiotic, showed (*24*) that the 32-membered ring structure (Fig. 13) complexes K^+ by the four oxygen atoms from the furan ring and the four keto oxygen atoms. A large number of other compounds with peptide and ester linkages also show a high degree of monovalent cation specificity (*25*). Kohn and Furda (*26*) showed that the binding of Ca^{2+} and K^+ to pectins is strongly dependent on methylation—that is, when the degree of methylation of the carboxyl groups of pectin exceeds 80 percent, K^+ is preferentially bound over Ca^{2+}. These data are consistent with the participation of the peptide backbone of proteins in the binding of monovalent cations. The enzyme–monovalent cation complex might then be completed by the interaction of the enolate or potential enolate transition state of the substrate in the enzyme catalyzed reaction. Klotz (*27*) has already indicated an analogous role for divalent cations in esterases and peptidases. Perhaps the monovalent cations act as a bridge between the enzyme and the substrate, which in principle may be similar to the pyruvate kinase–Mn^{2+}–phosphoenolpyruvate bridge structure demonstrated by Mildvan *et al.* (*28*). The bridge between the monovalent cation, enzyme, and substrate is strengthened by the observation of Ruben and Kayne (*29*) that Tl^+ is bound within 5 to 7 Å of Mn^{2+} in pyruvate kinase. These bridge structures may be important in the mediation of substrate synergism as discussed by Bridger *et al.* (*30*), or in homosterism suggested by McElroy *et al.* (*31*) when these cations are involved in the systems discussed by them.

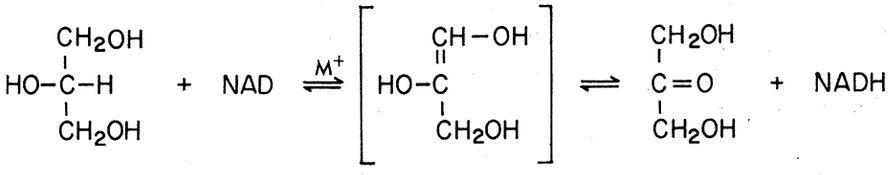


Fig. 11. Reaction catalyzed by monovalent cation activated glycerol dehydrogenase depicted with a hypothetical intermediate.

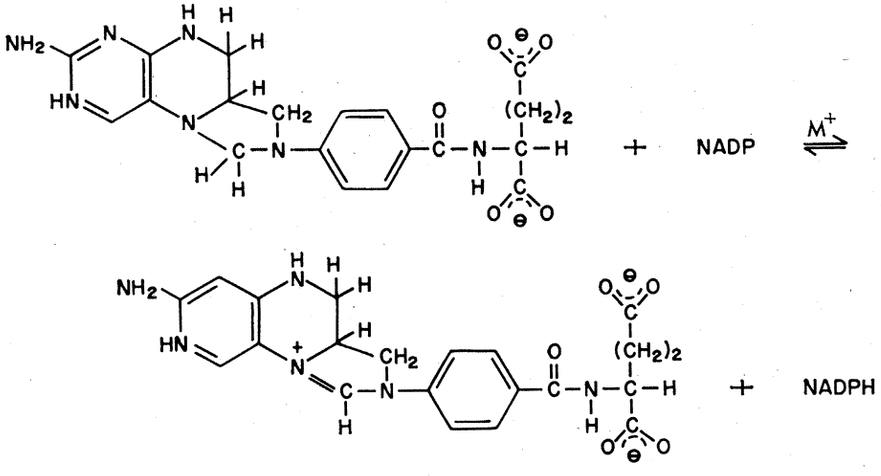


Fig. 12. Reaction catalyzed by 5,10-methylenetetrahydrofolic dehydrogenase.

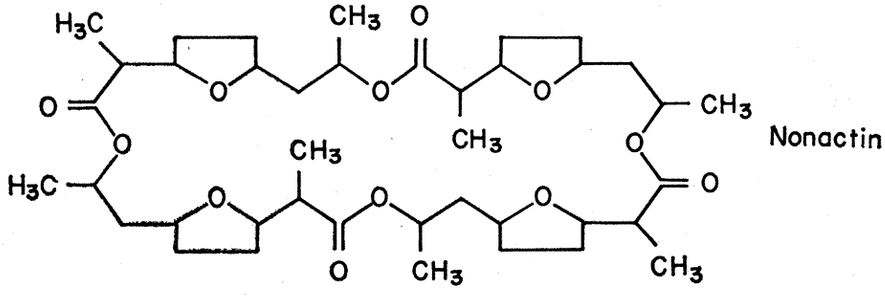


Fig. 13

Summary

The data from reactions catalyzed by enzymes activated by monovalent cations are consistent with a unique interaction of monovalent cation with the substrate and enzyme to form a functional ternary complex. While this complex cannot as yet be uniquely defined, the pattern of activation suggests that (i) phosphorylation of a carboxyl group or enolate anion, (ii) eliminations resulting in an enol-keto tautomer, and (iii) other reactions in which an enol-keto tautomer or a potential enol-keto tautomer can be considered as a logical intermediate in the hypothetical sequence of events between reactants and products are candidates for monovalent cation activation.

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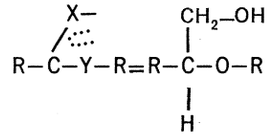
10. In the furanose ring configuration, position 1 has the same relation to the ring oxygen as position 3′ of a nucleoside triphosphate, the phosphorylation of which is also activated by monovalent cations (*11*, *12*). The latter configuration in which



would also be consistent with the monovalent cation activation of the phosphorylation of fructose-1-phosphate catalyzed by fructose-1-phosphate kinase (V. Sapico and R. L. Anderson, private communication). These hemiacetals, hemiketals, and perhaps the acetals and ketals might be considered as potential enol-keto tautomers.
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