The Allosteric Regulation of Hexokinase C from Amphibian Liver*

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A type C hexokinase (ATP:d-hexose-6-phosphotransferase, EC 2.7.1.1) was partially purified from the liver of the frog Calyptocephalella caudiverbera. The enzyme is inhibited by glucose levels in the range of normal blood sugar concentrations. The extent of the inhibition by glucose depends on the concentration of ATP, being most marked between 1 and 5 mM ATP. Fructose, although a substrate, was not inhibitory of its own phosphorylation.

The inhibitory effect of high glucose levels exhibited a strong, reversible pH dependence being most marked at pH 6.5. At pH 7.5 the inhibition by high glucose levels was a function of the enzyme concentration, the effect being stronger at high enzyme concentrations, whereas no inhibition was observed when assaying very diluted preparations. At all enzyme concentrations studied, high levels of glucose caused no inhibition at pH 8.5, whereas at pH 6.5 strong inhibition was always observed.

Short times of photooxidation of hexokinase C as well as incubation with low concentrations of p-chloromercuribenzoate resulted in the loss of the inhibition by excess of glucose.

Glucose 6-phosphate was found to be a strong inhibitor of hexokinase C but only at high glucose levels. The inhibitory effect of glucose-6-P follows sigmoidal kinetics at low (about 0.02 mM) glucose concentrations, the Hill coefficient being 2.3. The kinetics of the inhibition became hyperbolic at high (>0.2 mM) glucose levels.

These results suggest that the inhibition of hexokinase C by excess glucose is due to the interaction of glucose with a second, aldose-specific, regulatory site on the enzyme. The modification of the inhibitory effect by ATP, glucose-6-P, enzyme concentration, and pH, all of them at physiological levels, indicates a major role for hexokinase C in the regulation of glucose utilization by the liver.

The ATP-dependent phosphorylation of glucose in vertebrates is catalyzed by four isozymes named hexokinases A, B, C, and D, (ATP:d-hexose-6-phosphotransferases, EC 2.7.1.1). Their kinetic and physicochemical properties, tissue distribution, phylogenetic, developmental, and adaptive behavior have been studied with some detail (for reviews see Refs. 1 to 6).

One of the four glucose phosphotransferases, hexokinase C,1 was found to be inhibited by its own substrate (7-9). Since the inhibition occurs in the normal range of blood sugar concentrations this property may be considered as a regulatory mechanism probably involved in the channeling of glucose to the several pathways starting at the glucose-6-P crossroad. The “antiparallel” behavior of hexokinase D, i.e. the fact that its velocity increases precisely at the same sugar concentrations (Km for glucose = 6 mM), supports the notion that the inhibition by glucose of hexokinase C is relevant to the control of sugar utilization.

Further work on the regulation of hexokinase C activity has not progressed because it is present in very low amounts in rodent liver. Recently however, a major hexokinase presenting the same inhibition feature of rat hexokinase C has been found in the liver of some anurans.1 This work describes the partial purification of this isozyme and the study of the substrate inhibition. The data obtained suggest the existence of two catalytically different forms of hexokinase C (inhibited and uninhibited forms), the interconversion of which can be brought about by several physiological factors, indicating that this isozyme is a major regulatory entity in the hepatic utilization of glucose.


*This work was supported by Grant 70A from the Servicio de Desarrollo Científico y Creativo Artistico, Universidad de Chile, and by the Multinational Project on Biochemistry, Chile, of the Organization of American States.

1 A logical nomenclature for the hexokinase isozyme system awaits further knowledge of the structural basis of the isozymes. We have dealt with this problem elsewhere (1) proposing the provisional names hexokinase C for the isozyme inhibited by excess glucose, and hexokinase D (the so-called glucokinase) for the isozyme with a high Km (~6 mM) for glucose, irrespective of their chromatographic or electrophoretic mobilities, or the number of isozymes actually found in a given tissue or organism. Hexokinase A and hexokinase B are those isozymes eluting in the first and second position of the DEAE cellulose chromatograms, respectively, provided they are not inhibited by excess glucose or do not have a high Km for glucose.
Animals—An endemic Chilean leptodactylid frog, *Calyptocephalella caudiverbera* (— *Caudiverbera caudiverbera*) (10), was used throughout this study. The frogs were caught in the vicinities of Santiago and maintained in aquaria with cold tap water.

**Enzyme Preparation**—The frogs were killed by decapitation without anesthesia, thoroughly bled, and the liver excised and weighed. All further operations were performed at 0-4°C unless otherwise stated. The pooled livers were finely minced with scissors and squeezed through a Harvard tissue press. The 50% homogenate (w/v) were prepared using a Potter-Elvehjem apparatus in a medium containing 0.01 M Tris-HCl (pH 7), 0.001 M EDTA (Tris buffer). The homogenates were centrifuged at 105,000 × g for 60 min in a Spinco ultracentrifuge. The supernatant liquid was then chromatographed in a DEAE-cellulose column equilibrated with the Tris buffer and the glucose-phosphorylating isozymes eluted with a linear gradient from 0 to 0.5 M KCl in the same buffer (8). The procedure can be performed with as little as 500 mg of liver or scaled up to 100 g of material. The active fractions obtained from the columns were concentrated by the addition of moist DEAE-cellulose to the dialyzed enzyme solution until all the activity was retained by the resin. After addition of a small amount of 0.5 M KCl in Tris buffer the eluted activity was recovered by filtration.

**Enzyme Assay**—Hexokinase activity was measured by either of the following two procedures: Method a is measurement of glucose-6-P formation by coupling the phosphotransferase reaction with NADP and glucose-6-P dehydrogenase (11). NADPH formation at 30°C was followed spectrophotometrically at 340 nm in a medium containing (final concentrations): 10 mM KCl, 100 mM Tris-HCl buffer (pH 7.5), 0.5 mM NADP, 0.2 i.u. of glucose-6-P dehydrogenase, substrates, and enzyme in a final volume of 0.5 ml. When fructose was used as a substrate, measurement of glucose-6-P was accomplished by the addition of 1 i.u. of phosphoglucose isomerase. Blanks with ATP or glucose omitted were routinely run. Method b is that measurement of ADP formation made by coupling the phosphotransferase reaction to pyruvate kinase and lactate dehydrogenase (8). NADH oxidation at 30°C was followed spectrophotometrically at 340 nm in a medium containing (final concentrations): 10 mM KCl, 100 mM Tris-HCl buffer (pH 7.5), 0.5 mM NADH, 1 i.u. of lactate dehydrogenase (containing pyruvate kinase), 2.5 mM phosphoenolpyruvate, substrates, and enzyme in a final volume of 0.5 ml. A similar system with sugar omitted was used as a blank. Modifications of these standard assay mixtures are indicated on the figures. The concentration of Mg**2+** was adjusted in each case according to the ATP concentration, so that a level of free divalent ion of 1 mM was always present. The metal ion was added as the chloride salt. A Gilford spectrophotometer model 2400 with thermospacers was used. Full scale sensitivities of 0.25 to 0.5 optical density units and chart speeds from 1 to 4 inches per min were used. One unit of hexokinase activity is that amount of enzyme that would catalyze the phosphorylation of 1 nmol of glucose/min at 30°C. Specific activity is defined as units/mg of protein. Protein was measured by the method of Lowry (12) using bovine serum albumin as standard.

**Materials**—ATP, NADP, NADH, diithiothreitol, Hepes, Mes, Bicine, phosphoglucose isomerase, lactate dehydrogenase (containing pyruvate kinase), and glucose-6-P were the products of Sigma Chemical Co. Glucose-6-P dehydrogenase and phosphoenolpyruvate (cyclohexylaminium salt) were supplied by Boehringer. DEAE-cellulose (DE52) was from Whatman. All other reagents were of the highest purity commercially available.

**RESULTS**

**Hexokinase C Purification**—A typical chromatographic separation of the isozymes catalyzing glucose phosphorylation in frog liver is illustrated in Fig. 1. The first hexokinase elutes at about 0.12 M KCl and is inhibited by excess glucose. This isozyme is often contaminated with a small amount of a low K**m** hexokinase eluting at 0.15 M KCl. A high K**m** glucose phosphotransferase elutes off the column at 0.22 M KCl and has been characterized as a typical isozyme D similar, although not identical, to the well known glucokinase of rodent liver. Fractions containing the enzyme inhibited by excess glucose, hereafter referred to as hexokinase C, were pooled, concentrated, and rechromatographed, after dialysis, in DEAE-cellulose columns to remove the small amount of hexokinase not inhibited by excess glucose. After rechromatography the specific activity of the pooled fractions was usually 6 units/mg of protein. The enzyme preparations at this stage are reasonably stable when stored at 0-4°C. Further attempts to purify the isozyme using ammonium sulfate fractionation and hydroxylapatite chromatography led to the partial loss of activity. It is not possible to state yields and extent of purification of the preparations of hexokinase C used in this study since, due to the peculiar kinetic features of the two major isozymes present, their proportions cannot be estimated in crude extracts with any certainty. We believe that our preparations represent about 50- to 100-fold enrichment over the homogenates with yields near 100%.

In some individuals, the enzyme as isolated by DEAE-cellulose chromatography did not show inhibition by excess substrate. In those cases no relationship could be established with respect to age (weight), site of capture, sex, or nutritional state of the animals. As the phenomenon occurs more frequently during springtime, a circannual rhythm may be involved, but the correlation awaits further observations.

**Effect of Hexose Concentration**—The most conspicuous kinetic feature of hexokinase C is the decrease of its velocity of glucose phosphorylation at high levels of glucose (Fig. 2). Other substrates, such as mannose, 2-deoxyglucose, and galactose (data not shown), were also inhibitors of their own phosphorylation. Maximal inhibition was observed at about 10 mM aldose and was usually not more than 50% of the observed maximal velocity. Higher sugar levels (up to 200 mM) did not result in stronger inhibition. The maximal activity was observed at about 0.2 to 0.5 mM glucose dependence on the conditions of the assay (see below). Fructose was not inhibitory of its own phosphorylation at any level up to 100 mM (Fig. 2).
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A theoretical saturation curve for glucose phosphorylation was calculated using the velocity values obtained at very low, presumably noninhibitory, substrate concentrations (Fig. 2). This curve shows that the theoretical $V_{\text{max}}$ for aldoses is the same as the one observed experimentally using fructose as substrate. The apparent Michaelis constant for glucose was 0.056 mM while the $K_m$ value for fructose was 1.35 mM.

**Effect of ATP Concentration**—Fig. 3 shows the effect of varying ATP concentrations on the velocity of hexokinase C measured at three fixed levels of glucose: 0.02 mM, a low, noninhibitory concentration; 0.2 mM, a glucose concentration at which the highest velocity is obtained (see Fig. 2); and 100 mM, a high inhibitory level. Nonlinear double reciprocal plots were observed in all cases (Fig. 3, lower left). Hill plots of the same data are also shown in Fig. 3 (lower right). Hill coefficient values ($n_H$) of about 1.4 were calculated at 100 and 0.2 mM glucose. On the other hand, at the lowest glucose level (0.02 mM) a $n_H$ value of 0.6 was found. Other nucleoside triphosphates (GTP, CTP, ITP, TTP) were not phosphoryl donors (data not shown).

The inhibition by high levels of glucose was found to be dependent on the ATP concentration, being substantially decreased at high levels (10 to 25 mM) of the phosphoryl donor (Fig. 4). At low glucose concentrations (up to 0.1 mM) the variation of ATP levels from 5 to 25 mM had only a marginal effect on the velocity of the reaction (Fig. 4). No inhibition by high fructose concentrations was observed even when using very low ATP levels (not shown).

**Inhibition by Glucose-6-P**—As it happens with most hexokinases, glucose-6-P was found to be a strong inhibitor of hexokinase C activity (Fig. 5). However, at very low glucose concentrations almost no effect was observed, the inhibitory action being most marked at high glucose concentrations. Also, the substrate concentration at which the highest velocity was observed diminished as the glucose-6-P concentration increased.

Fig. 6, left, shows the effect of varying the glucose-6-P concentration at several fixed levels of glucose. At glucose levels of 0.2 mM or higher, the inhibition follows an hyperbolic curve whereas at lower concentrations of glucose the inhibition becomes progressively sigmoidal. Hill plots of the data (Fig. 6, right) show $n_H$ values ranging from 1 at 0.2 mM or higher glucose concentrations, to 2.3 at 0.02 and 0.01 mM glucose.

The effect of varying the ATP concentration in the absence or presence of fixed levels of glucose-6-P on the velocity of the reaction at 0.2 mM glucose is presented in Fig. 6. Nonlinear
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Fig. 5. Hexokinase C activity as a function of glucose concentration in the absence or presence of glucose-6-P. ATP concentrations were 5 mM. Velocities were measured at pH 7.5 using Method b and are expressed as units/ml of enzyme preparation.

Fig. 6. The effect of glucose-6-P concentration on the activity of hexokinase C at several fixed concentrations of glucose. ATP levels were 5 mM. Velocities were measured at pH 7.5 using Method b and are expressed at left as the percentage of inhibition. The same data are shown at right as a Hill plot. $V_\text{m}$, velocity in the absence of glucose-6-P; $v_n$, velocities at the indicated glucose-6-P concentrations.

Fig. 7. Hexokinase C activity as a function of ATP concentration in the absence or presence of glucose-6-P. Glucose level was 0.2 mM. Velocities were measured at pH 7.5 by Method b and are expressed as units/ml of enzyme preparation. Left, direct plot; right, double reciprocal plot of the same data.

Fig. 8. Hexokinase C activity as a function of pH. ATP levels were 5 mM. Velocities were measured with Method a at two glucose levels: 10 mM (closed symbols) and 0.2 mM (open symbols). Buffers used were: Mes (♀, ♀), Heps (♂, ♂), and Bicine (○, ■). The same data is expressed in the inset as the ratio of the velocities measured at the high (♀) and low (♂) glucose concentrations.

Fig. 9. Hexokinase C activity as a function of glucose levels at four fixed pH values. ATP concentrations were 5 mM. Velocities were measured by Method a and expressed as the percentage of the maximal velocity at each pH value.

double reciprocal plots were observed in all cases (Fig. 7, right).

Dependence of Activity on pH—The phosphorylation of glucose by hexokinase C was tested at different hydrogen ion concentrations at 0.2 and 10 mM glucose (Fig. 8). Maximal enzyme activity was found between pH 8 and 9. The ratio of the velocities obtained at the high and low glucose levels varied markedly according to the pH of the assay medium. At pH values between 5.8 and 6.6 a ratio of 0.5 was observed indicating a strong inhibition by glucose whereas from pH 7.8 to 9.0 no inhibition could be seen, i.e., the high to low level of glucose ratio was about unity (Fig. 8, inset). These results suggest a pH-dependent transition from an enzyme form susceptible to inhibition by glucose to a form insensitive to that effect. To further explore this point, the effect of varying glucose concentration was measured at four different pH values (Fig. 9). The results are expressed as the percentage of the highest velocity observed at each pH value, and show the expected marked inhibition by excess of glucose at pH 6.5 and no inhibition at pH 9.4. Intermediate behavior was observed at pH values of 7.5 and 8.7. Also, a gradual increase of both the glucose concentration at which the highest activity is obtained and of the apparent $K_m$ value were observed as the pH values
changed to the alkaline side. The pH effect is reversible and occurs with no detectable lag (Fig. 10). No inhibition by high fructose concentrations was observed when using fructose as substrate at pH 6.5.

**Influence of Enzyme Concentration**—At pH 7.5 a marked effect of the enzyme concentration on the high to low ratio was observed (Fig. 11). At high enzyme concentrations the inhibition by glucose was marked (high to low ~0.5) but almost nonexistent (high to low ~1) at low enzyme levels. This dependence was seen neither at pH 8.5, value at which no inhibition was observed at any enzyme concentration, nor at pH 6.5, value at which the inhibition remained constant (Fig. 11).

**Effect of Photooxidation**—Illumination in the presence of methylene blue for variable periods of time (13) was performed at pH 7 (Fig. 12). The enzyme was assayed afterward at pH 6.5 at the high and low glucose concentrations. The inhibition by excess glucose became less pronounced as the time of photooxidation increased, reaching a high to low ratio of unity after 15 min (Fig. 13, inset). This was due mainly to a marked increase of the velocity measured at 10 mM glucose. No effect was observed on the enzyme illuminated in the absence of methylene blue, or on the enzyme treated with methylene blue but not illuminated.

**Effect of p-Chloromercuribenzenesulfonic acid**—The presence of varying amounts of pCMB (Fig. 13) did not affect the velocities of hexokinase C measured at 0.2 mM glucose except at very high concentrations of the sulfhydryl-reducing agent (>25 nmol). On the other hand, low pCMB levels (10 to 30 nmol) increased the activities measured at 10 mM glucose therefore raising the high to low ratio toward unity (Fig. 13, inset). Dithiothreitol prevented the effect of pCMB (data not shown).

**Discussion**

We have been concerned for some time with the four isozymes catalyzing the phosphorylation of glucose in rodent liver (1, 3, 6–8, 11, 14). One of them, the high-activity isozyme D or glucokinase, has been shown to be of adaptive nature, its levels being controlled by the concerted action of glucose and several hormones (3, 6). Furthermore, the high Michaelis constant for glucose (about 6 mM) of the rat isozyme and the fact that it exhibits a sigmoidal saturation function for glucose (15) make it especially and specifically suited to deal with the "tides" of glucose reaching the hepatocyte.

On the other hand, the low-activity isozymes from rat liver are generally considered as devoid of regulatory properties. Nevertheless, the inhibition of isozyme C by glucose in the range of normal blood sugar concentrations makes this isozyme a very likely candidate for a regulatory role in the utilization of glucose by the liver. The very low concentration of isozyme C in rodent liver has so far precluded a thorough investigation of the inhibition property. Fortunately, frog liver has proved to be an excellent source of hexokinase C.

Although substrate inhibition does not necessarily involve more than one site on the enzyme molecule (16, 17), I would like nevertheless to propose that the inhibition of hexokinase C by substrate is due to the interaction of glucose at an inhibitory site different from the sugar subsite of the active center based on the following arguments. (a) Fructose, although a substrate, is not inhibitory at any concentration; (b) no inhibition by excess glucose is observed at alkaline pH values, the inhibition being most marked below pH 7. This pH effect is reversible; (c) treatment with sulfhydryl-oxidizing agents (pCMB) or photooxidation densensitize the enzyme to the inhibitory effect of excess glucose. The most simple explanation for all these observations is that a second site exists which can interact with aldoses but not with ketoses. Protonation of the site would allow a second molecule of glucose to bind to the enzyme eliciting a conformational change which would result in a form catalytically less active. Conversely, the ionization of the site would block the allosteric interaction between glucose and the second site. Limited photooxidation or interference with —SH groups would result in the alteration of an amino acid essential for operation of the putative second site.

Additional sites may be involved in the catalytic performance of hexokinase C. The variations of ATP levels at any glucose concentration result in nonlinear double reciprocal
The glucose-6-P site becomes functional only when the glucose
ATP. In a similar way, the sigmoidal inhibition by glucose-6-P
postulated early in 1954 the presence in brain hexokinase
catalytic site is occupied by the substrate. Crane and Sols (18)
case, however, the fact that the inhibition by glucose-6-P is
almost nil at low glucose concentrations may indicate that the
isozyme A, the strong inhibition by the product is not reversed
of enzyme preparation. ATP levels were 5 mhr. The same data is shown in
Method a at the indicated glucose levels and are expressed as units/ml
the inset as the ratio of the velocities obtained at the high (H) and low
(1) glucose concentrations.
plots suggesting a cooperative interaction of different sites for
ATP. In a similar way, the sigmoidal inhibition by glucose-6-P
at low glucose concentrations (Figs. 5 to 7) suggest an
independent site for the effect of the phosphoric ester. In this
case, however, the fact that the inhibition by glucose-6-P is
almost nil at low glucose concentrations may indicate that the
glucose-6-P site becomes functional only when the glucose
catalytic site is occupied by the substrate. Crane and Sols (18)
postulated early in 1954 the presence in brain hexokinase
(presumably hexokinase A) of a binding site specific for
glucose-6-P, probably of a regulatory character. In the case of
isozyme A, the strong inhibition by the product is not reversed
by an increase in the concentration of glucose (2, 4, 5, 18, 19),
whereas in the case of hexokinase C the inhibition by glu-
cose-6-P is actually stronger when glucose concentrations are
higher (Figs. 5 and 6).
The lack of inhibition by glucose when assaying low enzyme
levels at pH 7.5 would suggest that the inhibition by substrate
may be the result of enzyme association. Dilution of the
enzyme would thus induce its dissociation and the loss of the
inhibitory property, i.e., the loss of the second site. Preliminary
experiments using gel filtration and sucrose gradient centri-
guration of the enzyme under several conditions have not
disclosed association-dissociation phenomena. Also, the avail-
able information on the quaternary structure of vertebrate
hexokinases seems to indicate the absence of more than one
polypeptide chain (20–22).
Whatever the mechanism of the inhibition by glucose of
hexokinase C, the observations reported in this paper show
that the isozyme qualifies as a regulatory enzyme at the key
phosphorylation step of glucose utilization. The inhibition by
substrate occurs at physiological levels of glucose and its extent
depends on the combined action of several factors.
Glucose concentration appears to be the most important
condition regulating the activity level of hexokinase C. At
physiological ATP concentrations (1 to 5 mM) maximal activity is
observed at 0.2 to 0.5 mM glucose decreasing markedly at
higher, but still physiological sugar levels (1 to 5 mM in frogs
(23)). If a naive extrapolation to in vivo situations is permitted,
it may be postulated that when glucose input to the liver is
high, hexokinase C activity diminishes and at the same time,
the velocity of hexokinase D increases due to its K, for glucose
(1.5 mM in frogs3). The reverse should hold when glucose input
to the liver is low. It can be surmised that these kinetic features
are accompanied by a functional or otherwise compartmen-
tation of glucose-6-P formation and utilization, and that at high
glucose input a pathway in which hexokinase D participates
becomes important and a pathway in which hexokinase C is
involved becomes less active. The reverse would occur when
substrate occurs at physiological levels of glucose and its extent
depends on the combined action of several factors.
Besides its role as substrate ATP affects hexokinase C
activity probably acting as a deinhibitor of the glucose effect
(Fig. 3). At physiological concentrations of ATP (~1 mM) and
glucose (1 to 5 mM) the activity of hexokinase C in vivo should
be very low because the effect of high glucose levels is more
marked at these ATP concentrations (Fig. 3). The increase of
ATP levels should therefore result in an enhanced activity of
the enzyme especially when glucose input to the liver is high.
Glycolysis is inhibited by high levels of ATP through its action
on phosphofructokinase (25–28) and pyruvate kinase (29, 30).
Thus, it seems logical to propose that hexokinase C produces
hexokinase D to a pathway in which glucose is stored,
e.g. glycogen synthesis, and in fact, that very function was
proposed by Viñuela et al. (24) when the enzyme was discov-
ered in rat liver. Conversely, hexokinase C should be linked to a
quite different pathway as discussed below.
J. Radojković and T. Ureta, preliminary results.
glycolysis through its strong inhibitory action on phosphofructokinase (33-37). The participation of hexokinase C in glycolysis seems doubtful as discussed in the previous paragraph. It would be worthwhile to search intermediates of the pentose phosphate or uronic acid pathways as activators or deinhibitors of the enzyme for a more precise assignment of the function of hexokinase C.

At the pH values expected to exist in the hepatocyte, isozyme C is inhibited by glucose but the effect becomes less marked at higher pH values (Figs. 8 to 10). In the absence of information about pH variations in the cell, the physiological meaning of this observation can only be uncertain. Negative cooperativity and slow transients markedly pH-dependent have been described for yeast hexokinases (31, 32).

Inhibition by excess glucose at pH values near 7.5 was found to be linearly dependent on hexokinase C concentration (Fig. 11). At low enzyme concentrations the high to low glucose ratio approaches unity to decrease to values of about 0.5 with a 10- to 20-fold increase in the amount of enzyme-glucose. In the absence of hexokinase C, the inhibition by ATP is very pronounced, the high to low glucose concentration ratio at pH 7.5 being about 0.2. Further studies on these enzymes are in progress in this laboratory and will be soon reported.

While writing this report I learned of a paper by Siano et al. (44) on the kinetic mechanism of bovine liver hexokinase C. However, all the experiments reported by Siano et al. were performed at glucose concentrations below 0.15 mM and therefore no comparisons with the present data are possible.

Acknowledgments—I thank Dr. Frank Marcus for the suggestion of several key experiments. I have benefited by very helpful discussions with Dr. Catherine C. Allende, Dr. H. Niemeyer, Dr. J. Babul, and their collaborators. I am deeply indebted to Mr. J. C. Slebe, Mr. Carlos Lozano, and Mr. Rodrigo Bravo who collaborated in different stages of this work. The assistance of Miss Jasna Radajovic in the completion of this research is gratefully acknowledged.

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