The crystal structure of a dual specificity phosphogluco-
ose isomerase (PGI)/phosphomannose isomerase from

Pyrobaculum aerophilum (PaPGI/PMI) has been deter-
mined in native form at 1.16-Å resolution and in complex
with the enzyme inhibitor 5-phosphoarabinonate at
1.45-Å resolution. The similarity of its fold, with the
inner core structure of PGIs from eubacterial and eu-
karyotic sources, confirms this enzyme as a member of
the PGI superfamily. The almost total conservation
of amino acids in the active site, including the glutamate
base catalyst, shows that PaPGI/PMI uses the same cat-
alytic mechanisms for both ring opening and isomeriza-
tion for the interconversion of glucose 6-phosphate (Glc-
6-P) to fructose 6-phosphate (Fru-6-P). The lack of
structural differences between native and inhibitor-
bound enzymes suggests this activity occurs without
any of the conformational changes that are the hallmark
of the well characterized PGI family. The lack of a suit-
able second base in the active site of PaPGI/PMI argues
against a PMI mechanism involving a trans-enediol in-
termediate. Instead, PMI activity may be the result of
additional space in the active site imparted by a threo-
nine, in place of a glutamine in other PGI enzymes,
which could permit rotation of the C-2—C-3 bond of
mannose 6-phosphate.

Phosphoglucone isomerase (PGI; EC 5.3.1.9) catalyzes
the interconversion of D-glucose 6-phosphate to D-fructose 6-phos-
phate via an aldose-ketose isomerization reaction. This equi-
librium reaction is part of glycolysis and gluconeogenesis but
also impacts other pathways in sugar metabolism such as the
pentose phosphate pathway. The enzyme from bacterial and
mammalian sources has been well characterized. Crystal struc-
tures show the enzyme to be a tight homodimer in which the
two active sites are located at the domain interface and are
formed by elements from both subunits (1–3). These structures
support a catalytic mechanism for isomerization in which a
glutamate (e.g. Glu-357 in rabbit PGI) acts as a base catalyst to
remove a proton from C-1 or C-2 (depending on the direction of
the reaction), forming a cis-enediolate intermediate. Because
the open chain forms of its substrates are expected to be pres-
ent in vivo in trace amounts (4), PGI also catalyzes a ring-
opening reaction. This reaction is acid-catalyzed by a histidine
(e.g. His-388 in rabbit PGI) (5, 6), and a lysine (Lys-518) also
appears to assist this reaction by abstracting a proton from C-1
of Glc-6-P (or C-2 of Fru-6-P) (7).

Sequences homologous with PGI cannot be recognized
readily within the genomes of Archaea. In some species, such as
the euryarchaeons Pyrococcus furiosus and Thermococcus litoralis,
PGI activity appears to be catalyzed by a novel en-
zeyme that is structurally and mechanistically distinct from the
PGI superfamily (8–10). Crystal structures of this protein from
P. furiosus show it to contain a cupin fold (11) at the heart of
which is a metal ion that is believed to mediate a hydride shift
mechanism of catalysis (12). An interesting facet of this struc-
ture is the lack of any obvious amino acids that might catalyze
ring opening, leading to suggestions that, in the extremely high
temperatures in which P. furiosus thrives, the proportions of
sugars in their straight chain form is sufficient to support the
demands of metabolism (12).

In some aerobic crenarchaeota, genes are present in which
sequence similarity to some, but not all, of the highly conserved
active site motifs of PGI can be detected, suggesting that,
unlike the euryarchaeota, these archaean species may contain
PGIs that are distantly related to eubacterial and eukaryotic
PGIs (13). The proteins from three of these genes, from Aero-
pyrum pernix, Thermoplasma acidophilum, and Pyrobaculum aerophilum,
have been characterized and show PGI activity (13, 14). Most interestingly, these enzymes also exhibit phos-
phomannose isomerase (PMI) activity and can catalyze the
interconversion of mannose 6-phosphate (Man-6-P) (the C-2
epimer of Glc-6-P) to Fru-6-P at an equal rate as Glc-6-P to
Fru-6-P (13, 14) (Fig. 1). The lack of any recognizable pmi
gene in these species suggests that this PMI activity may have a
function in vivo. Together with homologues from Sulfolobus
species, Thermoplasma volcanium, and Aquifex aeolicus,
these enzymes appear to comprise a novel PGI/PMI family
within the PGI superfamily (13).

The mechanism of PMI activity in these PGI/PMIs is inter-
data were collected at the SER-CAT beamline ID22 at the Advanced Photon Source (Argonne National Laboratory). These data were acquired on a MAR225 CCD detector with exposure times of 1 s per image, a crystal-to-detector distance of 100 mm, and an oscillation angle of 0.5°. To ensure high redundancy of the data, 360° were collected. Processing was performed using the HKL2000 software package (27). After refinement of the initial model against these data using REFMAC5 (28), the model was improved manually using XTALVIEW (29). Further refinement cycles consisted of the addition of solvent atoms using ARP/wARP, refinement with REFMAC5, and model building with XTALVIEW. Refinement of side chain alternative conformations and anisotropic temperature factors was included toward the end of the refinement process. The secondary structure of the final model was calculated using DSSP (30).

**RESULTS**

**Structure Determination**—The structure was solved by multiple isomorphous replacement using three derivatives, two gold and one iodine (Table I). Although three iodine peaks were visible in the Patterson map, this derivative had low phasing power and likely contributed little to the final phases. Phasing with SHARP at 1.8-Å resolution produced an experimental electron density map of excellent quality (Fig. 2a) and permitted automated model building of the entire structure except the methionines at each N terminus. After refinement against high resolution data extending to 1.16 Å, the final model has an R factor of 15.0% and R_factor of 16.4%, with excellent stereochemistry (Table II). This model comprises two subunits (of 300 and 301 residues respectively), 625 water molecules, as well as several molecules of sulfate and glycerol from the crystallization solution. A molecule of sulfate occupies the substrate phosphate-binding site in the active site of each subunit. Only the C-terminal glutamine of subunit B is not visible in the electron density due to apparent flexibility in the vicinity of the C terminus. The N-terminal methionine appears to be absent from the protein because the amino group of Ala-2 forms an electrostatic interaction with a neighboring aspartate, and there is no room for an additional residue. The extremely high resolution of the structure also permitted the modeling of 47 side chains and some main chain regions with alternative conformations: 22 in subunit A and 25 in subunit B. The final 2(|Fo| - |Fc|) electron density map at 1.16-Å resolution is shown in Fig. 2b.

**Structure Description**—The structure of PaPGI/PMI is a tight dimer of essentially identical subunits; the two subunits superimpose with an r.m.s. deviation of 0.71 Å for all atoms. The structure of one subunit and the dimer are shown in Fig. 3. The subunit comprises two domains, each of which is built around a parallel β sheet, five-stranded in the N-terminal domain and four-stranded in the C-terminal domain. The N terminus is located approximately between the two domains and extends across the face of the N-terminal domain before forming a β hairpin structure (β1 and β2). Thereafter, the N-terminal domain is comprised of alternating αβ segments with α-helices connecting β strands except for the connection between β4 and β5, which is not helical. After α7, the chain crosses over to the C-terminal domain where the same pattern

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**Crystal Structure of PGI/PMI from P. aerophilum**

EXPERIMENTAL PROCEDURES

**Structure Determination**—The crystallization of PGI/PMI from *P. aerophilum* (PaPGI/PMI) has been described previously (18). Briefly, the crystals belong to space group P21 with cell dimensions of a = 55.1 Å, b = 100.8 Å, c = 55.8 Å, and β = 113.2°, and an initial native data set extending to 1.6 Å was reported (18). The crystals were cryo-protected over a period of several hours by passage through a series of mother liquor solutions containing 26% glycerol and 5 mM of the PGI inhibitor 5-phosphoarabinonate (PAB) (31). Synchrotron data were collected at the SER-CAT beamline in the same way as the high resolution native data. PAB bound at the active site was visualized by refinement of the native model against the data collected from the ligand-soaked crystal, followed by examination of the 2Fo − Fc electron density map. After fitting of the PAB molecule, the structure was refined by using the same protocol used for the native structure and using the same free R assignments as the native data. Structure superimpositions were performed using the CCP4 program LSQKAB (32). Coordinates and structure factors for both structures have been deposited with the Protein Data Bank under code 1T7B for native and 1T7C for complex with PAB.

**Structure Description**—The structure of PaPGI/PMI is a tight dimer of essentially identical subunits; the two subunits superimpose with an r.m.s. deviation of 0.71 Å for all atoms. The structure of one subunit and the dimer are shown in Fig. 3. The subunit comprises two domains, each of which is built around a parallel β sheet, five-stranded in the N-terminal domain and four-stranded in the C-terminal domain. The N terminus is located approximately between the two domains and extends across the face of the N-terminal domain before forming a β hairpin structure (β1 and β2). Thereafter, the N-terminal domain is comprised of alternating αβ segments with α-helices connecting β strands except for the connection between β4 and β5, which is not helical. After α7, the chain crosses over to the C-terminal domain where the same pattern
of alternating αβ structure occurs. The C terminus is helical (α15) and is also located between the two domains.

The dimer is compact and globular in shape, with no significant extended structural features (Fig. 3b). Two short helical segments, α11 and α12, undergo domain swapping and are an integral part of the opposite subunit. At the dimer interface are numerous ionic interactions that may contribute to the thermostability of the enzyme.

Comparison with Conventional PGI—Even though the sequence similarity between them is barely detectable (13), PaPGI/PMI shares a common fold with conventional PGIs. The structure was superimposed with that of rabbit PGI (rPGI) (6), using an algorithm based on secondary structure matching (33), and shows the structural elements that are common to both proteins (Fig. 4). The overall domain structure is the same, but it is immediately obvious that PaPGI/PMI is far smaller and overlaps mostly with the protein core of rabbit PGI. This superimposition permits a structure-based alignment of the PGI sequences from rabbit and P. aerophilum, which shows the relationship between the two proteins more clearly (Fig. 5). A large part of the absent structure in PaPGI/PMI corresponds to the N-terminal end of rabbit PGI, consisting of seven α helices and two β strands, which together form the outer surface of the protein from rabbit. The absence of β1 and β2 (rPGI nomenclature) leaves a parallel four-stranded β sheet in PaPGI/PMI because in rabbit PGI these two strands are anti-parallel and so create a mixed parallel/anti-parallel six-stranded sheet in that enzyme. The C terminus is also shortened; the final helix (α24 in rPGI) is absent, and prior to that, α15 is only half the length of its equivalent in rPGI, α23. The latter helix is important because in conventional PGI it moves toward the active site after ligand binding and contains a lysine (Lys-518) that is critical for catalysis (34). Finally, in rabbit PGI, the structure that forms a "hook" (α20 and α21),
and extends to mediate intersubunit contacts in conventional PGIs (6), has no counterpart in PaPGI/PMI. In addition to these major differences, many of the connections are shorter in PaPGI/PMI.

**Complex with 5-Phosphoarabinonate**—To establish the identity of the active site of PaPGI/PMI, the structure was determined in complex with PAB, a well known inhibitor of PGI activity (31), at 1.45-Å resolution (Table II). PAB bound in an identical manner to both active sites in the dimer, and the view of molecule A is shown in Fig. 6. At one end of the active site, the phosphate group is oriented by three serines (Ser-48, Ser-87, and Ser-89) and one threonine (Thr-92). In the middle of the

| Table II: Data collection and refinement statistics of the native structure and the complex with PAB |
|---------------------------------|-----------------|-----------------|
| Data set                        | Native          | PAB             |
| Soak molarity (mM)              |                 | 5               |
| Soak time                       |                 | 5 days          |
| Resolution of data (Å)          | 36.0–1.16 (1.20–1.16)a | 36.0–1.45 (1.50–1.45) |
| No. measured reflections        | 1,062,444       | 287,701         |
| No. unique reflections          | 168,938         | 97,954          |
| Completeness (%)                | 87.7 (61.8)     | 97.8 (94.3)     |
| Mean I > 0.1 M                  | 38.6 (3.3)      | 13.4 (1.6)      |
| Rmergeb                         | 7.4 (34.7)      | 7.8 (46.2)      |
| Refinement                      |                 |                 |
| Resolution range                | 36.0–1.16       | 36.0–1.45       |
| No. water molecules             | 625             | 439             |
| R factor (%)                    | 15.0            | 17.0            |
| R work (%)                      | 14.9            | 16.9            |
| Rfree (%)                       | 16.5            | 19.2            |
| r.m.s. deviations from ideal stereochemistry |                 |                 |
| Bond lengths (Å)                | 0.006           | 0.008           |
| Bond angles (°)                 | 1.18            | 1.27            |
| B factors                       |                 |                 |
| Mean B factor (main chain) (Å²)| 11.7            | 15.3            |
| r.m.s. deviation in main chain B factor (Å²) | 0.34          | 0.43            |
| Mean B factor (side chains and waters) (Å²) | 16.2          | 19.8            |
| r.m.s. deviation in side chain B factors (Å²) | 0.78          | 1.40            |
| Ramachandran plot               |                 |                 |
| % residues in most favored region | 94.6          | 94.6            |
| % residues in additionally allowed regions | 5.2          | 5.2             |
| % residues in generously allowed regions | 0.2         | 0.2             |
| % residues in disallowed regions | 0.0           | 0.0             |

* Numbers in parentheses are for the outer shell of data.

b Where Rmerge = ΣhklΣiI(hkl) − (ΣhklΣiI(hkl))/(ΣhklΣiI(hkl)).

Fig. 3. The structure of PGI/PMI from *P. aerophilum*. a, ribbon representation of one subunit in which the molecule is color-ramped blue-to-red in the N-terminal to C-terminal direction. α helices and β strands are labeled individually. b, a ribbon representation of the dimer in which one subunit is colored red and yellow and the other is dark blue and light blue. For the respective subunits, the β strands are colored yellow and light blue. This figure was produced using MOLSCRIPT (41) and Raster3D (42).
inhibitor, the C-4 hydroxyl (equivalent to the ring oxygen in the substrate) is within hydrogen-bonding distance of Lys-298 and His-219 (the latter residue belonging to the adjacent subunit in the dimer); the C-3 hydroxyl is contacted by the amide of Gly-47 and the C-2 hydroxyl by the carbonyl group of His-219. In PAB, a carboxylate group replaces the C-1—C-2 region of the substrate such that O-1/H9251 is equivalent to C-1 and the carbon at position 1 is equivalent to C-2 of the substrate. Glu-203 is approximately equidistant from both of these atoms, showing that this residue is best placed to abstract and donate protons to the C-1 and C-2 positions of the substrate.

This structure permits a direct comparison with that of rabbit PGI in complex with the same inhibitor (35). The active sites of the two structures were superimposed by using the coordinates of PAB (Fig. 7). This shows that the majority of amino acids forming the active site are conserved between the substrate.
conventional PGI and PaPGI/PMIs. The cluster of threonines and serines that forms the sugar phosphate-binding site in conventional PGI (3) is conserved in PaPGI/PMI as Ser-48, Ser-87, and Thr-92 with just a threonine to serine change at position 89. Residues that are important for catalysis in conventional PGI are also conserved in PaPGI/PMI; Glu-357 in rPGI is represented by Glu-203 in PaPGI/PMI, His-388 by His-219, and Lys-518 by Lys-298. There are some differences, however, most notably a proline (Pro-134) in PaPGI/PMI in place of Gly-271, which lead to an alteration in the conformation of $\beta/6$ loop in comparison to the same loop in rPGI, and Thr-291 in place of Gin-511. The homology evident between the two active sites confirms PaPGI/PMI as a member of the PGI superfamily (13). In addition, the lack of any residue in

![Diagram](image)

**Fig. 6.** The structure of PGI/PMI from *P. aerophilum* in complex with PAB at 1.45-Å resolution. a, a stereo view showing PAB bound to the active site region. Shown is the active site from subunit B but the contacts are essentially identical in subunit A. The electron density shown around the inhibitor in blue is an unbiased ($F_o - F_c$) difference map, calculated from the final coordinates refined in the absence of ligand. The side chains of those residues surrounding the ligand are shown in bond form in which carbon, oxygen, and nitrogen are yellow, red, and blue, respectively, except for His-219 which is colored orange to indicate it is part of subunit A. PAB is colored with green bonds. Water molecules are shown as red spheres. Important contacts are shown as dashed lines. The figure was produced using PYMOL (40). b, a diagram of the distances (in Å) between atoms of PAB (colored green) and of amino acids in the active site (colored black).

**Fig. 7.** A comparison of the structure of PGI/PMI from *P. aerophilum* in complex with PAB with a structure of rabbit PGI in complex with the same inhibitor (35). In this stereo view, only the active sites of each structure (the B subunit in both cases) are shown. Residues surrounding the ligand, and the ligand itself, are colored yellow and green for the *P. aerophilum* and rPGI structures, respectively, and are numbered according to their respective sequences. The histidine residues (219 and 388) are colored orange (PaPGI/PMI) and cyan (rPGI) because in both structures this residue belongs to subunit A of the dimer. The figure was produced using PYMOL (40).
the vicinity of the carboxylate group of PAB, other than Glu-203, that might act as a base catalyst, shows that the PMI mechanism of this enzyme is unlikely to use a trans-enediol intermediate (discussed below).

Conformational Changes Upon Ligand Binding—To determine whether conformational changes occur in PaPGI/PMI in response to the binding of ligands at the active site in the same manner as PGI from eubacterial and eukaryotic sources (e.g. in rabbit PGI (6, 36)), the native structure and its complex with PAB were superimposed. The r.m.s. deviations calculated between all main chain atoms in the structures is 0.22 Å. Examining the superimposed structures reveals almost no structural differences between the native and PAB-bound structures (Fig. 8). The exception is a slight shift in the C-terminal helix in subunit B, which is due to an improvement in the ordering of this region compared with the wild-type structure. In particular, the C-terminal residue Gln-302 is now visible and hydrogen bonds a water molecule that is close to the PAB inhibitor. Other than this, the positions of all of the residues within the active site region are essentially unchanged. Moreover, given the very close overlap of residues in rabbit PGI and PaPGI/PMI when both complexed to PAB, it is clear that the native state of PaPGI/PMI is equivalent to the ligand-bound "closed" form of rabbit PGI.

DISCUSSION

A major goal of this work was to determine whether PaPGI/PMI belongs to the superfamily of PGI, as suggested by sequence similarity with some of the motifs that comprise conventional PGI (13, 18). Our crystal structure of this enzyme confirms this is indeed the case. The core structure of the enzyme has the same fold, and the main differences arise from extensions in conventional PGIs, at both termini and by the insertion of residues that corresponds to the hook structure, that together form an additional "layer" around the protein. Thus, PaPGI/PMI might represent a minimal PGI fold and that, during the course of evolution, the protein has increased in size by additions of ~100 residues at the N terminus, 30 residues between α2 and β1, 25 residues which form the hook structure, and 35 residues at the C terminus, as well as more gradual increases in the size of connecting loops. The similarity, however, is most pronounced at the active site. In conventional PGI this is formed by six motifs, and although only two of these could be recognized in the sequence for PaPGI/PMI with a tentative assignment for two others (13, 18), the structure shows that all six are present in PaPGI/PMI. Of the residues that comprise the immediate substrate-binding pocket, only two differ between PaPGI/PMI and mammalian PGIs. The evolutionary constraint to maintain these specific residues for the mechanism of isomerization must therefore be very restrictive, but at the same time, the differences between the two enzymes shed light on how this enzyme can also function as a phosphomannose isomerase.

Mechanism of Phosphoglucone Isomerase Activity—Although much of the catalytic mechanism of PGI has been elucidated from crystal structures of mammalian and bacterial PGIs (1, 3, 6, 35), the very high resolution of the structures presented here reveals it in greater detail. In this mechanism, a glutamate acts as a base catalyst and, in the aldose to ketose direction, abstracts a proton from C-2 and donates it back to C-1 (3, 6, 35). A separate proton moves between the carbon-bound oxygens, i.e. O-1 and O-2. The intermediate in this reaction is a cis-enediolate, and its negative charge is stabilized by an arginine. The presence of Glu-203 in the same position as Glu-357 in rabbit PGI and Arg-135 in place of Arg-272 (see Fig. 7) confirms that an identical mechanism for PGI activity operates in PaPGI/PMI. As the structure of PaPGI/PMI in complex with PAB shows, the architecture of the enzyme is well suited for this mechanism because the O-1 carboxylate oxygen of Glu-203 is approximately equidistant from O-1α and C-1 (2.7 and 3.1 Å, respectively), which are equivalent, respectively, to C-1 and C-2 of the substrates. First, this shows that proton abstraction/donation for the phosphoglucone isomerase reaction can take place from either carbon without any rearrangement in either the substrate or the active site. Second, it suggests that 3 Å is the ideal distance for proton abstraction to occur and that the precise binding interactions between substrate and active site residues serve to optimize this distance. Finally, it also illuminates why the reaction direction is determined by the relative concentrations of the two substrates in the cellular medium and not by an intrinsic property of the enzyme because, once a proton has been abstracted from C-2 of Glc-6-P, it could easily be re-donated back to the same atom, and Glc-6-P will be the product.

PaPGI/PMI Does Not Require Conformational Changes for Activity—A feature of crystal structures of PGIs from eubacterial and eukaryotic sources is a number of conformational changes that appear to occur upon the binding of inhibitor or substrate molecules (3, 6, 36–38). In rabbit PGI, for example, these comprise the closure of residues around the sugar phosphate, an inward shift of a 3/10 helix that carries His-388, and the movement of helix α23, which brings Lys-518 closer to the active site (6, 36). Because these shifts bring important residues, either for catalysis or substrate binding, closer to the active site, they appear to be essential for the catalytic functioning of PGI. Thus, the native state of conventional PGI is open in structure but, by an induced fit mechanism in response to substrate binding, it transitions to a closed form required for catalysis. By contrast, when PaPGI/PMI binds 5-phosphoarabinonate there are virtually no changes in the structure of the enzyme, and this is because the native enzyme is already in the closed form that is more akin to a conventional PGI bound by a ligand. Although this could be induced in part by the sulfates occupying the phosphate-binding site in each active site of the native enzyme, it would not explain the closed state of the remaining two regions that shift in conventional PGIs. The lack of any movement in the archaean enzyme in response to the binding of ligand may be due to its inherent thermostability,
which would tend to restrict any flexibility in the protein. Nevertheless, the question as to why conformational changes are apparently required in one branch of the PGI superfamily, but not another, is an interesting one.

Mechanism of Sugar Ring Opening in PaPGI/PMI—Absent from the discussion so far is the issue of sugar ring opening. PGIs from mesophilic organisms contain a conserved histidine that acts as an acid catalyst in ring opening by donating a proton to the ring oxygen, forming a hydroxyl at C-5 (6, 6). They also contain a lysine that may assist this reaction by concomitantly abstracting a proton from the C-1 hydroxyl (7). Both of these residues are conserved in PaPGI/PMI, as His-219 and Lys-298, respectively; hence, a similar mechanism for ring opening must also exist in P. aerophilum. The mere existence of a ring-opening apparatus, however, raises an interesting issue. Its presence in an organism that thrives at temperatures close to 100 °C (39) suggests that the proportion of sugar substrate present in the straight-chain forms is not significantly different from the trace amounts detected at 25 °C (4), and this has implications for other archaeal species. One of the most intriguing aspects of the crystal structure of cupin-type phosphoglucosamine isomerase from P. furiosus (PfPGI) was the apparent lack of any residues that might catalyze the opening of the sugar ring (12). Given this, it was tentatively suggested that at such extreme temperatures a greater proportion of straight-chain sugars might be present, thus precluding the requirement for a ring-opening step in the PGI reaction (12). In the light of the PaPGI/PMI structure presented here, in which the catalytic machinery for ring opening is overtly present, other hypotheses for the opening reaction catalyzed by PfPGI must be considered.

How PGI Catalyzes PMI Activity—At first sight, it would not appear difficult for a PGI to catalyze PMI activity; both reactions are aldose-ketose isomerizations and both involve the interconversion of the transfer of a proton between C-1 and C-2 (aldose to ketose direction). But in actual fact, the reversal of this isomerization, which would form Man-6-P, might be difficult for a PGI to catalyze PMI activity; both reactions are aldose-ketose isomerizations and both involve the opening of the substrate at C-2. The same situation is also likely in other PGIs/PMIs, in which the threonine is replaced by a valine or a leucine (13). A more detailed view of how such a rearrangement occurs within the active site of PaPGI/PMI, however, must await the determination of its structure in a complex with one or more of its substrates, Glc-6-P, Fru-6-P, and Man-6-P. Such a structure may also explain how eubacterial and euarkyotic PGIs can rotate the C-2—C-3 bond during the anomerization of Fru-6-P but at the same time prevent this during isomerization, which would form Man-6-P.

Acknowledgments—We are grateful to Klaus Schnackertz for the kind gift of 5-phosphorabino isonate used in this work and in parallel studies of other PGI enzymes. Data were collected at Southeast Regional Collaborative Access Team (SER-CAT) 22-ID beamline at the Advanced Photon Source, Argonne National Laboratory. Supporting institutions may be found at www.ser-cat.org/members.html. Use of the Advanced Photon Source was supported by the United States Department of Energy, Office of Science, Office of Basic Energy Sciences, under Contract W-31-109-Eng-38. We thank Zheng Lijun for assistance with the collection of the PAB data set used in this study. We also thank Graham Solomon for critical reading of the manuscript.

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Crystal Structure of PGI/PMI from P. aerophilum

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*J. Biol. Chem.* 2004, 279:39838-39845.
doi: 10.1074/jbc.M406855200 originally published online July 13, 2004

Access the most updated version of this article at doi: 10.1074/jbc.M406855200

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