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Theoretical study on the degradation of ADP-ribose polymer catalyzed by poly(ADP-ribose) glycohydrolase

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ABSTRACT

Poly(ADP-ribose) glycohydrolase (PARG) is the only enzyme responsible for the degradation of ADP-ribose polymers. Very recently, the first crystal structure of PARG was reported (Dea Slade, et al., Nature 477 (2011) 616), and a possible S_N1-type-like mechanism was proposed. In this work, we present a computational study on the hydrolysis of glycosidic ribose–ribose bond catalyzed by PARG using hybrid density functional theory (DFT) methods. Based on the crystal structure of PARG, three models of the active site were constructed. The calculation results suggest that the degradation of poly(ADP-ribose) follows an S_N2 mechanism, and the oxocarbenium expected by Dea Slade is a possible transition state but not an intermediate. The calculated reaction pathway agrees with the proposed mechanism. According to the computational models with different sizes, the roles of key residues are elucidated. Our results may provide useful information for the subsequent experimental and theoretical studies on the structure and functional relationships of PARG.

1. Introduction

Poly-adenosine diphosphate (ADP) ribosylation (PARylation) [1,2] is a transient, dynamic and reversible post-translational modification of nuclear proteins involved in cellular homeostasis as diverse as DNA repair [3], apoptosis [4,5], transcription [6,7], and chromosome stability [8]. Nowadays, many pathological studies have concentrated on the poly(ADP-ribose) (PAR) metabolic pathway. A primary enzyme involved in the post-translational modification is poly(ADP-ribose) polymerases (PARPs) [9,10]. It is a growing family of enzymes which transform nicotinamide adenine dinucleotide (NAD^+) into ADP-ribose (ADPR) and then catalyzes the polymerization of ADPR. To date, up to 17 different genes encoding enzymes capable of synthesizing PAR have been identified by genome-wide sequence analyses in human [11–13]. However, only three human poly(ADP-ribose) glycohydrolase (PARG) proteins [14–16] are characterized that degrade PAR, all of which are expressed from one sole PARG gene by alternative splicing. PARG is an endoxeoglycohydrolase that catalyzes PAR turnover via the hydrolysis of $\alpha(1''–2')$ and $\alpha(1'''–2'')$ ribosyl-ribose linkages to produce free ADPR [17]. The ADP-ribose polymerization cycles catalyzed by PARPs and PARG are depicted in Scheme 1. The activities of PARP and PARG are closely coordinated, causing a rapid polymer turnover with a half-life of less than 1 min after DNA damage [18]. PARP has been proved to participate in many biological functions, including regulation of cell survival and death programs, telomere cohesion and mitotic spindle formation, and transcription regulation [19–24].

After the first PARG gene was cloned in 1997 [25], the genes have been characterized in different species. PARG is mostly found to be cytoplasmic [26]. Recently, a splice variant containing a nuclear localization signal has been identified that targets PARG to the nucleus [27]. The levels of PAR can be increased by 10- to 500-fold in a fashion and are directly proportional to the number of DNA strand breaking in response to genotoxic stress [28–30]. During DNA damage, the increased PAR synthesis leads to caspase-independent cell death [31]. Furthermore, several knock-out experiments of PARG in *Drosophila* [27] and mice [32] show that deletion or knockout of the PARG gene results in hypersensitivity to DNA damage-induced cell death and causes profound neurodegeneration. It is concluded that PARG activity is critical for the prevention of PARP dependent cell death by regulating the intracellular levels of PAR.

Very recently, Slade and Dunstan reported the first PARG crystal structure from the bacterium *Thermomonospora curvata* [33]. Structures of PARG in complexes with ADP-ribose and the

Abbreviations: ADP, poly-adenosine diphosphate; PARylation, poly-adenosine diphosphate (ADP) ribosylation; ADPR, poly-adenosine diphosphate (ADP)-ribose; PAR, poly(ADP-ribose); PARG, poly(ADP-ribose) glycohydrolase; PARP, poly(ADP-ribose) polymerase.

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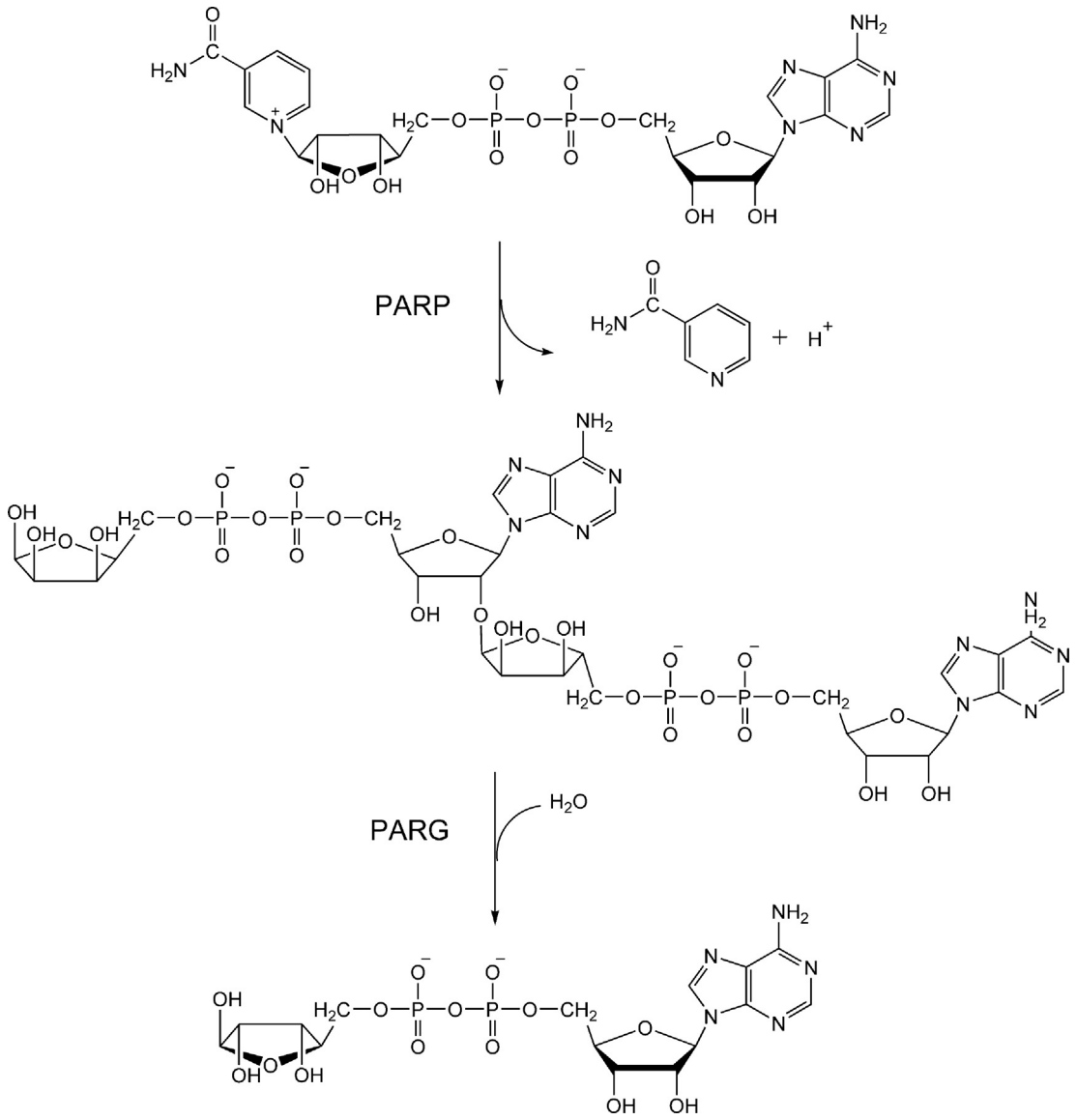


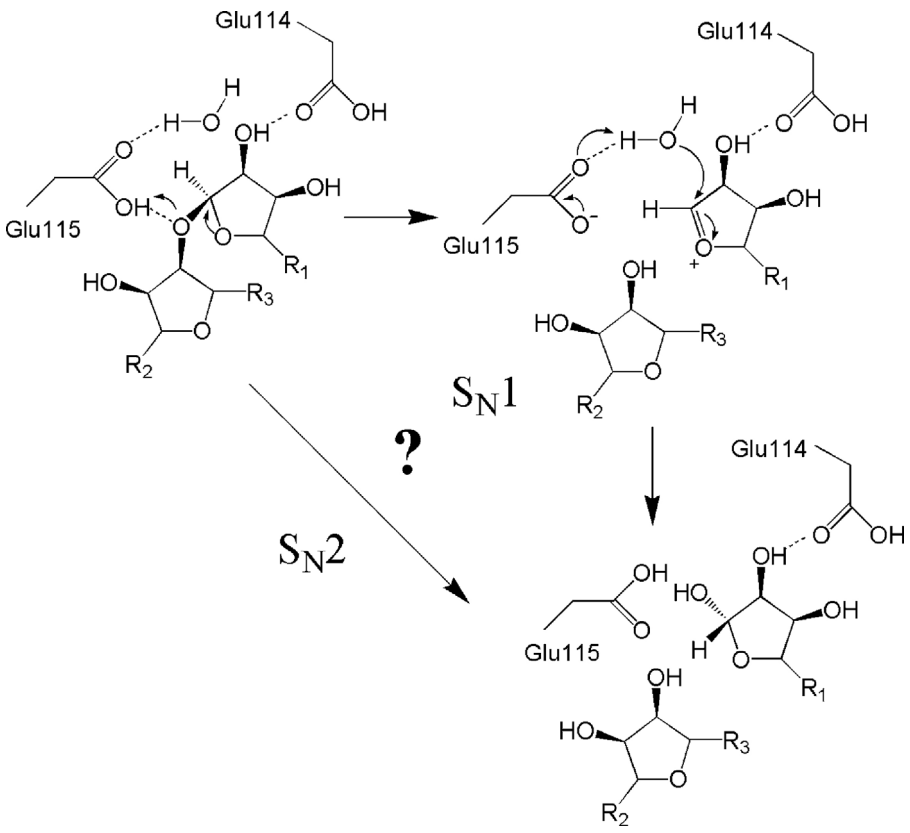
Scheme 1. ADP-ribose polymerization cycles catalyzed by PARPs and PARG.

inhibitor adenosine diphosphate (hydroxymethyl)-pyrrolidinediol (ADP-HPD) were obtained with high resolution of 1.5 Å. A model of PAR binding to PARG was also simulated by molecular dynamics [33]. On the basis of these studies, an S_N1-type mechanism for PARG catalytic reaction was proposed, as shown in Scheme 2. A putative oxocarbenium intermediate was formed firstly, and then a water molecule was activated to attack the intermediate to complete the catalytic process. Apart from these observations, little is known about the PAR degrading reaction. PAR is composed of repeating ADP-ribose units linked via unique glycosidic ribose–ribose bonds.

Although several computational studies on the hydrolysis of glycosidic bond have been presented (such as N-glycosidic bond of ribonucleosides [34–36], O-glycosidic bond between two glucoses or between hydroxyproline and galactosyl [37–39]), the computational study about the hydrolysis of glycosidic ribose–ribose bond is still very limited. In the present work, the quantum chemical methods are used to investigate the hydrolysis mechanism of ribose–ribose O-glycosidic bond catalyzed by PARG. Based on the crystal structure determined by Slade and Dunstan [33], the reaction models with different sizes were constructed, the reaction barriers and energies were calculated. In addition, the important roles of key residues were also discussed.

2. Computational methods

All calculations were performed using the density functional theory (DFT) functional B3LYP [40–44] as implemented in the Gaussian03 program package [45]. Molecular geometries were optimized using the 6-31G(d,p) basis set in gas phase. There are mainly two reasons for using this method. The first one is that this accuracy is usually sufficient to obtain reliable geometries. The second one is that the use of this method is fast enough for treating rather large models, even up to a few hundred atoms. During the optimization, some atoms were frozen to their crystallographic positions, and the fixed atoms are indicated by arrows in the figures given later. Single point energy calculations were performed at the B3LYP/6-311++G(2d,2p) level of theory in gas phase, and were corrected by using the polarizable continuum model (PCM) [46,47]. This strategy is reliable and significantly reduces the computational expense [48–50]. Two dielectric constants, $\varepsilon = 4$ and $\varepsilon = 80$, were chosen in our calculations. The dielectric constant of $\varepsilon = 4$ is usually used to model the protein environment, and $\varepsilon = 80$ for aqueous media. These two dielectric constants have been employed in many previous studies and yield remarkably good results [50–52]. Frequency calculations were performed for each optimized structure



Scheme 2. Proposed mechanism for PAR glycohydrolysis.

with the 6-31G(d,p) basis set to obtain the zero-point vibrational energies (ZPE), and to confirm that all the optimized geometries correspond to a local minimum that has no imaginary frequency mode or a saddle point that has only one imaginary frequency mode. The transition states are also confirmed by analyzing the highest imaginary frequency which is dominated by a stretching vibration involving the bonds that are formed/broken in the reaction. To keep the model reasonably close to the X-ray structure, a few atoms of the model were frozen to their crystallographic positions. This is usually not a critical part of the procedure, and a few small negative eigenvalues usually appear, typically in the order of 10 cm^{-1}. But these frequencies do not contribute significantly to the zero-point energies and can be ignored. The constraints can normally be released at the final geometries without big effects [50–54]. The energies reported here are corrected for zero-point vibrational effects.

3. Results and discussion

Three models of PARG active site were constructed based on the X-ray crystal structure (PDB code: 3SIG) [33] (see Fig. 1). Model A consists 59 atoms. In this model, ribose″ linked with an additional $(n-1)$ ribose′ through an α(C1″–C2′) O-glycosidic bond is constructed to simulate ADP-ribose dimer, which is a sufficient model to reproduce the properties of the ribose–ribose O-glycosidic bond. The glutamic acids Glu114 and Glu115 are both protonated and modeled by propionic acid. One water molecule is also included. As shown in Fig. 2, in the reactant R_A, Glu114 and Glu115 establish two hydrogen bonds with the substrate, as indicated by the calculated H-bond distances of 1.75 Å and 1.82 Å respectively. The water molecule (W1) which is 3.24 Å away from C1″ of ribose″ is stabilized by a strong hydrogen bond from Glu115. In the structure of TS_A, Glu115 has already donated one hydrogen atom to the

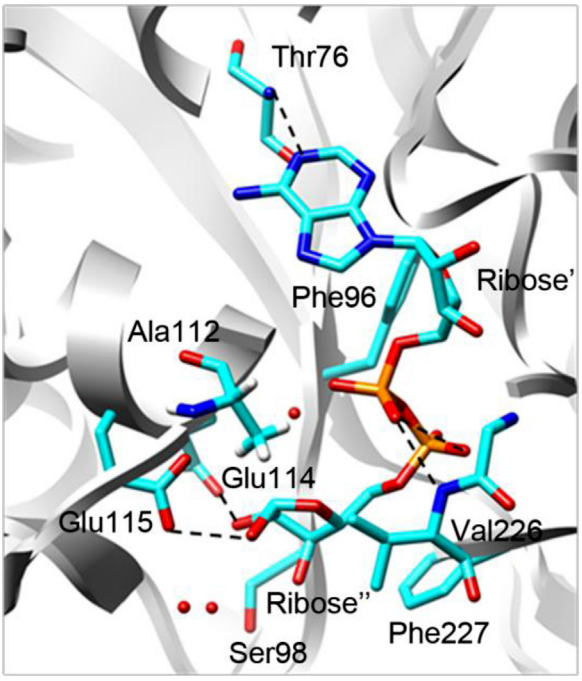


Fig. 1. X-ray structure of the active site of PARG in complex with ADP-Ribose. Coordinates taken from Protein Date Bank entry 3SIG.

glycosidic oxygen, and the glycosidic bond is much weakened with the distance changes from 1.42 to 2.35 Å. The structural parameters indicate that C1″ is an sp^3 hybrid carbon in the reactant R_A, and becomes sp^2 hybridized at the transition state. In the product P_A, the water molecule has decomposed to two parts that the

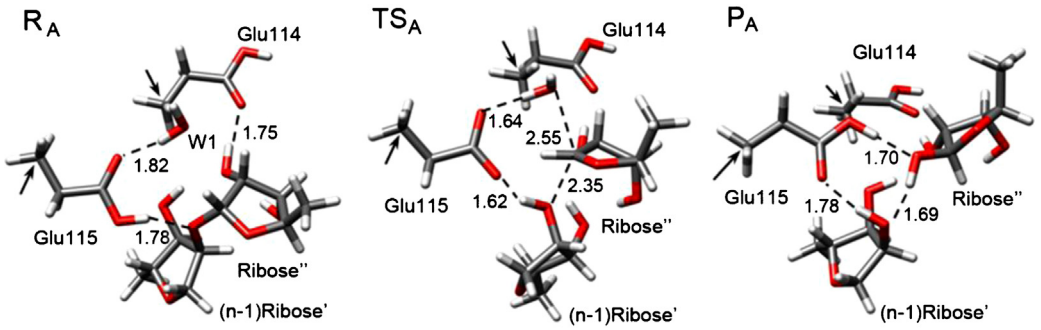


Fig. 2. Optimized structures of reactant (R_A), transition state (TS_A) and product (P_A) for Model A. Arrows indicate that atoms are kept to their crystallographically observed positions in calculations. Distances are given in angstrom.

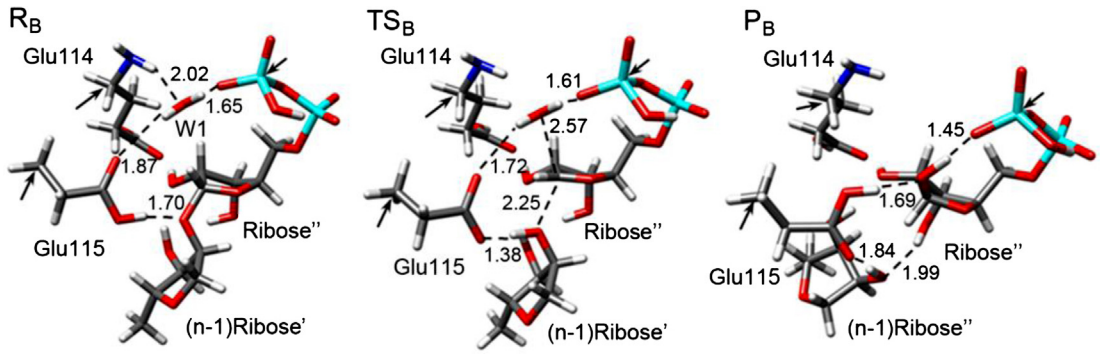


Fig. 3. Optimized structures of reactant (R_B), transition state (TS_B) and product (P_B) for Model B.

hydroxyl group bonded to C1″ and the proton attached to Glu115, yielding protonated Glu115 and dissociative ribose″ with an inversion of configuration. Thus, PARG can be classified as an inverting exo-glycohydrolase. The calculated energy barrier for this step is 28.5 kcal/mol, and the reaction is exothermic by −5.1 kcal/mol. To approximately estimate the energetic effects of enzyme environment, we also applied a homogeneous dielectric field according to the polarizable continuum model (PCM), with two dielectric constants, $\varepsilon = 4$ and $\varepsilon = 80$. As shown in Table 1, the barrier is slightly reduced to 26.0 and 25.0 kcal/mol, respectively. The reaction energies also decrease when the solvation effects are considered.

It should be noted that our calculations support a highly concerted but asynchronistically mechanism for the hydrolysis reaction, which is a little different from the proposal of Slade and Dunstan [33]. Frequency calculations indicate that the oxocarbenium is a transition state but not an intermediate, as proved by an imaginary frequency of $65i\,cm^{-1}$. Therefore, we believe that the configuration inversion mechanism is an S_N2-type mechanism. It is interesting to see that Glu115 works as a proton donor to the glycosidic oxygen as well as a proton acceptor from the activated water molecule. The other residue Glu114 forms a strong hydrogen bond to C2″–OH throughout the whole process, which significantly stabilizes ribose″.

Considering the diphosphate group is connected with the ribose″ and in close proximity to C1″, we constructed the second model (Model B), in which the diphosphate group and the amino group on Glu114 were added. The optimized structures of reactant R_B, transition state TS_B and product P_B are shown in Fig. 3. In R_B, the water molecule is strongly stabilized by three hydrogen bonds from Glu114, Glu115 and the diphosphate group. In TS_B, the breaking glycosidic bond is 2.25 Å, and the unique imaginary frequency is $110i\,cm^{-1}$. Without solvation, the energy barrier is 15.0 kcal/mol, which is much lower than that in Model A. It can be explained from two aspects. On the one hand, the hydrogen bond between the diphosphate group and W1 makes the O (W1) slightly more negative. In Model A, the O (W1) bears a Mulliken charge of −0.65, while in Model B the Mulliken charge is −0.70. Meanwhile, the positive Mulliken charge of C1″ varies from 0.38 in Model A to 0.41 in Model B. All these changes will somewhat facilitates the neucleophilic attack of OH^- at the C1″ site. On the other hand, compared with Model A, the relative orientations of ribose″ and Glu114 in Model B have also changed, which is more similar to the crystal structure. A rational explanation is that the diphosphate group influences the steric orientation of ribose″ which would lead to the rotation of the carboxyl group of Glu114. We can conclude from these results that the negative diphosphate group not only provides a strong hydrogen bond to the water molecule, but also influences the steric orientation of ribose″.

It has been reported by experimental studies that the mutation of Phe227 rendered the enzyme inactive [33]. Therefore, we

Table 1
Summary of the calculated energies (kcal/mol) for the hydrolytic reaction catalyzed by PARG. And the energies reported here are corrected for zero-point vibrational effect.

	Model A (59 atoms)		Model B (73 atoms)		Model C (93 atoms)	
	Barrier	Reaction energy	Barrier	Reaction energy	Barrier	Reaction energy
No solvation	28.5	−5.1	15.0	−3.3	14.5	−3.5
$\varepsilon = 4$	26.0	−7.6	20.9	−1.0	18.7	−1.5
$\varepsilon = 80$	25.0	−9.1	22.2	−0.5	20.2	−2.2

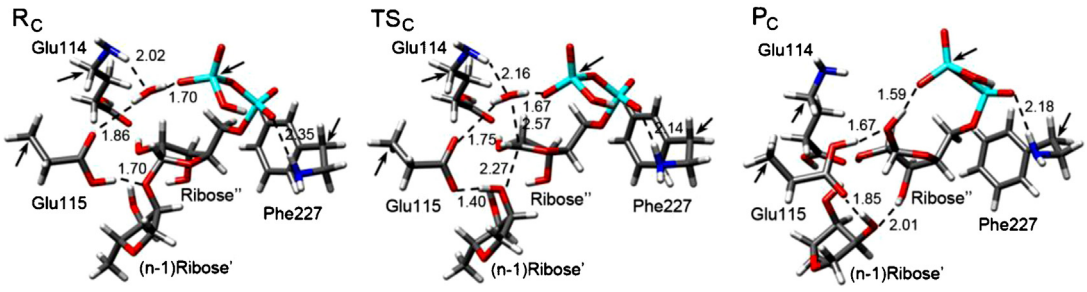


Fig. 4. Optimized structures of reactant (R_C), transition state (TS_C) and product (P_C) for Model C.

created an even larger model (Model C) with Phe227 included. The optimized structures of R_C, TS_C and P_C are shown in Fig. 4. A hydrogen bond with the distance of 2.35 Å between the amino group of Phe227 and the diphosphate group is formed in R_C. The geometric parameters obtained from the optimized TS_C are very similar to those of Model B. However, the hydrolytic reaction based on Model C requires a little lower activation energy of 14.5 kcal/mol in the gas phase, and the reaction is exothermic by 3.5 kcal/mol. Compared with Model B, the barrier is also found to be reduced, 18.7 kcal/mol and 20.2 kcal/mol when $\varepsilon = 4$ and $\varepsilon = 80$ are applied respectively. Thus, the role of Phe227 is providing spacial effects to position the terminal ribose″.

4. Conclusions

In summary, our calculations confirm that PARG catalyzes the hydrolysis of PAR via an S_N2-like mechanism. By using different active site models, the roles of key residues have been illustrated. Glu115 works as a proton donor to the glycosidic oxygen as well as a proton acceptor from the activated water molecule. The other glutamic residue Glu114 plays an important role in stabilizing ribose″ by forming a hydrogen bond to the C2″–OH of ribose″. The negative diphosphate group significantly lowers the reaction barrier by providing a strong hydrogen bond to the water molecule and influencing the steric orientation of ribose″. And Phe227 provides the spacial effects to position the terminal ribose″. Our mechanism picture described here is expected to present a versatile paradigm of the mechanisms of ribose–ribose O-glycosidic bond hydrolysis. Mutation of the key residues which are proved serve as nucleophile or general acid in the catalysis will decrease the activity of PARG. Moreover, our calculation results also could be exploited for the development of potent PARG inhibitors.

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