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分子动力学研究F₁-ATP合酶对三磷酸腺苷的稳定和定位作用

伍绍贵^{1,2,*} 高晓彤¹ 李 权¹ 廖 杰¹ 徐成刚¹¹四川师范大学化学与材料科学学院, 成都 610068;²中国科学院理论物理研究所理论物理国家重点实验室, 北京 100190)

摘要: F₁-ATP合酶通过与ATP之间建立广泛的相互作用, 实现对ATP的位置进行精确的定位. 这些相互作用为ATP的合成/水解创造了稳定的环境. 理解这些相互作用是理解ATP的合成/水解机理的基础. 我们通过分子动力学模拟方法研究这些相互作用, 找出在稳定化过程中起到重要作用的残基. 通过检测ATP和F₁-ATP合酶之间的非键相互作用, 发现残基段158–164所形成的loop区域及残基R189, Y345对ATP存在显著相互作用. 其中, 该loop区域对ATP的三磷酸部分形成一个半包围结构, 封闭活性位点区域, 并通过氢键网络约束ATP三磷酸的运动, 为ATP合成/水解创造稳定的环境. 此外, 关键残基Y345通过 π - π 叠加相互作用对ATP的碱基进行约束, 但是ATP的碱基可以在平行于Y345芳香环的平面内进行滑动, 我们推断这种滑动运动有利于促进ATP的水解.

关键词: F₁-ATP合酶; 氢键; 分子动力学; 突变

中图分类号: O641; Q641.12

F₁-ATPase Stabilizes and Positions Adenosine Triphosphate Revealed by Molecular Dynamics Simulations

WU Shao-Gui^{1,2,*} GAO Xiao-Tong¹ LI Quan¹ LIAO Jie¹ XU Cheng-Gang¹¹College of Chemistry and Material Science, Sichuan Normal University, Chengdu 610068, P. R. China; ²State Key Laboratory of Theoretical Physics, Institute of Theoretical Physics, Chinese Academy of Sciences, Beijing 100190, P. R. China)

Abstract: F₁-ATPase makes extensive interactions with ATP through forming a network of interactions around ATP. These interactions create a steady environment for ATP synthesis/hydrolysis. Thus understanding these interactions between ATP and F₁-ATPase is essential for understanding ATP synthesis/hydrolysis mechanism. We performed all-atom molecular dynamics (MD) simulations to elucidate these interactions and attempted to identify key residues which play important roles in stabilizing and positioning ATP. By examining the non-bonded energies between ATP and residues of β_{TP} subunit in F₁-ATPase, it is found that residues 158–164, R189, Y345 have significant interactions with ATP. The loop segment (residues 158–164) and R189 surround ATP by a half and they interact with β and γ phosphates through forming a network of hydrogen bonds to constraint the motion of ATP triphosphate. The interaction network seals off the conformation of the catalytic site, creating a steady environment for ATP synthesis/hydrolysis. Additionally, ATP base is positioned by the π - π stacking interaction from Y345. However, ATP base can slide and move paralleling to the aromatic group of Y345. It is deduced that this motion may facilitate ATP hydrolysis.

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*Corresponding author. Email: wsgchem@foxmail.com; Tel: +86-28-84760802.

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Key Words: F_1 -ATPase; Hydrogen bond; Molecular dynamics; Mutation

1 Introduction

F_0F_1 -ATP synthase is a central enzyme in the energy conversion that produces high-energy compound adenosine triphosphate (ATP) for all living organisms.¹ It synthesizes ATP from adenosine diphosphate (ADP) and inorganic phosphate (P_i) using the energy released by the passive flux of protons across the membrane down their electrochemical gradient.² Due to its biological importance, F_0F_1 -ATP synthase receives extensive research interests both experimentally and theoretically.³ F_0F_1 -ATP synthase consists of two parts: F_0 and F_1 moieties. The water insoluble F_0 domain is embedded in membrane and the hydrophilic F_1 domain protrudes into matrix space.⁴ The F_1 moiety, usually termed as F_1 -ATPase, is a typical ATPase responsible for both ATP synthesis and hydrolysis. It is composed of five types of subunits ($\alpha, \beta, \gamma, \delta, \epsilon$) in the stoichiometry $(\alpha\beta)_3\gamma\delta\epsilon$ and only the β subunits are catalytically active. The β subunits have three different conformations: two closed (β_{DP} and β_{TP}) and one open (β_E).⁵ The β_{DP} and β_{TP} states are similar in conformation while contain bound ADP and ATP, respectively. The β_E is an empty conformation without nucleotide. ATP synthesis/hydrolysis reactions occur in a steady environment in the catalytic site to shield the interfluence of intense thermal oscillation. Thus these interactions between protein and ATP are essential to guarantee successful ATP synthesis/hydrolysis reaction. Understanding the interactions between ATP and F_1 -ATPase is essential for understanding ATP synthesis/hydrolysis.

Researchers have been focusing on how F_1 -ATPase works on a very efficient mode for more than 30 years.⁶ To understand the basic interactions between substrate ATP and F_1 -ATPase is undoubtedly helpful for uncovering the 'secret' of the high efficient working mechanism of F_1 -ATPase. Although experimental studies can solve high resolution structures of proteins with X-ray crystallography which provide a wealth of information, it is still challenging to obtain dynamics information from experiments at atomic resolution.⁷ Protein dynamics are thought to be fundamental to protein function as protein structure.⁸ Molecular dynamics (MD) simulations, a powerful complementary tool for experiments, can provide valuable dynamic information at atomic resolution.⁹ By using physical force fields, all-atom MD simulations can reproduce detailed atomistic interactions between protein and ligands or between residues of protein.¹⁰ These interactions can be analyzed by electrostatic interaction (E_{ele}), van der Waals interaction (E_{vdw}), hydrophobic contact, base-pairing, base stacking and so on. Therefore, computer simulations can complement experimental approaches by providing information inaccessible to experiments and helping address many remaining important questions.¹¹

In the current study, high-resolution X-ray crystal structure of the catalytic β subunit in F_1 -ATPase adopting β_{TP} conformation with bound ATP was used as the basic model for simulations. MD simulations were performed with F_1 -ATPase β sub-

unit-ATP complex in explicit water to study the interactions between F_1 -ATPase and ATP. By analyzing the non-bonded interactions, we attempted to identify these critical residues which play important roles in positioning and stabilizing ATP in a catalytically competent conformation. It is expected that our study delivers a clear picture to describe F_1 -ATPase interacting with ATP at atomic scale.

2 Details of MD simulation

All-atom MD simulations were performed with the F_1 -ATPase β subunit-ATP complex in explicit water using GROMACS software, which is one of the fastest and most popular simulation packages available. Amber 03 force field¹² was used to describe protein residues and other Amber 03 force field parameters for ATP were developed by Meagher *et al.*¹³ High resolution (0.19 nm) structure (PDB ID code 2JDI) reported by Walker *et al.*¹⁴ was used as the basis for the F_1 -ATPase model. F_1 -ATPase consists of ~5400 residues and amounts to ~26400 atoms in total. If the entire crystal structure is fully solvated in explicit water, the whole system will be computationally expensive for simulation. On the other hand, β subunit can serve as an ATPase to hydrolyze ATP independently. Therefore, only the β subunit with bound 5'-adenylyl- β - γ -imidodiphosphate (AMP-PNP) was separated from the original F_1 -ATPase crystal structure and the ligand AMP-PNP was modified to ATP by substituting the atom N connecting β and γ phosphates by an atom O. Additionally, the catalytic metal ion Mg^{2+} and crystal water molecules were conserved for their important roles in forming essential interactions with protein or ligand (i.e. salt bridge/hydrogen bonds). The initial β subunit-ATP complex was solvated with 16199 three-point transferable intermolecular potential (TIP3P) water molecules¹⁵ in a rectangular box of 6.73 nm $\times$ 7.82 nm $\times$ 10.94 nm. The distance from the surfaces of the box to the closest atoms of the solutes is ~1 nm, which is large enough to prevent F_1 -ATPase complex from contacting with its periodic images. All amino acid residues of F_1 -ATPase were set to protonation states at pH = 7. Sodium and chloride ions were added to make the system electrically neutral at a concentration of ~0.15 mol $\cdot$ L⁻¹, close to the physiological ionic concentration. The final size of the system reaches ~57000 atoms. A typical 1.0 nm cutoff was used for van der Waals and short-range electrostatic interactions. Long-range electrostatic interactions were treated using particle mesh Ewald (PME) method.¹⁶ Berendsen barostat¹⁷ and the velocity rescaling thermostat¹⁸ were applied to control pressure and temperature at 1.01×10^5 Pa and 300 K, respectively. A linear constraint solver (LINCS) algorithm was used to constrain all bonds involving hydrogen atoms.¹⁹ Periodic boundary condition was applied in three dimensions of the simulation box. Motion equations were solved numerically with a time step of 2 fs and the neighbor list was updated every 10 steps. The solvated

system was firstly subjected to a thorough energy minimization using the steepest descent minimization method followed by a 200 ps MD simulation with position restrains on the heavy atoms of the solute. The final configurations were used for production simulations. To generate a representative ensemble of structures, each production simulation was performed for 100 ns and trajectories were saved at 2 ps intervals. The detailed conformation analysis and interaction calculations were conducted using the built-in tools of GROMACS. All the snapshots for protein-ligand complex were prepared with PyMOL (version 0.99) software.

3 Results and discussion

F₁-ATPase makes extensive interactions with ATP through forming a network of hydrogen bonds/electrostatic interactions around ATP. Crystal structure shows that the bound ATP lies in a deep pocket of β subunit in F₁-ATPase. The binding pocket of β subunit is responsible for the catalytically active reaction site. As shown in Fig.1, the binding pocket is enclosed by three helices (residues 156–178, residues 335–343, and residues 420–427) and two loops (residues 415–419 and residues 344–347). The triphosphate moiety of ATP is surrounded by a helix (residues 161–178) and a loop (residues 157–160). Owing to the charged nature of ATP triphosphate, multitude of hydrogen bond/electrostatic interactions are established between ATP triphosphate and F₁-ATPase, which helps to seal off the catalytic site and leads to the closure of the previously open β_E pocket.²⁰

GROMACS has provided a set of trajectory analysis tools, which are convenient for molecular conformation characterization and energy measurement. Non-bonded interaction energy ($E_{\text{non-bonded}}$) can be determined by electrostatic interaction (E_{ele}) and van der Waals interaction (E_{vdw}), which is an easy, simple but effective approach to elucidate the interactions between two specified groups. In order to identify these residues which have important roles in positioning and stabilizing ATP, the non-bonded interactions between ATP and each residue of β subunit were determined. As shown in Fig.2A, residues 158–164,

R189, Y345 have significant attractive interactions with ATP, with the strong to weak sequence of K162 > R189 > V164 > V160 > G161 > G159 > T163 > A158 > Y345 > F424. The loop segment (residues 158–164) surrounds ATP by a half and interacts with the β and γ phosphate groups through forming a network of hydrogen bonds to constraint the motion of ATP triphosphate. Residues G157, E188, E192, and D256 have a certain repulsive interactions with ATP, with the strong to weak sequence of E188 > G157 > D256 > E192. If the non-bonded interaction is decomposed into electrostatic interaction and van der Waals interaction, it is easy to find that the non-bonded interactions are mainly contributed by electrostatic interaction. In particular, Y345 interacts with ATP mainly through van der Waals interaction. As shown in Fig.1B, the spatial position distribution of these groups suggests that Y345 interacts with ATP base through π - π stacking interaction, which serves to constraint the position of ATP base. Additionally, due to the presence of the catalytic metal ion Mg²⁺, strong electrostatic interactions are existing between T163 and ATP triphosphate. Owing to the rich charged/polar natures of T163, the triphosphate group, and Mg²⁺, their interactions are very robust.

ATP is composed of three parts: a base (adenine), a ribose, and a triphosphate (Fig.3A). The numbers of hydrogen bonds formed between protein and each part of ATP were determined as shown in Fig.3B. The triphosphate moiety forms 7–12 hydrogen bonds with protein, which forms a hydrogen bond network between protein and the triphosphate moiety. These interactions seal off the catalytic site conformation and create a steady environment for ATP synthesis/hydrolysis. For other two parts, expect only one hydrogen bond between ATP base and protein occasionally, nearly no hydrogen bonds are formed. It suggests that the hydrogen bond interactions between F₁-ATPase and ATP are chiefly located at the triphosphate moiety.

As above mentioned, due to the charged nature of ATP triphosphate-Mg²⁺ complex, there exists multitude of hydrogen bond/electrostatic interactions between ATP's triphosphate and F₁-ATPase, which form an interaction network to seal off the open conformation of the catalytic site. To obtain a clear picture of the interaction network, the hydrogen bond interactions

Fig.1 (A) X-ray crystal structure of F₁-ATPase β subunit with bound ATP in β_{TP} conformation, the box denotes the location of catalytic site; (B) enlarged drawing of the binding pocket involving the ATP and surrounding residues, Y345 interacting with ATP base through π - π stacking interaction
r: residue

Fig.2 Interactions between F₁-ATPase β subunit and ATP

(A) non-bonded interaction ($E_{\text{non-bonded}}$), (B) local amplification of the $E_{\text{non-bonded}}$ for residues 157–164, (C) electrostatic interaction (E_{elec}), (D) van der Waals interaction (E_{vdw})

between the ATP triphosphate and the surrounding residues were examined as shown in Fig.S1, with a hydrogen bond existence map as given in Fig.S2. ATP's triphosphate moiety is surrounded by a helix (residues 161–178) and a loop (residues 157–160). The surrounding residues can be classified into two types according to the number of their hydrogen bonds formed with ATP triphosphate. The first type is single-hydrogen-bond residue, which forms only one hydrogen bond with the ATP triphosphate, such as G159, V160, G161, T163, and V164. The single hydrogen bond is formed between nitrogen atom in these residues and β or γ oxygen atom in ATP triphosphate, with normal occupancy values 60%–80%, such as $\text{N}-\text{H}\cdots\text{OB}_1$ on V160 (occupancy = $60.0\% \pm 6.8\%$), $\text{N}-\text{H}\cdots\text{OB}_1$ on G161 (oc-

cupancy = $73.7\% \pm 7.7\%$) and $\text{N}-\text{H}\cdots\text{OB}_2$ on T163 (occupancy = $77.7\% \pm 3.5\%$). The strongest hydrogen bond $\text{N}-\text{H}\cdots\text{OA}_2$ is formed on V164 with occupancy as high as $100\% \pm 0\%$ while the weakest hydrogen bond $\text{N}-\text{H}\cdots\text{OG}_3$ is formed on G159 with occupancy = $37.1\% \pm 13.4\%$. The second type is multi-hydrogen-bond residue, such as K162, R189. Similar to single-hydrogen-bond residue, a robust hydrogen bond $\text{N}-\text{H}\cdots\text{OB}_1$ is formed between the nitrogen atom of K162 and β oxygen atom in ATP triphosphate with a high occupancy ($97.1\% \pm 0.6\%$). The other hydrogen bonds on K162 are formed between the amino group of K162 and the ATP triphosphate. K162's amino group has three hydrogen atoms, which are able to alternatively form hydrogen bonds with β or γ oxygen

Fig.3 (A) ATP is composed of a triphosphate, a ribose and a base; (B) time evolution of hydrogen bond number for each component of ATP

atoms in ATP triphosphate due to the rotational feature of the bond $C_\epsilon - N_\epsilon$ of K162. Another multi-hydrogen-bond residue is R189 with two amino groups, which can form robust hydrogen bonds with ATP triphosphate: $N_{\eta 1} - H \cdots OG_2$ (occupancy = $62.9\% \pm 9.8\%$) and $N_{\eta 2} - H \cdots OG_1$ (occupancy = $91.9\% \pm 6.0\%$). It should be noted that except hydrogen bond, hydroxyl oxygen OG_1 on T163 establishes strong electrostatic interactions with the atoms OB_2 , OG_2 on ATP triphosphate through a catalytic ion Mg^{2+} .

As above mentioned, the ribose and base of ATP have nearly no hydrogen bond interactions with F₁-ATPase. As shown in Fig.2D, a significant van der Waals interaction was detected between ATP base and Y345. As shown in Fig.4A, the spatial position distribution of these groups suggests that Y345 interacts with ATP base through π - π stacking interaction, which serves to position the ATP base. Single point mutations at Y345 were prepared as the starting configurations and MD simulations were carried out to further investigate the role of Y345. π - π stacking interactions are generally formed between aromatic groups. Considering the aromaticity of Y345's side chain, several aromatic amino acid residues were chosen to substitute for Y345, such as histidine (HIS), phenylalanine (PHE). HIS has a side chain of imidazole group which is aromatic under any pH value.²¹ PHE is a nonpolar α -amino acid with an aromatic benzyl side chain. These mutated protein-ATP complexes were solvated and ionized following the same procedure as the WT system. MD simulations with each mutated system were carried out for 50 ns. For clarity, the distances between the center of masses (COMs) of ATP base and the aromatic groups of Y345, Y345F, and Y345H are referred as D_{Y-base} , D_{F-base} , D_{H-base} respectively. Here, the time evolutions of these distances were monitored with their distributions as shown in Fig.4B. It is significant that D_{Y-base} for WT system is small with a narrow distribution, suggesting the π - π stacking interaction between the hydroxyphenyl group of Y345 and ATP base is robust. The D_{H-base} distribution curve for Y345H has one peak near 0.375 nm as well. However it has wider distribution with respect to the D_{Y-base} distribution curve for WT system. This is attributed

to the weak interaction between the imidazole ring of H345 and ATP base. A detailed examination of the MD simulation trajectory shows that the orientation of H345's imidazole ring can be easily deflected from the plane parallel to the ATP base, leading to a poor stacking on ATP base. Therefore the substitution of Y345 to HIS apparently decreases the stability of π - π stacking interaction in WT system. PHE has a similar structure to TYR except one less hydroxy in the benzyl ring. Our simulations show the mutation Y345F can also establish π - π stacking interaction with ATP base. However, as shown in Fig.4B, the peak of D_{F-base} curve is located near 0.43 nm, a larger value than those of D_{Y-base} , D_{H-base} , which means that a weaker π - π stacking interaction was established in the Y345F system. However, regardless of weak or strong interactions, these residues with aromatic side chains can establish π - π stacking interaction with ATP base. Compared with residue PHE, TYR has one more hydroxyl group. Although the additional OH group does not hydrogen bond with ATP, the above analysis suggests that it may help to strengthen the π - π stacking interaction between Y345 and ATP base.

Additionally, the time evolution of the distance between the triphosphate and base of ATP, was determined as shown in Fig.5. It is interesting to find that at time $t = 50, 60, 80$ ns, many peaks are observed in the distance curve, suggesting that the distance between ATP triphosphate and its base is increased suddenly and then restores to its original value. The MD trajectory movie shows that these peaks are corresponding to the sliding motions of ATP base, which are still parallel to the aromatic ring of Y345. Known from the above analysis, protein almost does not impose constraint on ATP base through hydrogen bonds. Compared to electrostatic interaction, van der Waals interaction is a weak but essential interaction. Among these residues, Y345 has a strongest van der Waals interaction with ATP (Fig.2D). This interaction is mainly manifested as the π - π stacking interaction between Y345 aromatic ring and ATP base. It is evident that Y345 applies a two-dimensional constraint on ATP base and ATP base can make sliding motions parallel to Y345's aromatic ring. This motion can widen the distance

Fig.4 (A) Definition of distance between these π - π stacking interaction groups; (B) histograms of the distance distribution for D_{Y-base} , D_{F-base} , D_{H-base}

D_{Y-base} , D_{F-base} , D_{H-base} represent the distances between the hydroxyphenyl group in Y345 (WT system), the benzene ring in F345, the imidazole ring in H345 and ATP base, respectively.

Fig.5 (A) Definition of the distance, d , between the COMs of ATP's triphosphate and base; (B) time evolution of d
These peaks denote the sliding motions of ATP base.

between ATP triphosphate and base. On the other hand, the phosphate terminal of ATP is firmly held by the hydrogen bond network imposed by F_1 -ATPase. In view of the hydrolysis of ATP is the process to separate terminal phosphate from ATP, it is deduced that this motion may have a favorable contribution to ATP hydrolysis.

4 Conclusion remarks

ATP synthesis/hydrolysis reactions occur in steady environments to shield the disturbance from thermal oscillation. F_1 -ATPase makes extensive interactions with ATP through forming a network of interactions around ATP. The interactions between protein and ATP provide a powerful guarantee for successful ATP synthesis/hydrolysis. Understanding these interactions between ATP and F_1 -ATPase is essential for understanding ATP synthesis/hydrolysis. In this work, all-atom MD simulations were performed using the β_{TP} subunit in F_1 -ATPase with bound ATP in explicit water to elucidate these interactions. By scanning the non-bonded interactions between ATP and each residue of the β_{TP} subunit in F_1 -ATPase, it is found that residues 158–164, R189, Y345 have significant interactions with ATP. The loop segment (residues 158–164) and R189 surround ATP by a half and they interact with the β and γ phosphates through forming a network of hydrogen bonds to constraint the motion of ATP triphosphate. The interaction network seals off the catalytic site conformation, and creates a steady environment for ATP synthesis/hydrolysis. In addition, ATP base is constrained by the π - π stacking interaction from Y345. However, ATP base can make sliding motions parallel to Y345's aromatic ring. It is deduced that this motion may have relationship with ATP hydrolysis.

On the other hand, it is evidenced that ATP interacting with F_1 -ATPase adopts a different way from that in transcription. RNA polymerase adopts a three-component (hydrophobic contact, base stacking, and base pairing) mechanism for correctly positioning the incoming NTP base and the motion of the incoming NTP base is minimized. For ATP hydrolysis in F_1 -ATPase, ATP base is constrained only by the π - π stacking interaction from Y345 and it can move in the two-dimensional

plane parallel to Y345's aromatic group. The nucleotide moiety of NTP is incorporated into the 3' terminal of a nascent RNA with a pyrophosphate (PP_i) which is released from the active site. For ATP hydrolysis in F_1 -ATPase, ATP is hydrolyzed into an ADP and a P_i while both of them are released from the active site. Their resemblance lies in the fact that a steady environment is needed for chemical reactions. It is expected that our study throws light on the interactions between F_1 -ATPase and ATP and provides useful information for understanding the mechanism of ATP synthesis/hydrolysis.

Supporting Information: The snapshots of the hydrogen bonds between ATP triphosphate and F_1 -ATPase have been shown. Additionally, the existence map for these hydrogen bonds has been included. This information is available free of charge via the internet at <http://www.whxb.pku.edu.cn>.

References

- (1) Ueno, H.; Suzuki, T.; Kinoshita, K.; Yoshida, M. *Proc. Natl. Acad. Sci. U. S. A.* **2005**, *102*, 1333. doi: 10.1073/pnas.0407857102
- (2) (a) Mitchell, P. *Nature* **1961**, *191*, 144. doi: 10.1038/191144a0
(b) Rastogi, V. K.; Girvin, M. E. *Nature* **1999**, *402*, 263.
- (3) (a) Abrahams, J. P.; Leslie, A.; Lutter, R.; Walker, J. E. *Nature* **1994**, *370*, 621. doi: 10.1038/370621a0
(b) Zhou, Y.; Duncan, T. M.; Cross, R. L. *Proc. Natl. Acad. Sci. U. S. A.* **1997**, *94*, 10583.
(c) Okuno, D.; Iino, R.; Noji, H. *J. Biochem.* **2011**, *149*, 655.
(d) Iino, R.; Hasegawa, R.; Tabata, K. V.; Noji, H. *J. Biol. Chem.* **2009**, *284*, 17457.
- (4) Al-Shawi, M. K.; Nakamoto, R. K. *Biochemistry* **1997**, *36*, 12954. doi: 10.1021/bi971477z
- (5) Masaike, T.; Mitome, N.; Noji, H.; Muneyuki, E.; Yasuda, R.; Kinoshita, K.; Yoshida, M. *J. Exp. Biol.* **2000**, *203*, 1.
- (6) Dittrich, M.; Schulten, K. *J. Bioenerg. Biomembr.* **2005**, *37*, 441. doi: 10.1007/s10863-005-9487-7
- (7) Da, L. T.; Avila, F. P.; Wang, D.; Huang, X. *PLOS Comput. Biol.*

- 2013**, 9, e1003020.
- (8) (a) Moustafa, I. M.; Shen, H.; Morton, B.; Colina, C. M.; Cameron, C. E. *J. Mol. Biol.* **2011**, 410, 159. doi: 10.1016/j.jmb.2011.04.078
(b) Hammes-Schiffer, S.; Benkovic, S. J. *Annu. Rev. Biochem.* **2006**, 75.
- (9) Zhang, H.; Lu, J. R.; Mu, J. B.; Liu, J. B.; Yang, X. Y.; Wang, M. J.; Zhang, R. B. *Acta Phys. -Chim. Sin.* **2015**, 31, 566. [张 贺, 卢俊瑞, 穆江蓓, 刘金彪, 杨旭云, 王美君, 张瑞波. 物理化学学报, **2015**, 31, 566.] doi: 10.3866/PKU.WHXB 201501061
- (10) Ai, Y. X.; Lu, J. R.; Xin, C. W.; Mu, J. B.; Yang, X. Y.; Zhang, H. *Acta Phys. -Chim. Sin.* **2015**, 30, 559. [艾义新, 卢俊瑞, 辛春伟, 穆江蓓, 杨旭芸, 张 贺. 物理化学学报, **2014**, 30, 559.] doi: 10.3866/PKU.WHXB201401132
- (11) Wu, S. G.; Sun, T.; Zhou, P.; Zhou, J. *Acta Phys. -Chim. Sin.* **2012**, 28, 978. [伍绍贵, 孙 婷, 周 萍, 周 俊. 物理化学学报, **2012**, 28, 978.] doi: 10.3866/PKU.WHXB201202142
- (12) Duan, Y.; Wu, C.; Chowdhury, S.; Lee, M. C.; Xiong, G.; Zhang, W.; Yang, R.; Cieplak, P.; Luo, R.; Lee, T. *J. Comput. Chem.* **2003**, 24, 1999.
- (13) Meagher, K. L.; Redman, L. T.; Carlson, H. A. *J. Comput. Chem.* **2003**, 24, 1016. doi: 10.1002/jcc.v24:9
- (14) Bowler, M. W.; Montgomery, M. G.; Leslie, A. G.; Walker, J. E. *J. Biol. Chem.* **2007**, 282, 14238. doi: 10.1074/jbc.M700203200
- (15) Miyamoto, S.; Kollman, P. A. *J. Comp. Chem.* **1992**, 13, 952.
- (16) (a) Essmann, U.; Perera, L.; Berkowitz, M. L.; Darden, T.; Lee, H.; Pedersen, L. G. *J. Chem. Phys.* **1995**, 103, 8577. doi: 10.1063/1.470117
(b) Darden, T.; York, D.; Pedersen, L. *J. Chem. Phys.* **1993**, 98, 10089.
- (17) Berendsen, H. J.; Postma, J. P. M.; van Gunsteren, W. F.; DiNola, A.; Haak, J. *J. Chem. Phys.* **1984**, 81, 3684. doi: 10.1063/1.448118
- (18) Bussi, G.; Donadio, D.; Parrinello, M. *J. Chem. Phys.* **2007**, 126, 014101. doi: 10.1063/1.2408420
- (19) Hess, B.; Bekker, H.; Berendsen, H. J.; Fraaije, J. G. *J. Comput. Chem.* **1997**, 18, 1463.
- (20) Oster, G.; Wang, H. *Biochim. Biophys. Acta* **2000**, 1458, 482. doi: 10.1016/S0005-2728(00)00096-7
- (21) Mrozek, A.; Karolak-Wojciechowska, J.; Kieć-Kononowicz, K. *J. Mol. Struct.* **2003**, 655, 397. doi: 10.1016/S0022-2860(03)00282-5

分子动力学研究 F_1 -ATP 合酶对三磷酸腺苷的稳定和定位作用

伍绍贵^{1,2,*} 高晓彤¹ 李 权¹ 廖 杰¹ 徐成刚¹

(¹ 四川师范大学化学与材料科学学院, 成都 610068;

² 中国科学院理论物理研究所理论物理国家重点实验室, 北京 100190)

F_1 -ATPase Stabilizes and Positions Adenosine Triphosphate Revealed by Molecular Dynamics Simulations

WU Shao-Gui^{1,2,*} GAO Xiao-Tong¹ LI Quan¹ LIAO Jie¹ XU Cheng-Gang¹

(¹ College of Chemistry and Material Science, Sichuan Normal University, Chengdu 610068, P. R. China; ² State Key Laboratory of Theoretical Physics, Institute of Theoretical Physics, Chinese Academy of Sciences, Beijing 100190, P. R. China)

*Corresponding author. Email: wsgchem@foxmail.com; Tel: +86-28-84760802.

Fig.S1 Snapshots of the hydrogen bonds between ATP triphosphate and F₁-ATPase. These involved residues include (A) G159, (B) V160, (C) G161, (D) K162, (E) T163, (F) V164, (G) R189

These hydrogen bonds form an interaction network to constraint the motion of ATP triphosphate.

Fig.S2 Mapping of the existence of hydrogen bonds

Conformations were sampled every 20 ps and a total number of 1000 conformations were taken from each trajectory. The average occupancies and corresponding standard deviations are calculated from 12 independent trajectories of 20 ns.