

AT10A_HUMAN 63 RDKTQKYLTLSPFPPKNELEQFRRPANNVTFIALLNFPAVHAFQFGLALAPVIFLALTT
AT11C_HUMAN 47 RIVSFKYTLNPFPPKNELEQFRRRANFVPHIFLVOVTVDTPTSPVTSGLPLFFVITVT
AT8A1_HUMAN 53 HVSTAKYNTITFPPRFVYEQFRRRANSPVPHIFALLOQIFDVSPTGRYTTLVPLLIILAVA
AT8A2_HUMAN 72 QISTAKYSVLTFFPPRFVYEQFRRRANSPVPHIFALLOQIFDVSPTGRYTTLVPLLIILVIA
AT8B1_HUMAN 96 AIKTYKYNATFPPMNLVYEQFRRRANLVPHIFALLILOVFOISTLAWYTTLVPLLVLVQVT
AT8B2_HUMAN 52 CLKTKYKYLTLTFPPVNLVYEQFQEVANTVPHIFLLILOLFOISLQSWFTTIVPLVVLVIT

AT10A_HUMAN 123 AFRDLWEDYSRRRSDHKINHLGCLVFSREKKYVNRFMKEINVGDFVRLRCNEIFPADIL
AT11C_HUMAN 106 AIKQGYEDCLRRRADNEVNNKSTVYIIE..NAKRVRKESKEMVGDDVEVQADETFPCDII
AT8A1_HUMAN 113 AIKEIIEDIKRRKADNANNKKQTIVLR..NGAWKIVHKKVAVGDIVKVTNGENLPADII
AT8A2_HUMAN 132 GIKEIIEDFKRRKADNANNKKKTIVLR..NGMWHITMKVAVGDIVKVVNGQYLPADVV
AT8B1_HUMAN 156 AIKDLVDDVARRKMDKEINNRITCEVIK..DGRFKVAKMKEIYVGVIRLKKNDVFPADIL
AT8B2_HUMAN 112 AVKDATDDYFRKSKDNNVNNRQSQVLI..NGILQEQEMNVVGVDIKLENNQFVAQDL

AT10A_HUMAN 183 LSSSEDPDGLCHIEETANLDGETNLKRRQVVRGFSE..LVSEFNLFITFSVTECRPPNDLS
AT11C_HUMAN 164 LSSCTIDGTQYVITASLDGETNCKTHYAVRDTIA..LCTAESIDTLRAAIECEPPDPLIY
AT8A1_HUMAN 171 SLSSSEFPQAMCYVETANLDGETNLKRRQGLPATSD..IKDVSIMKRLSGRIECEPPNRRLIY
AT8A2_HUMAN 190 LSSSEFPQAMCYVETANLDGETNLKRRQGLSHTAD..MQTREVLMKLSGTIECEPPNRRLIY
AT8B1_HUMAN 214 LSSSEFPNSLCYVETANLDGETNLKSKMSLEITDQYQREDTIAITFDGPIECEPPNRRLD
AT8B2_HUMAN 170 LSSSEPHGLCYIETANLDGETNMMVRRQALFVISE..LGDISKIAKFDGVEICEPPNRRLD

AT10A_HUMAN 242 RFRGCTIHDNGK...KAGLYKENSLELQCTLRNTDAVVGVIVYAGHETKALLNNSGPRY
AT11C_HUMAN 223 RFRGCRINIYNSLEAVARSLEPENLLEKATLRNTEKIYGVAVYDMEETKALLNMYQKSSQ
AT8A1_HUMAN 230 DFVGNIRLDGHG...TVPLGADQILLRQALRNTQWVHGIVVYDHDTKLMOHSTSPFL
AT8A2_HUMAN 249 DFTGNIRLDGKS...LVALSPDQILLRQALRNTQWVHGIVVYDHDTKLMOHSTKAPL
AT8B1_HUMAN 274 RFTGTLFWRN.T...SFFLDADKILLRQALRNTDFCHGLVIFAGADTKIMKNSGKTRF
AT8B2_HUMAN 229 RFRGCTLYWKE.N...KFFPSNQNILLRQALRNTDWCFLVIFAGADTKLMOHSTGRTKF

AT10A_HUMAN 298 RRSKLERQMNCDVINCYLLVCHSFSAVGRLIMRYQEKSLFYFPKSDGS.SLSPVT
AT11C_HUMAN 283 RRSAAVEKSNAFLLVYLFLLTKAAVCTILKYVWGSTFYND.EPWNQKTKERETLKV
AT8A1_HUMAN 286 RLSNVERIRVQILLIFCILLVMSLVCSVGSANRRRSHGK..DNYLNLNYGG...ASN
AT8A2_HUMAN 305 RLSNVEKYRVQILLVFGILLVMAVSSAGALYNRRSHGK..NMYIKKMDTT...SDNF
AT8B1_HUMAN 329 RRTKIDYLRNMYVTIFVVLILLSAGLAIGHAYEAQVGN.SMYLYDGEDD...TFSY
AT8B2_HUMAN 284 RRSIDRRLNMTLVLMIFGFLVCMQVILAGNATWREVEGMRPQVLPWDEAVD...SAFF

AT10A_HUMAN 357 AAVYSFLMTIIVLQVLTIPSLSVYSREIVKACOVYF1HDDMQLYDEETDQLQCRALNIE
AT11C_HUMAN 342 KMFTDFLRFMVLNPF1IPVSMYVTVKQKFLGSPF1SWDKDFYDEINEGALVNTSDLNE
AT8A1_HUMAN 341 ..GLNPLTFIILFNNLSPISLVTIYVVKYTAQYF1HWDLDMHYEPTDAMARTSNLNE
AT8A2_HUMAN 360 ..GYNLLTFIILYNNLSPISLVTIYVVKYTAQYF1HWDTDMYIYGNDFAMARTSNLNE
AT8B1_HUMAN 384 RGFLIFWGYIIVLNTMVPISLVSVEVIRLQGSF1HWDLQMYAEKDTFAKARTTNLNE
AT8B2_HUMAN 341 SGFLSFWYIILNLTVPVPSLVSVEVIRLGRSYF1HWDKKMFCKKRTFAKARTTNLNE

AT10A_HUMAN 417 L L G Q V Y I F D K T G T L T N K M V F R G C T V S G V E Y S H D A N A Q R L A R Y Q E A D S E E E E V V P R G G
AT11C_HUMAN 402 L L G Q V D Y I F D K T G T L T N S M S F I E C I D G H K Y K G V T Q E V D G L S Q T D G T L T V F D K
ATSA1_HUMAN 399 L L G Q V Y I F D K T G T L T N V M F F K K C T I A G V A Y S H V P E P E D Y G C
ATSA2_HUMAN 418 L L G Q V Y I F D K T G T L T N I M F F K K C S I A G V T Y S H F P E L A R E P S
ATSB1_HUMAN 444 L L G Q V Y I F D K T G T L T N I M F F K K C I N G Q I V G D H R D A S Q R N H
ATSB2_HUMAN 401 L L G Q V Y I F D K T G T L T N I M F F K K C I N G H S Y G D V F D V L G H K A E L

AT10A_HUMAN 477 S V S O R G S I G S H Q S V R V V H R T Q S T K S H R R T G S R A E A K R A S M L S K H T A F S S P M E . K D I T F D F
AT11C_HUMAN 446 S V S O R G S I G S H Q S V R V V H R T Q S T K S H R R T G S R A E A K R A S M L S K H T A F S S P M E . K D I T F D F
ATSA1_HUMAN 443 S P D E N Q . N S Q F G D E K T F D S
ATSA2_HUMAN 462 S D O F C R M F P C S D S C D F D F
ATSB1_HUMAN 488 N K I E Q V D F S N N T Y A D G K L A F Y D H
ATSB2_HUMAN 447 G E R P E P V D F S F N P L A D K K F L F D F

AT10A_HUMAN 536 K L L E K Y S E C D K S L A V A R H Q E H L L A H L S F E L S D V F D F F I A L T C N I F V Y T S P D Q P R T K V R V
AT11C_HUMAN 457 V L I D K N R E E L F L R A L C H M V E I K T N D A
ATSA1_HUMAN 462 S L L E N I O N N H F T A F I C E F L T M M A V G G V V F E
ATSA2_HUMAN 482 R L L K N E D R H F T A P C I O E F L T L L A V G G V V F E
ATSB1_HUMAN 511 Y L I E Q I O S G . K E P E V R C F F L L A G G I I A I V M V D
ATSB2_HUMAN 471 S L L E A V K I G . D F H T H E F F L L I S G G I I A I V M S E

AT10A_HUMAN 596 R F E L K S P V K T I E D F L R R F T P S C L T S G C S S I G S L A A N K S S H K L G S S F P S T P S S D G M L L R L E
AT11C_HUMAN
ATSA1_HUMAN
ATSA2_HUMAN
ATSB1_HUMAN
ATSB2_HUMAN

AT10A_HUMAN 656 E R L G Q P T S A I A S N G Y S S Q A D N W A S E L A Q E Q E S E R E D R Y E A E S P D E A A L V Y A R A Y N C V L V
AT11C_HUMAN 483 V D G A T E S A E L T Y I S S S P D E A A L V K G A K R Y G F T F L
ATSA1_HUMAN 494 R E G D K I I Y Q A A S P D E A A L V R A A K Q L N F V F T
ATSA2_HUMAN 514 K D G D N I I Y Q A A S P D E A A L V K G A K L G F V F T
ATSB1_HUMAN 541 R T D G Q L N Y Q A A S P D E A A L V N A A R N F G F A F L
ATSB2_HUMAN 500 E K N E G E L Y I K A G S P D E A A L V F A R N F G F V F R

AT10A_HUMAN 716 E R L H D Q V S V E L P H L G R L T P E R H T L S P D V R R R M S V I V R H P L T D E T N V Y T K G A D S V V M D L
AT11C_HUMAN 517 G N R N G Y M R V E N Q R K E I E E Y E D H T L N F D A V R R R M S V I V K T Q E . G D I L L F G K G A D A V F F R
ATSA1_HUMAN 524 G R T P D S V I I D S L G . Q E E R Y E D N V L N F T S A R R R M S V I V R T P S . C K L R L Y C K G A D T V I Y D R
ATSA2_HUMAN 544 A N T P F S V I I E A M G . Q E Q T F G D N V L S P S D R R R M S V I V R T P S . C R L R L Y C K G A D N V I F E R
ATSB1_HUMAN 571 A M T Q N T I T I S E L G . T E R T Y N V A I L S P N S D R R R M S I V R T P E . C N I K R L Y C K G A D T V I Y E R
ATSB2_HUMAN 531 S E T P K T I T V H E M G . T A I T Y Q E A I L S P N N T R R R M S V I V R N P E . C K I R L Y C K G A D I L L D R

AT10A_HUMAN 776 L Q P C S S V D A R G R H K K I R S K T Q N Y L N V Y A A E G G R T L C I A K R V L S K E E Y A C M L Q S H L E A E S
AT11C_HUMAN 576 V Q N H E I E L T K V H V E R N A M D G Y R T L C V A F K E I A P D D Y E R I N R Q L I E A E M
ATSA1_HUMAN 582 L A E T S K . Y K E I T L K H L E Q F A T E G G R T L C F A V A K I S E S D F Q E M R A V Y Q R A S T
ATSA2_HUMAN 602 L S K D S K . Y M E E T L C H L E Y F A T E G G R T L C V A Y A D L S E N E Y E E M L K V Y Q E A S T
ATSB1_HUMAN 629 L H R M N F T . K Q E T Q D A L D I F A N E T L R T L C L C Y K E I E E K F T E M N K K F M A S V
ATSB2_HUMAN 589 L H H S T Q E L L N T F M D H L N E Y A E G G R T I V L A Y K D L D E E Y E E M A E R R L O S L

AT10A_HUMAN 836 S L E N S E E L T F Q S A T R L E T N I R L G A T A I E D R L O G G V F E T I S K L R C A S L Q I W Y L T G D K S E T
AT11C_HUMAN 624 A L Q D R E E K M E K V F D I E T N M N L G A T A V E D R L O D Q A A T I E A L H A A S L K V W Y L T G D K S E T
ATSA1_HUMAN 632 S V Q N R L L K L E E S Y L I E E K N L L G A T A I E D R L O Q V F E T I E T L M K A D I K I W Y L T G D K S E T
ATSA2_HUMAN 652 I L K D R A Q R L E E C Y H I E E K N L L G A T A I E D R L O A G V F E T I A T L K A E I K I W Y L T G D K S E T
ATSB1_HUMAN 679 A S T N R D E A L D K V Y H E I E K D L I G A T A I E D R L O G V F E T I S K L A R A D I K I W Y L T G D K S E T
ATSB2_HUMAN 640 A Q D S E D R L A S I Y E V E N M M L G A T A I E D R L O G V F E T I A I L T L A W I K I W Y L T G D K S E T

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AT10A_HUMAN 896  A V N I A T A C K L L D H D E E V T I N A T Q E A C A L L D Q C . L C Y V Q S R G L Q R A P E . K T G K V . . .
AT11C_HUMAN 684  A K S T C H A C R L F Q T N T E L L E I T T K T E E S E A K E D R L H E L L I E Y R K K L L H E F F . K . . . . .
AT8A1_HUMAN 692  A H N I G R S C K L L K K N M G M I V I N E G S . L D G T I E T L S . . . . . R . . . . . H C T T L G D A . . .
AT8A2_HUMAN 712  A H N I G T S C R L V S Q N M A L L L K E D S . L D A T A A A I T . . . . . Q . . . . . H C T D L G N L . . .
AT8B1_HUMAN 739  A E N I G F A C E L L T E D T T I C Y G E D I M S L L N A R M E N Q . . . . . R N R G G V Y A K F A P P V Q E S F . .
AT8B2_HUMAN 700  A V N I G S C K M L T D D M T E V F I V T G H T V L E V E E L R . . . . . K A R E K M M D S S . R S V G N G F T Y

AT10A_HUMAN 951  S M R F S S L C P P F S T S T A S G R R P S R W I D G . . . . .
AT11C_HUMAN 736  . . . . . S T R S F K K A W T E H Q E Y C R I D C S T L S L I L N S S . . . . .
AT8A1_HUMAN 734  . . . . . L R K E N D F A R I D G . . . . .
AT8A2_HUMAN 754  . . . . . L G K E N D V A R I D G . . . . .
AT8B1_HUMAN 791  . . . . . F P F G G N R A R I T C S W L N E I L L E K K T K R N K I L K L K F P R T E E E R R M R T Q
AT8B2_HUMAN 753  Q D K L S S S K L T S V L E A V A G E Y A R I N G . . . . .

AT10A_HUMAN 977  . R S L A Y A L E K N L E D K F L F L A K Q C R S V H C C R S T P H Q K S M V K I V R S K L . K A M T L A I G D G A N
AT11C_HUMAN 767  . . . . . Q D S S S N N Y K S I F L Q I C M M C T R V L C C R N A P Q K A Q I V R N V K N L K G S P I T L I G D G A N
AT8A1_HUMAN 747  . K T L K Y A L T F G V R Q Y F L D L A L S C K R V H C C R V S P H Q K S E V V E N V K Q V . K V V T L A I G D G A N
AT8A2_HUMAN 767  . H T L K Y A L S F E V R R S F L D L A L S C K R V H C C R V S P H Q K S E I V D V V K R Y . K A I T L A I G D G A N
AT8B1_HUMAN 838  S M R R L E A K K E Q R Q K N F V D L A C C S R V H C C R V T P H Q K A M V V D V V K R Y . K A I T L A I G D G A N
AT8B2_HUMAN 779  . S L A H A L E A D M E L E F L E T A C A C K R V H C C R V T P H Q K A Q V E V V K Y K . K A V T L A I G D G A N

AT10A_HUMAN 1035 D V M I Q V A D V G G I G E G N Q A V M A S D F A V F K F R Y L E R L L I I H G H N C Y S R I A N V I L Y F F Y
AT11C_HUMAN 823 D V M I L E S H V G G I G K E G R Q A N R N S D Y S V F K F H L K M L L L A R G H L Y Y V R I A H L V Q Y F F Y
AT8A1_HUMAN 805 D V M I Q T A H V G G I G E G N Q A N S D D Y S I A Q F Y L E M L L I H G A N N Y N R V S K I L Y F F Y
AT8A2_HUMAN 825 D V G M I Q T A H V G G I G E G N Q A T N N S D Y A I A Q F Y L E M L L L V R G A N S Y N R V T K I L Y F F Y
AT8B1_HUMAN 897 D V M I K T A H I G V G I G E G N Q A V M S D D Y S F A Q F R Y L Q L L L V R G R M S Y I R A C K L Y F F Y
AT8B2_HUMAN 837 D V M I K T A H I G V G I G E G N Q A V L A S D Y S F S Q F R F L Q L L L V R G R M S Y L A N C K L Y F F Y

AT10A_HUMAN 1095 K N T M F V G L L F N F C F F C G S A G M I D W Y L I F F N L L F S S L P V T V G V L D R D V F A N V L T N P
AT11C_HUMAN 883 K N L C F I L P Q F L Y C F F C G S S Q P L Y D A A Y L T M Y N I C F T S L P L A Y S L L E Q H I N I D T L T S D P
AT8A1_HUMAN 865 K N I V L Y I E I N F A F V N G S S G O I L F E R W C I G L Y N V M F T A M P P T L G I F E R S C R K E N M L K Y P
AT8A2_HUMAN 885 K N I V L Y I E I N F A F V N G S S G O I L F E R W C I G L Y N V I F T A L P P T L G I F E R S C T Q E S M L R F P
AT8B1_HUMAN 957 K N F A F T L V H F W Y S F N G S S A C T A Y E D W F I T L Y N V L Y T S L P V L L M G L L Q D V S D K L S L R F P
AT8B2_HUMAN 897 K N F A F T M V H F W F C F F C G S A C T A Y E D Y F I T L Y N I V Y T S L P V L A M G V F D Q D V F E Q R S K E Y P

AT10A_HUMAN 1155 C L Y K S G N M E E Y R P R I F F N M D A A F Q G L V C F S I F Y L A Y Y D S R . . . . . V D L F T W G T P F
AT11C_HUMAN 943 R L Y M K I S G N A M L Q L G F F L Y M T F L A A F E G T V F F G T Y F L F O T A S L E E N G K V Y G N W T F G T I V
AT8A1_HUMAN 925 E L Y K T S Q N A L D F M T K V F V H C I N G L F H S V L F W F F L K A L O Y C T A F G N G K T S D Y L L L G N F V
AT8A2_HUMAN 945 C L Y K I T O N G E G F M T K V F N G H C I N A L V H S L I L F W F F M K A L E H D T V L T S G H A T D Y L F V G N I V
AT8B1_HUMAN 1017 C L Y I V G Q R D L L F N Y K R F V S L H G V L T S M I F F I F L G A Y L Q T V Q D G E A P S D Y Q S F A V T I
AT8B2_HUMAN 957 K L Y E P G Q L N L L F N K R E F I C I A G G I Y T S V L M F F E Y G F P A D A T R D D G T Q L A D Y Q S F A V T I

AT10A_HUMAN 1208 V I I A L L T F L H L G I E T K T W T M L N W I T C G F S V L F F T V A L I Y . N A S C A T C Y F S . N F Y W T X
AT11C_HUMAN 1003 F T V L V F T V L K L A L D T R F M T M I N H F V I N G S L A F V V F F F F . N G G I N P F F L K Q Q . R M Y F V F
AT8A1_HUMAN 985 Y F V V I V T C L K A G L E T S Y M T M F S H I A I W S I A L V V V F F . G I . Y S S M F A I F M A F D M S G E A
AT8A2_HUMAN 1005 Y Y V V V V T C K A G L E T T A N T K F S H L A V W S H L T L V F F . G I . Y S T M P T I F I A F D M R G Q A
AT8B1_HUMAN 1077 A S A L V I T V N F Q I G L D T S Y W T F V N A F S I F G S I A L Y F G I M F D F R S A G I H V L F F S A F Q F I C T A
AT8B2_HUMAN 1017 A S L V I V V S V Q I G L D T G W H A I N H F F I W S L A V F F A I L F A M S N G I F D M F F N Q P R F V G N A

AT10A_HUMAN 1266 Q A L L C G P V F V T L C L M T P V A A L I P R L F F R S Q G R V F F P Q L Q L A R Q L T R K S P . . . . .
AT11C_HUMAN 1061 A Q M L S V S T W L A I I L L I F I S L F P E I L L I V L K N V R R R S A R R N S C R R A S . . . . . D . . . . . S
AT8A1_HUMAN 1043 A M L F S G V F M G L L F I P V A S L L D V V Y K V I K R T A F K T L V D E V O E L E A K S Q D P G A V V L . . .
AT8A2_HUMAN 1063 T M V L S A R F M L G L L V P T A C L I E D V A M A A K H T C K K T L L E E V O E L E T K S R V L G K A V L R D S
AT8B1_HUMAN 1137 S N A L R P Y I W L T I L A V A V C L L P V V A I R F L S M T I N P S E S D K I Q K H R K L K A E E . . . . .
AT8B2_HUMAN 1077 Q N T L A P T V M L T V V L T V V C I M P V V A F P F R L N L K P D L S D T R Y T Q L V R K K Q K . . . . .

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Figure S1. Sequence alignment of ATP8A1 and other P4-ATPase. UniProt accession numbers: ATP8A1 (UniProt: Q9Y2Q0), ATP8A2 (UniProt: Q9NTI2), ATP8B1 (UniProt: O4352), ATP8B2 (UniProt: P98198), ATP10A (UniProt: O60312), ATP11C (UniProt: Q8NB49). This alignment was performed with online server ENDscript (<https://esript.ibcp.fr/ESPrpt/ENDscript/>).

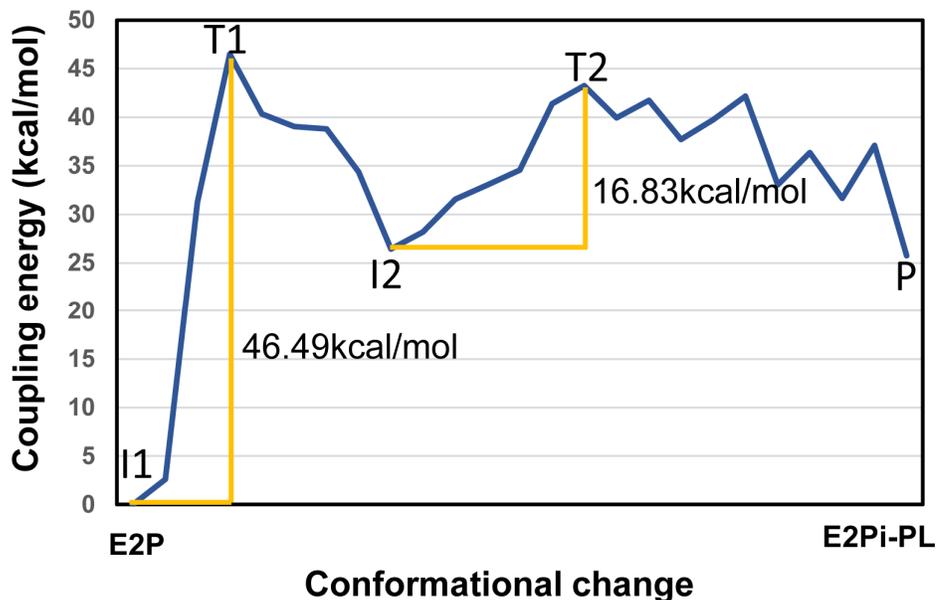


Figure S2. The coupling energy of the system during the conformational changes.

Table S1. The energy decomposition of I1, T1, I2, T2, P state (unit: kcal/mol).

	E_{Form2MC}^1	$E_{\text{Scaled size}}^2$	E_{Hydro}^3	E_{VDW}^4	$E_{\text{-DG UF}}^5$	E_{POLAR}^6	E_{total}^7	STD^8
I1	-45.30	254.49	-946.28	-24.83	0.96	-66.02	-826.98	0.41
T1	-24.70	254.49	-923.85	-25.88	0.96	-63.30	-782.28	1.36
I2	-34.60	254.49	-943.07	-24.45	0.96	-66.52	-813.19	0.20
T2	-22.28	254.49	-943.83	-24.50	0.96	-67.30	-802.46	0.67
P	-19.53	254.49	-956.36	-24.00	0.96	-65.40	-809.84	0.40

¹ Electrostatic energy term obtained using whole residue charges (0 or ± 1), which minimize electrostatic energy in the MCPT method. ² Empirical term that takes into account the effect of protein size on folding free energy. ³ Scaled hydrophobic energy term. ⁴ Scaled van der Waals energy term. ⁵ Negative of a scaled charge-charge energy estimate of an unfolded protein. ⁶ Polar energy contribution term. ⁷ The sum of E_{Form2MC} , $E_{\text{Scaled size}}$, E_{Hydro} , E_{VDW} , $E_{\text{-DG UF}}$, and E_{POLAR} . ⁸ The standard deviation.