

Hypothesis

A common topology of proteins catalyzing ATP-triggered reactions

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Abstract A protein fold, six parallel β strands surrounding the central α helix, is likely to be a common structure in protein families known to have a typical set of nucleotide binding consensus sequence motifs A and B and to catalyze ATP-triggered reactions. According to this ATP-triggered protein fold, the conserved Glu (or Asp), which acts as a general base to activate a water molecule for an in-line attack of the γ -phosphate, is at the exit of the second β strand. The fifth β strand may be involved in propagation of conformational change triggered by ATP hydrolysis.

Key words: ATP binding domain; ABC transporter; MDR folding; SecA folding; Lon protease; Proteasome

1. Introduction

Since Walker and his colleagues first reported two consensus sequence motifs A (GXXXXGKT/S; X can be varied) and B (ZZZZD; Z is a hydrophobic residue) associated with nucleotide binding [1], a large number of proteins have been shown to have these motifs. In all cases, motif A resides on the amino-terminal side relative to motif B and the distance in the primary structure between two motifs is 50–130 residues. During the study of essential residues of the F_1 -ATPase β subunit, which has a typical set of motifs A and B, we found that a conserved Glu located at 26 residues from the Lys in motif A is essential for ATPase activity; the elimination of the carboxyl group from this Glu by specific chemical modification with dicyclohexylcarbodiimide or by mutational analysis always resulted in almost complete loss of ATPase activity [2,3]. The modified or mutated enzymes retained the ability to bind substrate but were unable to catalyze even a single catalytic turnover. On the other hand, based on crystallography of the *Escherichia coli* recA protein which also has a typical set of motifs A and B, Story and Steitz proposed that Glu⁹⁶ of the recA protein is in a position to serve as a general base to activate a water molecule for an in-line attack of the γ -phosphate during ATP hydrolysis [4]. This Glu⁹⁶ is located at 24 residues from the Lys in motif A. Although there is no overall amino acid sequence similarity between the F_1 -ATPase β subunit and the recA protein, it appeared more than coincidental that the catalytic Glu's are located at almost the same position in both proteins and a similar topology of their ATP-binding domains was indicated

[5]. Indeed, the recently unraveled crystal structure of mitochondrial F_1 -ATPase (MF_1) [6] clearly showed that the folding topology of the ATP binding domain of MF_1 - β subunit is almost the same as that of the recA protein, and that the essential Glu (Glu¹⁸⁸) of MF_1 - β subunit above described is really located at the right position to act as a general base. Here, we propose that proteins containing a typical set of Walker's motifs A and B have the conserved Glu (or Asp) between the two motifs and that their topologies of the ATP binding domains are probably all common.

2. Conserved 'catalytic carboxylate' in various protein families

When the amino acid sequences of the region covering motifs A and B are aligned for several protein families which have a set of typical motifs A and B (Fig. 1), it becomes clear that occurrence of a Glu or Asp (Fig. 1, catalytic carboxylate, E) at 24 ± 2 residues from the Lys of motif A (Fig. 1, motif A, K) is a common feature (Fig. 1, distance of E-K). These Glu's (or Asp's) are well conserved in each of the protein families. Fig. 1 includes a variety of proteins which are supposed to catalyze ATP-triggered reactions and are expected to undergo conformational change upon hydrolysis (or binding) of ATP. Therefore, it is highly likely that the Glu's (or Asp's) indicated in Fig. 1 play the same functional role, activation of a water molecule to attack γ -phosphate of ATP in each of proteins as is proposed for the recA protein and F_1 -ATPase β subunit. Interestingly, F_1 -ATPase α subunit, the overall amino acid sequence of which is similar to the β subunit, has Gln instead of Glu at this position. This is quite reasonable since it has been well established that the ATP-binding site of the α subunit does not participate in ATP hydrolysis [7]. Similarly, TBP1, in which Glu is replaced by Gln, can probably bind ATP but hydrolyze it only very slowly, if at all. Examination of the primary and tertiary structure of nucleotide binding proteins which do not have a typical set of motifs A and B, such as *ras* p21 [8], EF-Tu [9], transducin- α [10], $G_{i\alpha 1}$ [11], adenylate kinases [12,13], Hsc70 ATP binding domain [14], actin [15], and myosin [16] revealed that such a catalytic Glu (or Asp) is not present at the corresponding position. Although Glu²⁰³ of transducin- α is assigned as a catalytic residue, its position in the primary structure is different from the Glu (or Asp) described here and the architecture of its ATP binding domain [10] is not similar to those of the recA protein and MF_1 - β subunit.

3. Putative 'catalytic carboxylate' in ABC transporters

In members of the ABC (ATP-binding cassette) transporter family [17] which have a typical set of motifs A and B, the

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Abbreviations: MF_1 , F_1 -ATPase from a bovine heart mitochondria.

	motif A		Catalytic carboxylate		motif B		Position		Distance	Function
	β_A	K	α_C	E	β_B	D	K	E		
RecA	R I V E I Y G P E S S G K T T L T L Q V I A A A Q R E K T C A F I D A E A L D E I Y A R K L G V						172	86	144	Uptake of ssDNA by ds DNA.
E. coli	R I E I V G P E S S G K T T V A L H A I A E V Q Q Q - R T S A F I D A E H A L D E I Y A Q K L G V						70	93	141	Mediates DNA recombination.
M. tuberculosis	R V I E I Y G P E S S G K T T V A L H A V A M A Q A G G V A A F I D A E H A L D E I Y A K K L G V						73	97	146	
H ⁺ -ATPase										
F ₁ - β										
bovine	K K I G L F G A G V G K T V L I M E L I M V A K A H G C Y S V F A G C E R T R E G M D L Y H E						162	186	266	ATP synthase catalytic subunit.
spinach	K K I G L F G A G V G K T V L I M E L I M V A K A H G C Y S V F A G C E R T R E G M D L Y H E						176	204	273	
E. coli	K K I G L F G A G V G K T V M M E L I R M I A I E H S G Y S V F A G C E R T R E G M D F Y H E						185	181	242	
Bacillus PS3	K K I G L F G A G V G K T V L I Q E L I E M I A Q E H G G I S V F A G C E R T R E G M D L Y H E						164	190	262	
F ₁ - α										
Bacillus PS3	Q R R L I I G D R Q T G K T S V A I D T I I N Q K - D Q M M I C I Y V A I G Q K K E S T V A T V V E T						176	200	281	ATP synthase non-catalytic subunit.
V _i 69% subunit										
Carrot	G T C A I P G A F G C G K T V I S Q A L S K Y S M S D T V V Y V G C E R G M E M A E V L M D F F Q						288	281	362	Vacuolar type ATPase catalytic subunit.
Thermophilus	G T A A I P G P F G C G K T V T Q Q S L A K M S M A D V V V Y V G C E R G M E M T D V L V E F F E						234	257	326	
Saccharomycetes	G T A A I P G P F G C G K T V T Q S L A K M S A A K V V I Y V G C E R G M E M T D E L R S F F K						230	262	330	
FliI family										
FliI	Q R I G I P A G S G V G K S T L M G M I A K Q T A D L M V I A L V G E R G R E V R E F I K K D L G						173	194	257	Flagellum-specific export.
Spa7	Q R M G I P A S A D C K T F L M M L I E H S G A D I Y V I G L I G D R G R E V T E T V D Y L K M						166	188	246	Surface Presentation of Ipa Antigen.
PulA family										
PulA	R Q V L M Y G P P G T G K T L M A R A V A N E T - G A F F F L I M G E V M S K M A G E S E S M L R						260	262	313	Cell cycle and cell division control.
CDC48 (N)	R Q V L M Y G P P G T G K T L L A K A V A T E V - S A M F I S V K G E L L S M N Y G E S E S M L R						633	666	866	
CDC48 (C)	R Q V L M Y G P P G T G K T L I A R A V A N E T - G A F F I L I M G E I M S K L A G E S E S M L R						261	273	304	Not known. Shows ATPase activity.
p97 (N)	K Q V L Y G P P G C G K T L L A K A I A M E C - Q A M F I S I K G E L L T M F W G S E A M V R						634	646	877	
p97 (C)	K Q V L Y G P P G C G K T L L A K A I G M L A R E P I V M G E I L N Y V G S E A M V R						274	297	336	Vesicle-mediated transport.
NSP (N)	V S V L L E C P P I S G K T A L A K I A E E S - M F P F I K I C S D K M I G E S E T A K C Q A M						657	679	811	
NSP (C)	V S V L L E C P P I S G K T A L A K I A E E S - M F P F I K I C S D K M I G E S E T A K C Q A M						467	490	625	Involved in peroxisome biosynthesis.
Pat1 (N)	S A I L D C Q G I G K T L L E V E S D H E I F V K V A C T L L E T S M L D K T Q						744	766	797	Secretory protein transport.
Pat1 (C)	S A I L D C Q G I G K T L L A S A V A Q C - G L M I F S V K G E I L N K F I C A S E S M I R						267	310	346	Cell division protein.
Sec18 (N)	K Q L L Y G P P G C K T L I A R K I G T M A K E K I V M G E I L S K Y G S E S M I R						680	682	623	Suppression of a transactivator mutant.
Sec18 (C)	V S L I E G A G S G K T A L A K I A L S G F F I R L I S P N E L S G M S E A K I A Y I D						196	201	261	HIV Tat-mediated transactivation.
PatH	K Q V L M Y G P P G T G K T L L A K A I A G A - K V P F F T I S G D F V E M F V G C A S V R						196	201	261	Interacts with HIV Tat transactivator.
SUG1	K Q V L M Y G P P G T G K T L L A R A V A N E T - D C F I R V S G A E L V Q K Y I G E S R M V R						222	244	276	Nitrogen fixation.
MSI1	K Q V L M Y G P P G T G K T L C A R A V A N E T - D A C F I R V I G S E L V Q K Y V G E C R M V R						196	220	261	Cell division inhibitor.
TBP1	K Q V L M Y G P P G T G K T L L A R A C A A Q T - K A T F L K L A G Q L V Q M F I G D C A K L V R						196	220	261	ATP driven As pump.
NiH family										
NiH	R Q I A P Y G K G I G K S T S Q M T L A A M A E M G Q R I M I V G C D P K A D S T R L M L H S K						19	43	128	Involved in chlorophyll synthesis.
MinD	I I V V T S K G G V G K T S S A I A T Q L A Q K G K T V V I D F I G L R M I D L I M G C E						16	40	120	Plasmid maintenance and replication.
Arx (N)	S I V F T G K G V G K T S I S C A T A I R L A Q K G K T V V I D F I G L R M I D L I M G C E						21	46	121	Protein export across the membrane.
Arx (C)	G I I M L M K G G V G K T T M A A I A V R L A D M C F D V H L T S D P A A H L S M L M G S L						340	364	417	Transcription termination factor.
PrnC	L T L A V Y G K G I G K S T S C M I S T A L A K R G K V L Q I G C D F K H D S T F T L T G F L						15	38	124	Binds to the origin of replication.
IocC	T L V T A M Q K G V G K T S T L V E L A P D F F E R G L A V A I D L D P Q G M A S Y T L K D F A						120	144	231	Chromosome replication factor.
SecA protein										
E. coli	R R C I A N M R T G K T L T A T L A Y L M A L T K I V E V V T V N D Y L A Q R D A N M M R R						108	133	209	ATP-dependent protease La.
Plutberli	D S K I A N M T G K T L V A I L A Y L M A L S G S V H I V T V N E Y L A K R D S L S V G R						104	129	206	
Rho Protein										
E. coli	Q R G L I V A P P K A G K T M L L Q M I A Q S I A Y M E P D C V L M V L L I D E R R E E V T E M Q R						184	210	265	
DnaA protein										
E. coli	M R I P L Y G G T G L K T T H L L E A V G M G I M A R K P A K V V Y M S E R F V Q D M V K A L Q						178	204	236	
DnaB protein	M R I P L Y G G T G L K T T H L L E A V G M G I M A R K P A K V V Y M S E R F V Q D M V K A L Q						157	183	214	
E. coli	D L I I V A A R S M G K T T F A M M L V E M A A M L Q D K E V L I F S L E M P E G Q I M M R S L A						237	262	343	
Staphylococcus	D L I I V A A R S M G K T T F A M M L V E M A A M L Q D K E V L I F S L E M P E G Q I M M R S L A						237	262	343	
Lon Protease										
E. coli	I I C L V G P P G V G K T S L Q S I A K A T O R K Y V R M A L G Q V R D A E I R G H R R T Y I						361	366	422	
Scerervase	K I I C F V G P P G V G K T S I Q S I A R A L M R K F F S V G G M T D V A E I K G H R R T Y I						636	663	899	
Hsp90	K I I C F V G P P G V G K T S I A R S I A R A L M R E Y F R S V G G M T D V A E I K G H R R T Y V						418	440	476	
Hsp70	I I C L V G P P G V G K T S L A R S V A R A L G R E F V R I S L G G V R D A E I R G H R R T Y V						338	363	399	

	motif A K	Catalytic carboxylate candidate 1 (E1)	Catalytic carboxylate candidate 2 (E2)		Position	Distance	Function
MDR1 (N)	GQTVALVGNSSGCGKSTTVQLMQRLYDFTTEGMVSVDDQDIRTIN	QEPVLFATTIAENIRY					
MDR1 (C)	GQTLALVGNSSGCGKSTTVQLLERFYDPLAGKVLLDGKEIKRLN	QEPILFDCSIAENIAY					
CFTR (N)	GQLLAVAGSTGAGKSTLLMMIMGELEPSEGGIKHSGRISFCSSQ	QFSWIMPQTIKENIIF					
CFTR (C)	GQRVGLLGRTGSGKSTLLSAFLRLN-TEGEIQIDGVSWDSIT	QKVFIFSGTFRKNLDP					
HisP	GDIVSIIIGSSGSGKSTFLRCINFLEKFESEGSIVVNGQTINLVR	EFNLWSHMTVLENVME					
MalK	GEFVVVFVGSFGCGKSTLLRMIAGLETTITSGDLFIGEKRMNDTP	SYALYFHLSSVAENMSF					
PstB	NQVTAFIGFSGCGKSTLLRTFNKMFELYFEQRAEGEILLDGDN	QKPTTFEEMS IYDNIAF					
FtsE	GEMAFLTGHSAGAGKSTLLKLLICGIERPSAGKIWFSGHDITRLK	DBHLLMDRTVYDNVAI					
RbsA	GRVMALVGENGAGKSTMMKVLTGIYTRDAGTLWLKETTFTG	ELNLIPQLTIAENIFL					
HlyB	GEVIGIVGRSGSGKSTLTKLIRFYIPENGQVLLDGHDLALAD	QDNVLLNRSIIDNLSL					
NodI	GECFGLLGENGAGKSTIARMLLMISPDGRGKITVLDPEVPSRA	FDNLEPEFTVR ENLLV					

	motif B D	K	E1	E2	D	E1-K	E2-K	D-E1	D-E2	Function
MDR1 (N)	RGAQLSGGQKQRIAIARALVRNEKILLLDEATSALDT	433	457	486	555	24	53	98	69	Multidrug resistance protein 1. (P-glycoprotein 1)
MDR1 (C)	KGTQLSGGQKQRIAIARALVRQPHILLLDEATSALDT	1078	1100	1129	1200	24	53	100	71	
CFTR (N)	GGITLSGGQRRARISLARAVYKDAADLYLLDSPFGYLDV	464	-	504	572	-	40	-	68	Cystic fibrosis transmembrane conductance regulator.
CFTR (C)	QCCVLSHGQKQRLMCLARSVLSKAILLDEPSAHLDP	1250	1276	1302	1371	26	52	95	69	
HisP	YFVHLSGGQKQRRVSIARALAMEFEVLLFDEPTSALDP	44	-	111	177	-	67	-	86	Histidine permease component.
MalK	KFKALSGGQKQRRVAIGRTLVAEFSVFLFDEPLSNLDA	42	64	94	158	22	52	94	64	Maltose permease component.
PstB	SGYSLSGGQKQRLCIAQIAIRFEVLLFDEPCSALDP	49	71	109	178	22	60	107	69	Phosphate transport system.
FtsE	FFIQLSGGQKQRRVGIAARAVNNKPAVLLADEPTGNLDD	41	65	98	162	24	57	97	64	Involved in cell division.
RbsA	LVGDLISIGDQQMVEIAKVLSFESKVIIMDEPTDALTD	43	67	98	166	24	55	99	68	Ribose permease component.
HlyB	QVAGLSGGQKQRIAIARALVNNPKILIFDEATSALDY	508	532	561	630	24	53	98	69	Export of hemolysin A.
NodI	RVSLSGGMKRRLTLARALINDEHLLVMDDEPTTGLDL	43	66	99	163	23	56	97	64	Acts in the nodulation process.

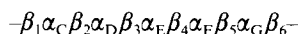
Fig. 2. Comparison of amino acid sequences of proteins of the ABC transporter family. In addition to the first candidate for catalytic carboxylate (E1), the region containing another candidate of catalytic carboxylate (E2) is also shown. In CFTR(N) and HisP sequences, candidate Glu (or Asp) is not found in the first candidate region. CFTR(C) has a replaced residue (Lys) at the second candidate position.

distance between motif A and B in the primary structure is 133–166 residues, much longer than other proteins listed in Fig. 1. Although we can find Glu (or Asp) in a region 24 ± 2 (Fig. 2, catalytic carboxylate candidate 1, E1) from the Lys of motif A in most cases, higher conservation was observed for a Glu (or Asp) in a region 59 ± 8 residues from the Lys (Fig. 2, catalytic carboxylate candidate 2, E2). There is a possibility that, in the case of the ABC transporter family, some additional structure comprising 32–41 residues is inserted in the loop region between the α_C helix and the β_2 strand (see next paragraph). The question of which one of the two conserved Glu's (or Asp's) acts as an essential residue will be easily answered by mutagenesis studies.

4. A common topology of ATP-triggered proteins

Conservation of three functional elements (motifs A, B, and a conserved Glu or Asp) among various proteins which catalyze ATP-triggered reactions might be an indication for the presence of the common structural motif in their ATP-binding domains. The following structure of the ATP-binding domain of the recA

protein, which is made up of six repetitive β - α structures, might be a prototype fold*.



The folding topology of the ATP binding domain of the MF₁- β subunit is the same as that of the recA protein except that there are two α helices between the β_4 and β_5 strands [6]. The essential feature of the structure is that the six parallel β strands and the α_C helix form the ATP binding domain (Fig. 3A). This folding motif is likely to be common to proteins listed in Figs. 1 and 2. Although there is no obvious overall sequence similarity among the protein families, distribution of amino acid residues in the sequences shown in Figs. 1 and 2 is consistent with the assumption of this protein fold. The first thirteen amino acid sequences of the proteins listed in Fig. 1 are consistent with a β strand-loop structure; several hydrophobic residues are followed by a cluster of Pro and Gly (shaded letters).

*Numbering of the α helices or β strands is corresponding to *Escherichia coli* recA protein.

Fig. 1. Comparison of amino acid sequences* of ATP binding domain in proteins which catalyze ATP-triggered reactions containing a set of typical nucleotide-binding motifs A and B. The sequence covering motif A and putative catalytic Glu (or Asp) and the sequence around motif B are shown. Lys in motif A, catalytic Glu (or Asp), and Asp in motif B are shown as K, E, and D (letters in black boxes), respectively. Pro and Gly, residues which tend to interrupt secondary structure, are shown by shaded letters. Hydrophilic residues are indicated by bold letters. Others are hydrophobic residues. In the case when a protein has duplicate sets of motifs A and B, a set at the amino-terminal side and at the carboxyl-terminal side are defined as (N) and (C), respectively. Secondary structures of the recA protein and MF₁- β subunits determined from X-ray crystallography are shown (column, α helix; arrow, β strand). Rho protein and Lon protease have another nearby conserved Glu which can also be candidates of catalytic carboxylate. The description of function for each protein is not complete; for example, SUG1, MSS1, and TBP1 probably play a regulatory role in the 26 S proteasome complex. *References from which sequence data were obtained are not cited here to avoid too many references.

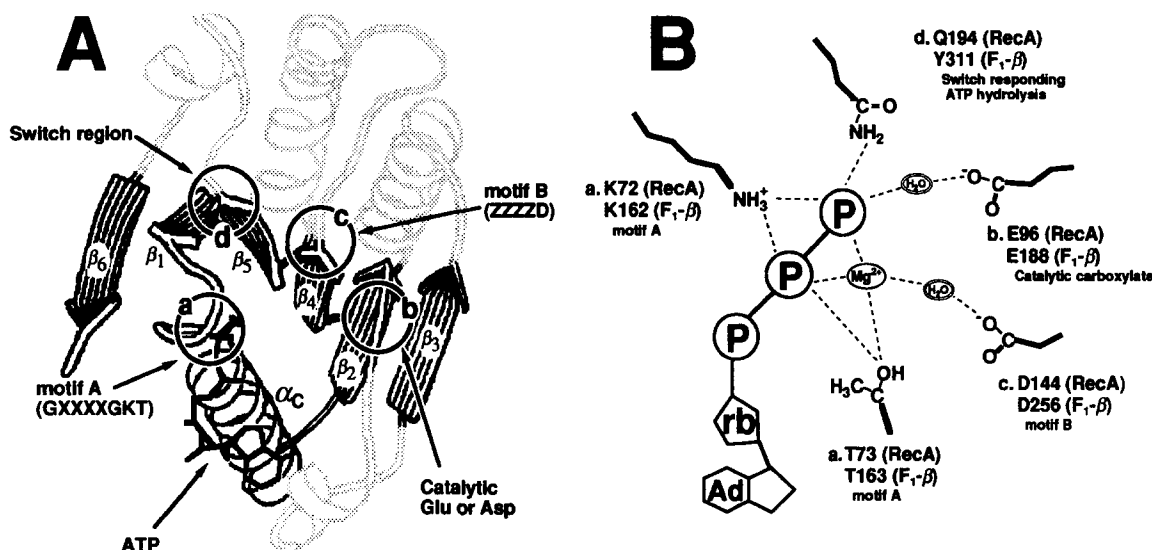


Fig. 3. (A) A common topology of the ATP binding domain of proteins which catalyze ATP-triggered reactions. Circle a, b, c, and d indicate the positions of motif A, catalytic carboxylate, motif B, and a 'switch' region, respectively. (B) Schematic illustration of residues interacting with a bound ATP molecule in this fold. Numbering of the residues in the recA protein and F_1 - β according to *E. coli* recA protein and bovine mitochondrial F_1 -ATPase β subunit, respectively.

The α_C helix starts from the Thr in motif A and shows amphiphilic characteristics in recA protein and MF_1 - β subunit [4,6]. It might also be the case in most proteins listed; hydrophilic residues (bold letters) appear periodically, 2nd, 5th (or 6th), and 9th (or 10th) positions counting from the Lys of motif A. As are observed for the recA protein and MF_1 - β subunit, the hydrophilic side of the helix is facing to the outside. There is no Pro in putative α_C helix region except secA protein**. After the α_C helix, a loop region, which tends to contain Gly and Pro, and then the relatively hydrophobic β_2 strand follow. The catalytic carboxylate, Glu (or Asp), is located immediately after the β_2 strand [4,6].

Except for the region from the β_1 strand to the β_2 strand, the length (or even number) of α helices and loops connecting each β strand might be varied from one protein family to another, thus accounting for the variable distances in the primary structures between conserved Glu (or Asp) and motif B (Fig. 1, distance of D–E). The motif B sequence in the recA protein and MF_1 - β subunit belongs to the β_4 strand which is located in the center of the ATP binding domain. The side chains of the residues in the β_4 strand are all hydrophobic and half of them are facing the hydrophobic side of the α_C helix. As demonstrated by high resolution X-ray crystallography for the Asp⁵⁷ in the non-typical motif B in *ras* P21 protein [8], the Asp in motif B (Fig. 1, motif B, D) is likely to be involved in binding of active-site Mg^{2+} through a water molecule and to also be hydrogen-bonded to the Thr of motif A (Fig. 3B).

5. 'Switch region'

In the recA protein structure, Gln¹⁹⁴ is located at the carboxyl end of the β_5 strand and is proposed to play a crucial role in

transmission of conformational changes; Gln¹⁹⁴, when interacting with the γ -phosphate of ATP, stabilizes the crystallographically disordered loop which connects β_5 strand and α_C helix, and hydrolysis of ATP destroys this interaction resulting in a change in conformation of the loop [4]. Also in the structure of MF_1 , conformation of the carboxyl end region of the β_5 strand in each of three copies of β subunits in a MF_1 molecule is substantially different from each other depending on the presence of bound nucleotide and on the interaction with the γ subunit [6]. Modification of Tyr³¹¹ in the β_5 strand by 7-chloro-4-nitrobenzofrazan in a single copy of β subunit in a MF_1 molecule is sufficient to inactivate catalytic turnover, probably by interfering with the inter-subunit conformational interaction [18,19]. Thus, it is reasonable to propose that the region at the carboxyl end of the β_5 strand of this fold is a switch region involved in propagating conformational change triggered by ATP hydrolysis. Successive conformational change occurs to the loop connecting the β_5 strand and the α_C helix which are interacting with another molecule, subunit, or functional domain of the protein. The β_6 strand provides the anchor for the α_C helix and two flanking loops, and stabilizes the β_1 strand.

6. Discussion

The occurrence of a similar folding topology among proteins with non-homologous amino acid sequences has recently been recognized for hexokinase [20], Hsc70 ATP binding domain [14], and actin [15]. Here, we point out that the proteins, the activities of which are coupled to or triggered by ATP hydrolysis, may have a common topology of the ATP-binding domain. The arrangement of catalytically important residues in the right positions in their tertiary structures may have been a consequence of convergent evolution. These residues include Lys and Thr in motif A, the catalytic Glu (or Asp), Asp in motif B, and the residue responsible for conformational transmission

**SecA protein is different from others in that it has a Pro residue in the middle of putative α_C helix and, therefore, the α_C helix of secA protein is likely to be interrupted and bent at this point.

(Fig. 3B). The validity of this postulation can be easily tested. For example, the mutagenesis of the putative catalytic Glu (or Asp) in these proteins would be easy to test.

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