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Domain Closure in Adenylate Kinase

Joints on Either Side of Two Helices Close Like Neighboring Fingers

Mark Gerstein[1], Georg Schulz[2] and Cyrus Chothia[1,3]

[1]*MRC Laboratory of Molecular Biology*
Hills Road, Cambridge CB2 2QH, U.K.

[2]*Institut für Organische Chemie und Biochemie der Universität*
Albertstrasse 21, 7800-Freiburg i. Br., F.R.G.

[3]*Cambridge Centre for Protein Engineering*
Hills Road, Cambridge CB2 2QH, U.K.

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In large variants of adenylate kinase the AMP and ATP substrates are buried by a domain rotating by 90°. Here conformational changes responsible for this domain closure are determined by an analysis of the open state of beef heart mitochondrial adenylate kinase and the closed state of *Escherichia coli* adenylate kinase. Although these two proteins have sequence differences, the principal structural changes responsible for the domain movements are large, and can clearly be distinguished from the effects of evolution.

The mobile domain is linked to the rest of the protein by two helices packed together in an antiparallel fashion. During the closure, deformations take place in four localized regions, called joints, near the N and C termini of these helices. Three of these joints have simple motions that can be well approximated by rotations of three torsion angles, but the joint that makes contact with the ligand involves motion throughout an extended loop: i.e. two torsions on either side of a reverse turn change significantly. The main chain atoms of the joints have few packing constraints. The first pair of joints is responsible for ~30° of the total rotation and the second pair for the remaining ~60°. These movements carries along the regions between the joints, the two helices and the rest of the mobile domain, to a first approximation, as rigid bodies. This jointed domain closure mechanism is contrasted with the shear mechanisms found in other enzymes.

Keywords: protein structure; conformational change; helix shear motion

1. Introduction

The mechanisms of domain movements in proteins are of interest because of their functional roles. In certain enzymes, they shield the substrate from water, surround it with catalytic residues, and prevent the escape of kinetic intermediates (Anderson *et al.*, 1979; Knowles, 1991). Domain movements in proteins also play a crucial role in cellular motion.

It has been shown that when the large variant of adenylate kinase binds its substrate, there is a dramatic change in the relative positions of its two domains (see Schulz, 1992 for a recent review). Here the principal conformational changes responsible for this dramatic movement are described and compared with those that produce domain movements in other enzymes.

2. Structure of Adenylate Kinase

Adenylate kinase is a small enzyme that catalyses the reaction: AMP + ATP⇌2 ADP. It occurs in two variants, both of which are monomeric. The small cytosolic variant has about 195 residues, and the large variant, found in mitochondria and bacteria, has about 225 residues. Both variants have a large domain that consists of a five-stranded β-sheet and nine or ten α-helices. The large variant has a second domain of 38 residues at a position where the small variant has a loop of 11 residues. This domain is called the INSERT domain and contains four strands of β-sheet, as shown in Figure 1 (Diederichs & Schulz, 1990, 1991; Dreusicke *et al.*, 1988; Müller & Schulz, 1988, 1992).

Phosphate transfer reactions require the exclusion of water. High-resolution crystal structures

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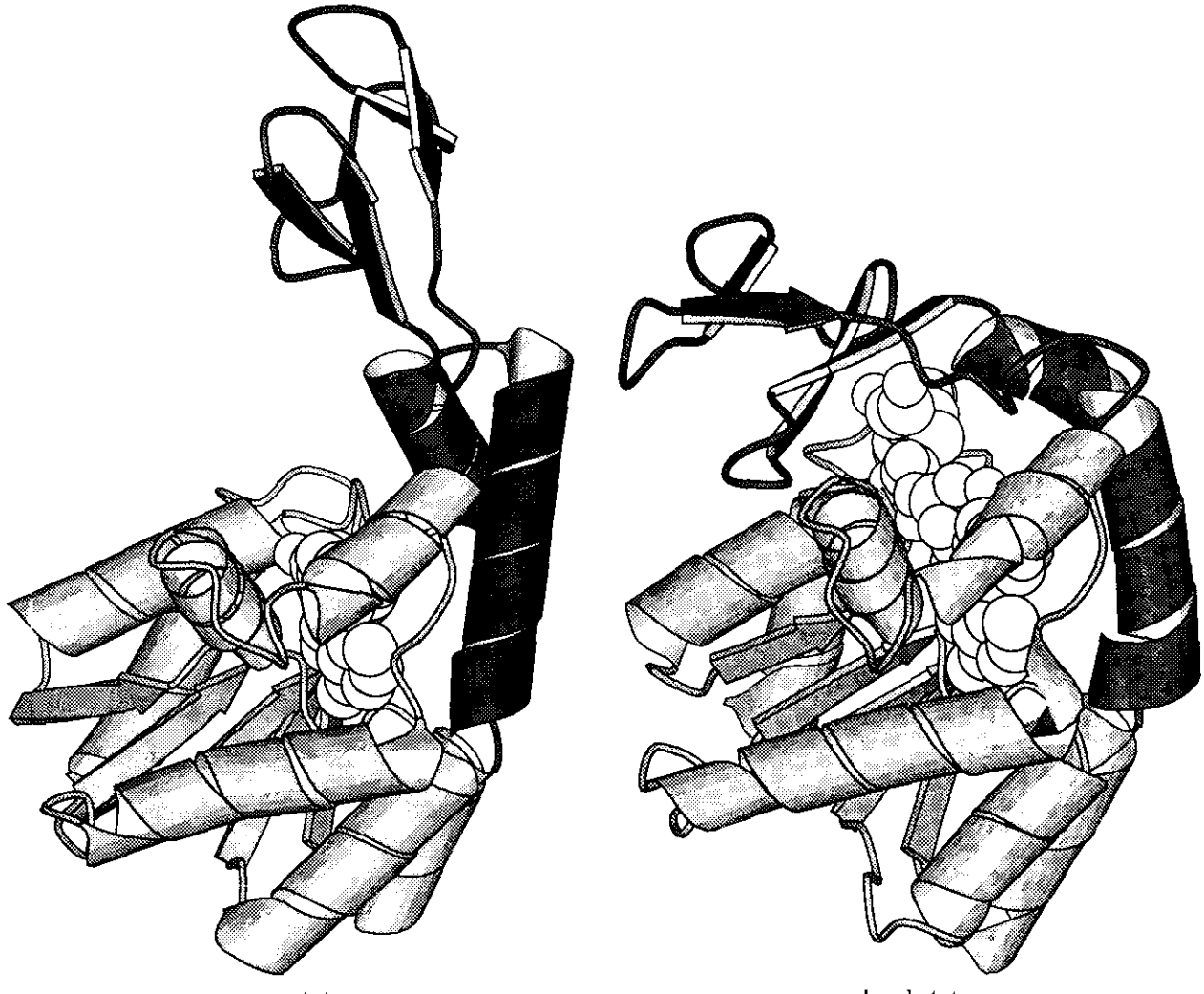

Figure 1. Domain closure in the large variant of adenylate kinase. This variant has a large domain, which contains a 5-stranded β-sheet and 9 α-helices, and an INSERT domain, which contains a 4-stranded β-sheet. On the left is shown the structure of the beef heart mitochondrial adenylate kinase with AMP bound (an example of the open state), and on the right, *E. coli* adenylate kinase with Ap_5A bound (an example of the closed state). Ap_5A mimics both the AMP and ATP substrates, and upon binding it, the INSERT domain rotates 88° and closes over the active site.

have been determined for an unliganded state of adenylate kinase (Schulz *et al.*, 1974; Dreusicke *et al.*, 1988), a state with AMP bound (Diederichs & Schulz, 1990, 1991), and a state with P^1,P^5-bis(adenosine-5'-) pentaphosphate (Ap_5A) bound (Müller & Schulz, 1988, 1992). The Ap_5A mimics both the AMP and ATP substrates. These studies indicate that the binding of each substrate is accompanied by conformational changes that bury it within the protein (Schulz *et al.*, 1990). Consequently, all but 50 Å^2 of the 1080 Å^2 of potential accessible surface of Ap_5A is inaccessible to water (1 Å = 0·1 nm).

AMP is buried by movements of two helices on one side of the large domain. These helix movements are produced by a combination of shear motions (Schulz *et al.*, 1990). Such movements have been discussed previously (Chothia *et al.*, 1983; Lesk & Chothia, 1984; Elber & Karplus, 1987; Rojewska & Elber, 1990) and so will not be addressed here.

In the large variant of adenylate kinase, binding of the second substrate results in the INSERT domain rotating by 92° to cover the active site. As shown in Figure 1a and b, C^α atoms shift by up to 32 Å. The movement of the domains is not produced by rotations around two single bonds but by a combination of conformational changes. Previously, obvious conformational changes were described, ignoring movements smaller than 3 Å (Schulz *et al.*, 1990).

3. Co-ordinates, Methods and Definitions

The structure of beef heart mitochondrial matrix adenylate kinase in a complex with AMP has been determined at a resolution of 1·85 Å (Diederichs & Schulz, 1991), and the structure of *Escherichia coli* adenylate kinase in complex with Ap_5A has been determined at a resolution of 1.9 Å (Müller & Schulz, 1992). Based on the position of the INSERT

domain in these two structures, they will here be referred to as the "open" and "closed" states, respectively. The atomic co-ordinates of these structures are available from the Brookhaven protein structure data bank with identifiers 1AK3 and 1AKE (Bernstein *et al.*, 1977).

The beef heart mitochondrial matrix and the *E. coli.* enzymes have 40% of their homologous residues identical. Sequence differences are accommodated by changes in structure (Lesk & Chothia, 1980). Consequently, for these two structures the conformational changes produced by ligand binding will be combined with those produced by sequence differences and insertions. However, the principal structural changes that occur upon ligand binding are so large that they can clearly be distinguished from those produced by evolution.

The structure comparison procedures used in the analysis have been described previously (Lesk & Chothia, 1984; Gerstein & Chothia, 1991; Lesk, 1991). Unless otherwise stated calculations were carried out using main-chain atoms i.e. N, C^{α}, C and O. Figures were generated with MOLSCRIPT (Kraulis, 1991).

The residue numbering in the beef mitochondrial matrix and *E. coli* variants differs because of insertions and deletions in certain loops. The mitochondrial numbering will be used throughout this paper. Table 1 lists structurally homologous residues in the two proteins and can be used to obtain the numbers of the equivalent residues in the *E. coli* variant. Table 2 lists definitions of the large and the INSERT domains and the linking regions connecting these domains. It also defines a well-fitting core of the large domain that consists of all but a few of the residues in the central sheet and helices 2, 4, 5 and 8. This corresponds to the part of the protein that does not have significant structural differences in the open and closed states. After fitting the cores of both states, the r.m.s.† deviation in main-chain atom positions is 0·75 Å and individual C^{α} atoms differ by no more than 1·4 Å. All differences in the relative positions of residues and helices are reported after fitting onto this core.

4. Conformational Changes that Produce the Domain Closure

The domain closure is the effect of conformational changes in four separate regions, which will be referred to as joints I, II, III and IV (Fig. 2a). These joints occur near the N and C termini of helices 6 and 7, which pack together in an antiparallel manner with their axes inclined at −50° and connect the INSERT domain to the core of the large domain. The motion of the four joints, in turn, results from a number of torsion angle changes. Some of these cancel, and the overall motion can be shown to result, principally, from changes in seven torsion angles.

† Abbreviation used: r.m.s., root-mean-square.

Table 1

Structurally equivalent residues in beef heart mitochondrial matrix and E. coli *adenylate kinases*

mitochondrial numbering		*E. coli* numbering		Change
6	81	1	76	−5
82	100	78	96	−4
101	190	98	187	−3
191	199	193	201	+2
200	211	203	214	+3

Structurally equivalent residues in beef heart mitochondrial matrix adenylate kinase (brookhaven file 1AK3) and *E. coli* adenylate kinase (file 1AKE) are shown. The difference in numbering between the equivalent residues is given in the last column. Mitochondrial numbering is used throughout the text. For all residues in the mobile INSERT domain and linking helices, the *E. coli* numbering is 3 less than the mitochondrial.

(a) *First joint: N terminus of helix 6*

The first joint mainly involves residue 118. As shown in Figure 2b, in the open state the residues around 118 are in the first turn of helix 6. The change to the closed state involves breaking four α-helical hydrogen bonds at the start of this turn and the consequent stretching and unwinding of the beginning of the helix. The bulk of this motion is accomplished by the torsion angle change of ψ_{118} by 38°. (Full details of all torsion angles changes are listed in Table 3.) The net effect of the changes is to rotate the helix axis by 35° so that C^{α} of residue 123 at the C-terminal end shifts by 4·7 Å.

Table 2

Definitions and fits of substructures

Substructure	Residues	r.m.s.	Max[a] difference substructure
A. *Definitions of the major substructures referred to in the text using mitochondrial numbering.*			
INSERT domain†	125–157		
large domain	6–114, 180–211		
linking regions	115–124, 157–179		
B. *Fits of substructures*			
INSERT domain	125–136, 142–153	0·75	1·0
Large domain (core)	6–11, 32–44, 66–78, 85–100, 107–113, 181–188, 192–194	0·75	1·4
Helix 1	21–28	0·25	0·5
Helix 6	119–123	0·20	0·25
Helix 7	166–173	0·25	0·35
Helix 9	202–210	0·35	0·75

For non-deforming (rigid) substructures, backbone fits were done of equivalent residues in open and closed states, and the resulting r.m.s. deviation of main-chain atom positions and maximum displacement of C^{α} atoms are reported in the last 2 columns. For the comparisons, molecule A was used from each of the brookhaven files (1AK3 and 1AKE). That is, in each case one of the 2 crystallographically independent molecules was selected.

† This definition of the INSERT domain is slightly different from previous usage (Schulz *et al.*, 1990), where it is defined as residues 125 to 162. An AMP-binding domain (AMPbd) was also previously defined to be residues 35 to 64.

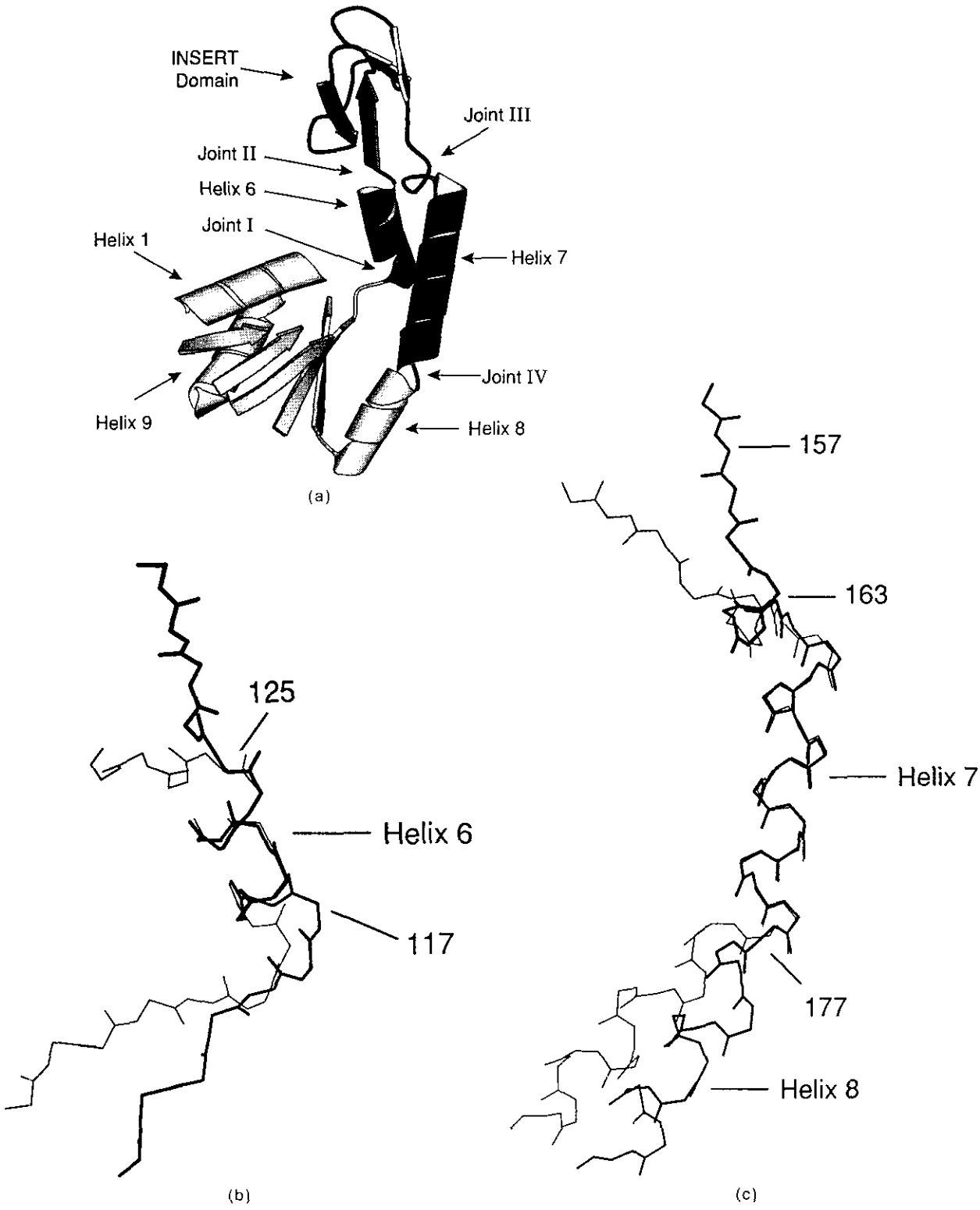

Figure 2. The 4 joints involved in domain closure. (a) The positions of the 4 joints (see the text) and the other major moving elements in the structure, helices 1, 6, 7 and 9, are indicated. The rigid sheets of the large and INSERT domains are also shown. The open state is shown, and on closure the INSERT domain comes into contact with helices 1 and 9. (b) Changes in main-chain conformation in the joint regions (I and II) around helix 6 are shown. The structures in the open state are shown in thick lines and those in the closed state are shown in thin lines. This Figure has roughly the same viewpoint as in (a). Residues 111 to 129 of the 2 states are superposed on the part of helix 6 that has same structure in both: residues 119 to 123. The changes in conformation mainly responsible for closure are residues 118 (joint I) and 125 (joint II). (c) This is drawn in the same style as (b). It shows changes in main-chain conformation in the joint regions (III and IV) around helix 7. Residues 156 to 188 of the 2 states are superposed on the part of helix 7 that has the same structure in both: residues 166 to 173. The changes in conformation mainly responsible for closure are in residues 157, 158, 162 and 163 at joint III (these are shown in greater detail in Fig. 3) and in residue 177 at joint IV.

Table 3
Details of torsion angle changes in the four joints

	Residue	$\Delta\phi$	$\Delta\psi$
I	115	−4	1
	116	−3	(19)
	117	(−15)	(17)
	118	(−16)	[38]
	119	−13	−7
	120	−1	2
II	122	4	−5
	123	7	−7
	124	30	[−41]
	125	−5	18
	126	15	9
III	154	4	−6
	155	7	(−14)
	156	(10)	−2
	157	−5	[25]
	158	13	[16]
	159	−1	−10
	160	{−4}	{−185}
	161	{171}	{48}
	162	−8	[58]
	163	[−33]	11
	164	4	(10)
	165	(−8)	−6
IV	174	0	−2
	175	−14	(12)
	176	(−15)	7
	177	[−53]	(25)
	178	(−17)	(−27)
	179	(17)	7
	180	. 2	3

Torsion angle changes that are boxed are the principal contributors to the overall domain closure motion. Changes in ψ_i and ϕ_{i+1}, the torsion angles on either side of the peptide bond, can be coupled. If $\Delta\psi_i \approx -\Delta\phi_{i+1}$ and both are small in magnitude, they approximately cancel. That is, while the peptide orientation changes considerably, the chain direction does not. Canceling pairs of $\Delta\psi_i$ and $\Delta\phi_{i+1}$ are indicated by () in the Table. For large torsion angle changes, the cancelation is not so simple, and as shown in Fig. 3, the peptide flip at residues 160 and 161 involves the cancelation of 3 large torsion angle changes, which are indicated by {} in the Table.

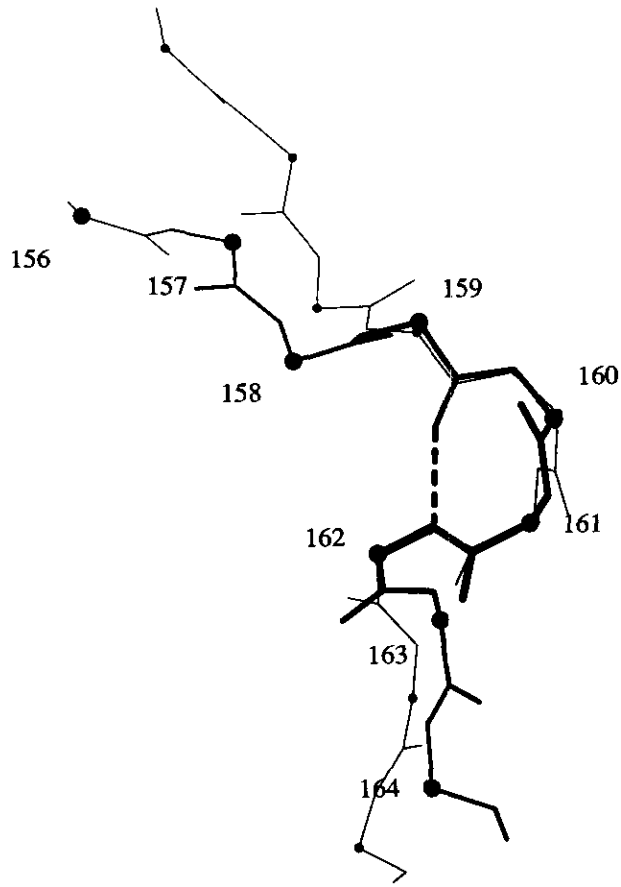

Figure 3. The complex nature of the conformational changes at joint III. Residues 156 to 164 in the 2 states are superposed by a fit of the residues that form the turn: 159 to 162. C^{α} atoms are indicated by dots. The significant conformational changes are mainly located on either side of the turn, i.e. in residues 157 and 158 on one side or in residues 162 and 163 on the other. The peptide flip in the middle of the turn does not contribute to the joint motion. The changes in 157 and 158 move the chain parallel to the plane of the drawing, and those in 162 and 163, perpendicular to the plane.

(b) *Second joint: C terminus of helix 6*

The second joint occurs at the C terminus of helix 6 in the loop connecting it with the INSERT domain (Fig. 2b). The deformation in this joint is highly localized, and most of its effect is produced by ϕ_{124} rotating by 41°.

(c) *Third joint: N terminus of helix 7*

In contrast to the simplicity of the second joint, the third joint involves a complicated set of changes. As shown in Figures 2c and 3, these occur in the loop connecting the INSERT domain to the top of helix 7, between residues 157 to 163. The middle of this loop contains a reverse turn from residues 159 to 162 with a hydrogen bond between 159-O and 162-N. Although the peptide in the center of this turn flips on going between the open and closed structures, the turn as a whole remains unchanged (Fig. 3). The changes that contribute to the domain closure are in the residues that flank the turn. The N-terminal side of the turn deforms through a change in ψ_{157} by 25° and a smaller change in ψ_{158}. The C-terminal side of the turn deforms principally through the changes in ψ_{162} and ψ_{163} (Table 3). The N- and C-terminal deformations are, interestingly, in perpendicular directions (Fig. 3).

The third joint is the only one to make extensive contact with ligand. Upon closure three charged residues on the reverse turn, Arg159, Asp161 and Asp162, make numerous hydrogen bonds to the ligand and to Arg170 and Arg126. These hydrogen bonds are absent in the open state, where only Arg159 is hydrogen-bonded to Asp161. The creation of these new hydrogen bonds changes the side-chain torsions considerably, in particular Arg159. With

this movement the active site is assembled, i.e. the arginines facilitating the phosphoryl transfer are put into place (Müller & Schulz, 1992).

(d) *Fourth joint: C terminus of helix 7*

As shown in Figure 2c, the fourth joint involves a change in the link between helices 7 and 8. These two helices are almost continuous. They are separated by a kink in the region of Pro180, where two helical hydrogen bonds are missing. Upon closure, the extent of the kinking increases mostly through a 53° change in ψ_{177} (see Table 3). This change is reduced by small twists in the succeeding torsions so that the overall effect of the fourth joint is to rotate helix 7 by 31° relative to the large domain. This rotation of helix 7 moves its N terminus (i.e. the C^{α} of residue 166) by 6·5 Å in a direction perpendicular to the original kink.

5. Rigid-body Motions

Beside the conformational changes at four joints, the major feature of the domain closure involves rigid body movements.

The four joints surround helices 6 and 7 which pack together in the open and closed structures. As shown in Table 2, upon domain closure residues 119 to 123 in helix 6 and 166 to 173 in helix 7 do not change their conformation. To a first approximation, they also move together. An exact comparison, however, shows small differences in their relative orientation in the two states. One helix is displaced relative to the other by a rotation of 14° and a shift of about 3 Å. This suggests that the relative shear movement between the helices accommodates the different effect of each joint movement. The extent of this shear movement is probably smaller than the value given here, which includes movements produced by sequence changes.

The region between joints II and III is the INSERT domain (125 to 157). To a first approximation, it moves as a rigid body (Schulz *et al.*, 1990). A sieve-fitting procedure (Lesk, 1991; Gerstein & Chothia, 1991) was used to examine this in greater detail. The procedure showed that small conformational changes shift residues 137 and 141 at the tip of the domain up to 3 Å. After subtracting these residues, the fits in Table 2 show the rest of the domain has no significant deformations.

There are small rigid-body movements within the large domain that are probably related to the closure. Helices 1 and 9 move as rigid bodies (Table 2) in a fashion that correlates with the contacts they make to the INSERT domain and substrates in the closed state. These movements are small: for the main-chain atoms 2 to 3 Å for helix 1 and 0·5 to 3·5 Å for helix 9. These values include significant contributions from the effects of sequence differences.

The C^{α} atoms in the region of helix 3 (48 to 62) differ in position between the open and closed states by up to 3·5 Å. However, the differing irregularities of helix 3 in the two proteins makes it difficult to characterize this movement simply.

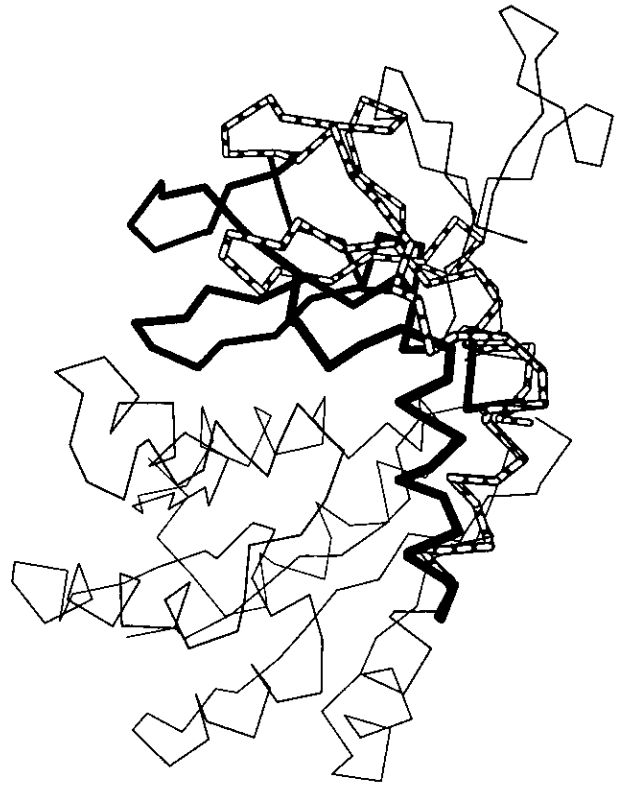

Figure 4. This figure shows the cumulative effects of the deformations in the joint regions upon domain closure. The thin lines show the conformation of the open state of adenylate kinase. The dotted lines show the position of the INSERT domain after the conformational changes at only joints II and III, and the thick black lines show its position after changes at all 4 joints.

6. Cumulative Effect of Conformational Changes

The closure is the cumulative result of changes at all four joints. It results in the INSERT domain rotating 88° and translating its center of mass by 21 Å into the active site. (These values are from the superpositions described in the Co-ordinates Methods and Definitions section. Alternate superpositions (Schulz *et al.*, 1990) give slightly different values.) The contributions of the joints I and IV can be separated from those of joints II and III. To isolate the effect of the first pair of joints, helices 6 and 7 in the closed state were fitted onto those in the open state. As shown in Figure 4, this produces an intermediate conformation, where effectively joints I and IV are still in the open state while joints II and III have closed. In this intermediate conformation, relative to the open state the rigid part of the INSERT domain has rotated by 29° and translated (its center of mass) by 7 Å.

It is also possible to calculate how much each individual joint has bent the path of the polypeptide chain. Such a calculation shows that

the first joint bends the chain, 35°; the second, 59°; the third, 68°; and the fourth, 31°. The bending of the chain at the joints is clearly shown in Figure 2b and c. The bending angles for the first and fourth joints are roughly in agreement with rotation found for the half-open conformation. The total rotation produced by the first and second joints ($35° + 59° = 94°$) is very close to that produced by the third and fourth joints ($68° + 31° = 99°$) and to the overall rotation of the INSERT domain (88°). The small discrepancies indicate that each pair of joints does not close in exactly the same direction.

7. Discussion

The mechanism of the domain closure in the large variant of adenylate kinase has been described. It has a complex character and involves four joints placed at the N and C termini of two helices. The deformation of each joint involves varying numbers of main-chain torsion angles: it is produced by rotations around essentially one bond in the case of joint II but four bonds in the case of joint III. The closure is accompanied by small shear motions between helices 6 and 7 and helices in the large domain.

Domain closure in adenylate kinase, which involves pairs of joints on either side of two helices, is similar to the bending of two neighboring fingers.

Comparison of the open state (beef mitochondrial matrix) and the closed state (*E. coli*) shows that the domain closure involves changes in the positions of the INSERT domain, helices 6 and 7 and, to a lesser extent, helices 1, 3 and 9. Shear motions of helices 3 and 4 were also reported to occur on AMP binding (Schulz *et al.*, 1990). The regions not seen to undergo significant conformational changes using the present structures are the β-sheet and helices 2, 5 and 8. Thus, ligand binding involves conformational changes in a large proportion of the molecule. Conformational changes may occur in the remaining part, but they must be small and cannot be distinguished from effects of the sequence differences in the present structures.

The use of hinges (or joints) to effect conformational change has been observed in a number of other enzymes, but the motion usually occurs on a smaller scale than found in adenylate kinase. For instance, the conformational change observed in lactate dehydrogenase (White *et al.*, 1976; Gerstein & Chothia, 1991) and triose phosphate isomerase (Alber *et al.*, 1981; Joseph *et al.*, 1990) involves the closure of a short loop over substrates in the active site. Triglyceride lipase presents an intermediate case. In this enzyme an α-helix moves 12 Å to close the active site through local changes in the peptides on either side of the helix (Derewenda *et al.*, 1992).

In contrast to adenylate kinase, the large-scale movements of domains found in hexokinase (Bennett & Steitz, 1978, 1980), alcohol dehydrogenase (Eklund *et al.*, 1981), aspartate aminotransferase (Borisov *et al.*, 1978; Eichele *et al.*, 1979; Arnone *et al.*, 1982) and citrate synthase (Remington *et al.*, 1982) do not involve hinges (or joints) to a great degree. In these enzymes the principal feature of the closure mechanism is shear motions, usually involving helices (Lesk & Chothia, 1984; McPhalen *et al.*, 1992). The shear motions are limited in size and occur both within and between domains. The overall closure movement is the cumulative effect of a number of such motions. Abrupt changes in main-chain conformation (i.e. as at hinges) are found in the links between the helices but they are usually small, and their role is to facilitate the shear motions.

The use of hinges rather than shear motions in adenylate kinase is clearly related to the structure of the interface between the domains. In the examples of shear motion discussed above the domains are in direct contact and have interfaces formed by close-packed segments of polypeptide, usually helices. Such close-packing places severe constraints on the movements that can occur at the interface, and so the closure is produced by a number of movements distributed over the protein (Lesk & Chothia, 1984). In adenylate kinase, on the other hand, the INSERT domain has no contact with the large domain except through the linking helices. This absence of packing constraints allows local changes in main-chain conformation to produce dramatic changes in the orientation of the domains.

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