Discussion Letter

Phosphate-binding sequences in nucleotide-binding proteins

W. Möller and R. Amons

Department of Medical Biochemistry, Sylvius Laboratories, PO Box 9503, 2300 RA Leiden, The Netherlands

Received 22 April 1985

In the three-dimensional model of adenylate kinase, the phosphate-binding site for AMP and ATP has been identified [Pai, E.F. et al. (1977) J. Mol. Biol. 114, 37–45]. In this region one can distinguish a sequence glycine XXXX glycinelysine. The same sequence is found in many other mononucleotide-binding proteins including elongation factors and oncogenic P21 proteins. Dinucleotide-binding proteins display a pyrophosphate-binding unit with a glycine pattern different from that of mononucleotide-binding proteins. It has been found that P21 *ras* protein possesses a strand motif typical for (pyro)phosphate binding of a mononucleotide. A single mutation at position 12 can confer oncogenic activity on the protein. Based on the assumption that amino acid residues which are critical for function are preferentially conserved, we predict from the sequence that glycine residue 15 rather than residue 12 is important for (pyro)phosphate binding.

Mononucleotide-binding protein *Dinucleotide-binding protein* *Adenylate kinase* *Elongation factor* *P21* ras *protein* *Phosphate-binding region*

1. INTRODUCTION

Guanine nucleotide-binding proteins are important in protein synthesis, hormone action and tubulin assemblage [1]. Their conformation depends on the state of the nucleotide bound and this fact may be instrumental for the association and the dissociation with their neighbors [2].

The transforming *ras* genes of Harvey and Kirsten murine sarcoma viruses encode for a guanine nucleotide-binding protein, named P21 [3]. A single nucleotide substitution of guanine into thymine in the normal cellular proto-oncogene leads to activation of the P21 protein gene [4,5]. This substitution corresponds to a Gly→Val replacement at position 12 of P21 protein, thereby possibly inducing T24 and EJ bladder carcinoma [4,5].

Although the precise biochemical function of P21 protein is unknown, comparative properties of P21 *ras* molecules coded for by viral and cellular *ras* genes have established that all known members of the *ras* gene family bind guanine nucleotides [6,7]. Interestingly, it has been noticed that the amino acid sequence surrounding position 12 of P21 protein resembles a loop which is part of a nucleotide-binding site in an ATP-binding [8] and in a dinucleotide-binding [9] protein. As a result the prediction has been made that the Gly→Val replacement would alter the nucleotide-binding properties such as to lead to induction of transformation [8,9]. However, the question can be raised as to how valid comparisons of P21 proteins with ATP- or dinucleotide-binding enzymes [8,9] are, especially since there is no evidence that ATP or dinucleotides bind to P21 protein. A comparison of P21 with guanine nucleotide-binding proteins in the region of the pyrophosphate moiety is therefore of interest. In addition, it is worth knowing whether the properties of the phosphate-binding region of nucleotide-binding proteins obey certain rules which are dependent on the nature of the base and are different for mono- and dinucleotides.

2. SEQUENCE CHARACTERISTICS OF MONONUCLEOTIDE-BINDING PROTEINS

We decided to focus first on possible common

Published by Elsevier Science Publishers B.V. (Biomedical Division)
00145793/85/$3.30

features in the amino acid sequence of mononucleotide-binding proteins. A search among this class of proteins gave a pattern as given in table 1.

A clue that the recurrent sequence GXXXXGK in the different mononucleotide-binding proteins of table 1 is not purely coincidental but reflects a special strand motif directed towards (pyro)phosphate binding came from X-ray crystallographic studies on adenylate kinase. It has been found by Pai et al. [10] that in the crystal structure of adenylate kinase the phosphate moiety of AMP is surrounded by a loop, connecting a β-sheet to an α-helix. The amino acid sequence of this loop, residues 16–23, coincides with the sequence ^{15}GGPGSGK^{21} of table 1. The wide-spread occurrence of the sequence GXXXXGK among mononucleotide-binding proteins suggests that in general it represents a structurally and energetically favorable strand design for binding the (pyro)phosphate group.

Inspection of table 1 shows that the oncogenic substitution Gly 12→Val 12 in the PEJ/T24 oncogene product P21 occurs at a position of an

Table 1

Mononucleotide-binding proteins

	Residue number	Sequence	Ref.
(A) Adenine nucleotide-binding proteins			
Adenylate kinase (porcine, human, rabbit)	9–23	K I I F V V G G P G S G K G T	[21–23]
GTP:AMP phosphotransferase (beef-heart mitochondria)	6–20	L L R A I M G A P G S G K G T	[24]
ATPase (β-subunit) (bovine)	150–164	G K I G L F G G A G V G K T V	[18,19]
Nitrogenase Fe-proteins (7 different species; two given)		R Q I A F Y G K G G I G K S T	[20]
		R Q C A I Y G K G G I G K S T	[20]
(B) Guanine nucleotide-binding proteins			
(a) P21 proteins			
v-ras H	4–18	Y K L V V V G A R G V G K S A	[25]
v-ras K	4–18	Y K L V V V G A S G V G K S A	[26]
pEC/normal c-has/bas 1	4–18	Y K L V V V G A G G V G K S A	[4,5]
pEJ/T24 oncogene cHa-ras-I	4–18	Y K L V V V G A V G V G K S A	[4,5]
YP2 (*S. cerevisiae*)	9–23	F K L L L I G N S G V G K S C	[27]
c-ras^{sc-1} (*S. cerevisiae*)	11–25	T K I V V V G G G G V G K S A	[28]
(b) Transducing G-proteins			
Transducin T_α 32		V K L L L L G A G E S G K S T	[14]
G-protein $G_{o\alpha}$ 37		V K L L L L G A G E S G K S T	[14]
(c) Elongation and initiation factors			
EF-Tu (*E. coli*)	12–26	V N V G T I G H V D H G K T T	[29–31]
EF-Tu (*S. cerevisiae* mitochondria)	49–63	V N I G T I G H V D H G K T T	[32]
EF-Tu (*E. gracilis* chloroplasts)	13–27	I N I G T I G H V D H G K T T	[33]
EF-1α (*Artemia*)	7–21	I N I V V I G H V D S G K S T	[34]
EF-1α (*S. cerevisiae*)	8–22	I N V V V I G H V D S G K S T	[35,36]
EF-G (*E. coli*)	10–24	R N I G I S A H I D A G K T T	[37]
IF-2 (*E. coli*)	392–406	P V V T I M G H V D H G K T S	[38]
(d) Tubulin proteins			
α-Tubulin (porcine brain)	136–150	S V F H S F G G G T G S G F T	[39]
β-Tubulin (porcine brain)	134–148	Q L T H S L G G G T G S G M G	[40]

amino acid that is quite variable in different P21 proteins as opposed to the invariant glycine residue at position 15.

Therefore, it is not a priori clear that substitution of Gly 12→Val 12 should decrease nucleotide binding to P21 protein due to steric hindrance of the phosphate moiety of bound GDP by a valine residue (cf. [9]). From this viewpoint a substitution at Gly 15 is expected to have a greater influence on GDP binding. In fact, the replacement Gly 12→Val 12 in P21 protein did not reveal a major alteration in its ability to bind guanine nucleotides [11]. It looks as if the transforming properties of PEJ/T24-P21 protein are related to an unknown change in the secondary structure of the (pyro)phosphate-binding region resulting in a lower GTPase activity and in a different gross conformation of the protein [11].

Earlier model calculations of the three-dimensional structure of the PEJ/T24 oncogene product indicate that the Gly 12 peptide has a conformation and flexibility which are larger than those of the Val 12 peptide [12]. These differences may well influence the rate of transition between a GTP and GDP conformation of the protein. Conformational differences between the GTP and GDP form of guanine nucleotide-binding proteins, for instance, elongation factor EF-Tu, have been observed by means of spectral and chemical means [2].

P21 protein resembles the class of transducing G-proteins [13] and its exchange of GDP for GTP proceeds somewhat analogously to that of EF-Tu under influence of EF-Ts. A clear, structural homology of P21 protein with G-protein or transducin has been demonstrated in the region purported to be essential for nucleotide binding (see table 1 and [14]).

Concerning the elongation factors, we prefer the alignment as given first by Halliday [15] for EF-Tu from *E. coli* rather than the EF-Tu sequence near Gly 222 and Gly 224, mentioned by Duisterwinkel et al. [16] as part of the (pyro)phosphate-binding loop. Although residues 222–229 of EF-Tu have the sequence ^{224}GXXXXGR^{229}, the likelihood that the N-terminal region of EF-Tu contains the phosphate-binding group seems to us greater for the following reasons: A better homology with all the other mononucleotide-binding proteins and the consistency of the proposed location of the (pyro)phosphate group near the N-terminal end of the protein. Publication of X-ray structure details of the binding of GDP to EF-Tu from *E. coli* will be an independent judge of the uniqueness of this consensus sequence for (pyro)phosphate binding.

The larger sequence homology within the group of protein synthetic factors, compared to other mononucleotide-binding proteins (table 1), is in line with the idea that these factors interact with a common region of the ribosome including proteins L7, L12, L10 and L11, known to be involved in GTP hydrolysis [17].

Similar sequences are also found in bovine ATPase (β-subunit) [18,19], and a number of Fe-proteins reviewed in [20] containing bound MgATP and MgADP (table 1). In the N-terminal region of Fe-proteins, resemblance in sequence to the loop region of adenylate kinase was noted and therefore this region was held to form a part of an adenylate-binding domain [20].

3. SEQUENCES IN DINUCLEOTIDE-BINDING PROTEINS

X-ray analysis of FAD- and NAD-binding enzymes has revealed striking structural similarities in nucleotide-binding fold patterns. Especially characteristic is the binding of the dinucleotide at the C-terminal ends of the parallel β-strands of Rossmann folds [41–44]. A detailed comparison of the three-dimensional structure of glutathione reductase and *p*-hydroxybenzoate hydroxylase in the FAD- and NAD-binding domains shows that, in all cases, the pyrophosphate group of the dinucleotide approaches a very short loop connecting the first β-strand and the following α-helix of a $\beta\alpha\beta$ unit [45]. In this connecting region one can distinguish two especially conserved glycine residues, the first having torsion angles (ϕ,ψ) in an exceptional region, the second having (ϕ,ψ) values at the border of the allowed region for glycine and being close to the pyrophosphate group. A third glycine or alanine is in the α-helix opposing the β-strand. The presence of the pyrophosphate group close to the second invariant glycine residue at the amino-terminal end of the α-helix is in agreement with the prediction of a neutralizing dipole field on a negative charge [46].

These three glycine residues are also recognizable in a number of other dinucleotide-

binding proteins if one aligns their primary structure against those of which the three-dimensional structure is known. Judged from the data of table 2, which includes recent examples given by Rice et al. [47], the sequence XhXhGXG, two hydrophobic amino acids, followed by two glycine residues which are separated by one amino acid, represents the minimal phosphoryl-binding region of a large number of dinucleotide-binding proteins.

A third glycine XhXhGXGXXG is often present but is sometimes replaced by alanine, XhXhGXGXXA (see table 2). In horse liver alcohol dehydrogenase [48], glutathione reductase [49], and *p*-hydroxybenzoate hydroxylase [45], the two invariant hydrophobic amino acids and the first invariant glycine residue are near the end of a β-sheet while the second and third glycine residues are in an α-helix and possess properties, described above for glutathione reductase and *p*-hydroxybenzoate hydrolyase (see also table 3).

It should be mentioned that a number of exceptions from the sequence XhXhGXGXX$^{A}_{G}$ occur. For instance, the phosphoryl-binding loop of lobster glyceraldehyde-3-phosphate dehydrogenase, located near the amino terminus of the protein, follows the dinucleotide consensus sequence ^{4}GIDGFGRIGR^{13} [50,51] with the exception of the second hydrophobic residue, which is replaced by an aspartic acid residue. Other examples of dinucleotide proteins in which the consensus sequence has not been found are mercuric reductase and yeast alcohol dehydrogenase (table 2).

4. A COMPARISON BETWEEN THE (PYRO)PHOSPHATE-BINDING SEQUENCES OF MONO- AND DINUCLEOTIDE-BINDING PROTEINS

In all cases studied one observes a β-strand connected to an α-helix via a short loop in the (pyro)-phosphate-binding region. In and bordering the loop, one can distinguish a number of critically placed glycine residues which facilitate the formation of a sharp bend in the loop region. Particularly noticeable is a glycine residue near the beginning of the α-helix and situated close to a

Table 2

Dinucleotide-binding proteins

	Residue number	Sequence	Co-enzyme	Ref.
Glutathione reductase, FAD-binding domain (human)	24–34	L V I G G G S G G L A	FAD	[52]
Glutathione reductase, NADPH-binding domain (human)	191–201	V I V G A G Y I A V E	NADP	[52]
p-Hydroxybenzoate hydroxylase	6–16	A I I G A G P S G L L	FAD	[53]
Alcohol dehydrogenase (horse liver)	196–206	A V F G L G G V G L S	NAD	[54]
Lactate dehydrogenase (dogfish, muscle)	24–34	T V V G V G A V G M A	NAD	[55]
Lactate dehydrogenase (pig, muscle)	23–33	T V V G V G A V G M A	NAD	[56]
Lactate dehydrogenase (pig, heart)	24–34	T V V G V G Q V G M A	NAD	[56]
D-Amino acid oxidase	4–14	V V I G A G V I G L S	FAD	[57]
Lipoamide dehydrogenase (pig heart)	8–18	T V I G S G P G G Y V	FAD	[58]
Lipoamide dehydrogenase (*E. coli*), FAD-binding domain	9–19	V V L G A G P A G Y S	FAD	[59]
Lipoamide dehydrogenase (*E. coli*), NAD-binding domain	178–188	L V M G G G I I G L E	NAD	[59]
Mercuric reductase, FAD-binding domain	102–112	A V I G S G G A A M A	FAD	[60]
Mercuric reductase, NADP-binding domain	274–284	A V I G S S V V A L E	NADP	[60]
Glyceraldehyde-3-phosphate dehydrogenase (lobster)	4–14	G I D G F G R I G R L	NAD	[51]
Alcohol dehydrogenase (*S. cerevisiae*)	196–207	R V L G I D G G E G K E	NAD	[61]

Table 3

Structure of phosphate-binding sites in mono- and dinucleotide-binding proteins, as determined by X-ray crystallography

	Residue number		Ref.
(A) Mononucleotide-binding proteins			
		β-sheet α-helix	
Adenylate kinase (pig)	10–25	I I F V V G G P G S G K G T Q C	[10,21–23]
(B) Dinucleotide-binding proteins			
		β-sheet * α-helix	
Glutathione reductase (FAD domain)	22–34	D Y L V I G G G S G G L A	[45,52]
p-Hydroxybenzoate hydroxylase (FAD-domain)	4–16	Q V A I I G A G P S G L L	[45,53]
		β-sheet α-helix	
Glyceraldehyde-3-phosphate dehydrogenase (lobster)	2–14	L I G I D G F G R I G R L	[50,51]

In adenylate kinase, the phosphate group of AMP is wrapped in the loop structure formed by residue 17–22, connecting the β-sheet and α-helix as shown. In dinucleotide-binding proteins, the pyrophosphate group is located near the glycine residue indicated by an asterisk, at the beginning of the α-helix. The sequence pattern of the phosphate-binding region in the given three-dimensional structures is in agreement with the proposed consensus sequences (see tables 1 and 2). For none of the other proteins discussed has the three-dimensional structure, including the (pyro)phosphate-binding site, been published

phosphate group. This feature is in agreement with the notion of an electrostatically favorable interaction between an anion and the positive end of an α-helix dipole [46]. Dinucleotide-binding proteins follow the sequence GXGXXG in which the first glycine is close to the purine neighboring ribose, the second close to the pyrophosphate and the third near the beginning of the α-helix. Following the third glycine, one usually sees a hydrophobic residue.

In mononucleotide-binding proteins the sequence GXXXXGK is part of a loop which in the case of adenylate kinase is larger (table 3). The presence of a lysine next to the second glycine is intriguing. The general occurrence of a positively charged residue at this position (see table 1) may reflect neutralization of the extra negative charge of a free vs an internal pyrophosphate group.

Although the consensus sequences of mononucleotide-binding proteins as reported here are rather short, they are representative of (pyro)phosphate binding loops, especially if one includes the glycine, serine or threonine residue found at the position following the common sequence GXXXXGK. This conclusion is based on a search of the Protein Segment Dictionary of Dayhoff et al. [62]. Apparently, this unique consensus sequence forms a subclass of a more general class of strand motifs in which certain hydrophobic amino acids stabilize β-sheet interactions and in which critically placed glycine residues induce the formation of a flexible loop, that accommodates a negatively charged group.

In L7/L12 proteins, this group is a sulphate ion bound at the beginning of an α-helix preceded by a β-sheet via a short loop [63]. The sequence in this β-sheet/α-helix unit is XhXhXXXG and is well conserved for 15 different prokaryotic and eukaryotic L7/L12 proteins ([64,65] and unpublished).

5. COMPLEMENTARY NUCLEOTIDE-BINDING SITES

Besides mutations in position 12 changes at position 59/61 of P21 proteins also alter the oncogenic and GTP-dependent properties of *ras* oncogene products [11,66]. At present, little is known about the possible reason for this effect at position 61.

Leberman and Egner [67] compared protein se-

quences around position 110 in P21 protein and found in this region of P21 certain homologies with EF-Tu and some adenine nucleotide binding proteins, including adenylate kinase. Interestingly, the homologous part of the chain, notably around position 110 of this kinase, runs in its three-dimensional structure [10] just behind the ribose and base moiety of AMP. Conceivably, homologies found in the region of position 110 in P21 protein and adenylate kinase reflect the conservation of a complementary nucleotide-binding site.

ACKNOWLEDGEMENTS

We thank Dr T.F.M. la Cour and Dr J. Nyborg for their information, help and kind discussion; Dr A. Liljas for suggesting improvements in the alignment and Drs H. Eklund, F. Müller, M.G. Rossmann, G.E. Schulz, S. Thirup and R.K. Wierenga for information and criticism.

REFERENCES

[1] Hughes, S.M. (1983) FEBS Lett. 164, 1–8.
[2] Kaziro, Y. (1978) Biochim. Biophys. Acta 505, 95–127.
[3] Shih, T.Y., Papageorge, A.G., Stokes, P.E., Weeks, M.O. and Scolnick, E.M. (1980) Nature 287, 686–691.
[4] Tabin, C.J., Bradley, S.M., Bargmann, C.I., Weinberg, R.A., Papageorge, A.G., Scolnick, E.M., Dhar, R., Lowy, D.R. and Chang, E.H. (1982) Nature 300, 143–149.
[5] Reddy, E.P., Reynolds, R.K., Santos, E. and Barbacid, M. (1982) Nature 300, 149–152.
[6] Scolnick, E.M., Papageorge, A.G. and Shih, T.Y. (1979) Proc. Natl. Acad. Sci. USA 76, 5355–5359.
[7] Papageorge, A.G., Lowy, D. and Scolnick, E.M. (1982) J. Virol. 44, 509–519.
[8] Gay, N.J. and Walker, J.E. (1983) Nature 301, 262–264.
[9] Wierenga, R.K. and Hol, W.G.J. (1983) Nature 302, 842–844.
[10] Pai, E.F., Sachsenheimer, W., Schirmer, R.H. and Schulz, G.E. (1977) J. Mol. Biol. 114, 37–45.
[11] McGrath, J.P., Capon, D.J., Goeddel, D.V. and Levinson, A.D. (1984) Nature 310, 644–649.
[12] Pincus, M.R., Van Renswoude, J., Hartford, J.B., Chang, E.M., Cartty, R.P. and Klausner, R.D. (1983) Proc. Natl. Acad. Sci. USA 80, 5253–5257.
[13] Gilman, A.G. (1984) Cell 36, 577–579.
[14] Hurley, J.B., Simon, M.I., Teplow, D.B., Robishaw, J.D. and Gilman, A.G. (1984) Science 226, 1860–1862.
[15] Halliday, K.R. (1984) J. Cyclic Nucl. Protein Phosph. Res. 9, 435–448.
[16] Duisterwinkel, F.J., Kraal, B., De Graaf, J.M., Talens, A., Bosch, L., Swart, G.W.M., Parmeggiani, A., La Cour, T.F.M., Nyborg, J. and Clark, B.F.C. (1984) EMBO J. 3, 113–120.
[17] Möller, W. (1974) in: Ribosomes (Tissières, A. et al. eds) pp.711–731, Cold Spring Harbor, NY.
[18] Walker, J.E., Saraste, M., Runswick, M.J. and Gay, N.J. (1982) EMBO J. 1, 945–951.
[19] Runswick, M.J. and Walker, J.E. (1983) J. Biol. Chem. 258, 3081–3089.
[20] Robson, R.L. (1984) FEBS Lett. 173, 394–398.
[21] Heil, A., Müller, G., Noda, L., Pinder, T., Schirmer, H., Schirmer, I. and Von Zabern, I. (1974) Eur. J. Biochem. 43, 131–144.
[22] Von Zabern, I., Wittmann-Liebold, B., Untucht-Grau, R., Schirmer, R.H. and Pai, E.F. (1976) Eur. J. Biochem. 68, 281–290.
[23] Kuby, S.A., Palmieri, R.H., Frischat, A., Fischer, A.H., Wu, L.H., Maland, L. and Manship, M. (1984) Biochemistry 23, 2393–2399.
[24] Wieland, B., Tomasselli, A.G., Noda, L.H., Frank, R. and Schulz, G.E. (1984) Eur. J. Biochem. 143, 331–339.
[25] Dhar, R., Ellis, R.W., Shih, T.Y., Oroszlan, S., Shapiro, B., Maizel, J., Lowy, D. and Scolnick, E. (1982) Science 217, 934–937.
[26] Tsuchida, N., Ryder, T. and Ohtsubo, E. (1982) Science 217, 937–939.
[27] Gallwitz, D., Donath, C. and Sander, C. (1983) Nature 306, 704–707.
[28] De Feo-Jones, D., Scolnick, E.M., Koller, R. and Dhar, R. (1983) Nature 306, 707–709.
[29] Jones, M.D., Petersen, T.E., Nielsen, K.M., Magnusson, S., Sottrup-Jensen, L., Gausing, K. and Clark, B.F.C. (1980) Eur. J. Biochem. 108, 507–526.
[30] Laursen, R.A., L'Italien, J.J., Nagarkatti, S. and Miller, D.L. (1981) J. Biol. Chem. 256, 8102–8109.
[31] Nakamura, S., Nakayama, N., Takahashi, K. and Kaziro, Y. (1982) J. Biochem. 91, 1047–1063.
[32] Nagata, S., Tsunetsugu-Yokota, Y., Naito, A. and Kaziro, Y. (1983) Proc. Natl. Acad. Sci. USA 80, 6192–6196.
[33] Montandon, P.E. and Stutz, E. (1983) Nucleic Acids Res. 11, 5878–5892.
[34] Van Hemert, F.J., Amons, R., Pluijms, W.J.M., Van Ormondt, H. and Möller, W. (1984) EMBO J. 3, 1109–1113.

[35] Nagata, S., Nagashima, K., Tsunetsugu-Yokota, Y., Fujimura, K., Miyazaki, M. and Kaziro, Y. (1984) EMBO J. 3, 1825–1830.
[36] Cottrelle, P., Thiele, D., Price, V.L., Memet, S., Micouin, J.Y., Marck, C., Buhler, J.M., Sentenac, A. and Fromageot, P. (1985) J. Biol. Chem. 260, 3090–3096.
[37] Ovchinnikov, Y.A., Alakhov, Y.B., Bundulis, Y.P., Bundule, M.A., Dovgas, N.V., Kozlov, V.P., Motuz, L.P. and Vinokurov, L.M. (1982) FEBS Lett. 139, 130–135.
[38] Sacerdot, C., Dessen, P., Hershey, J.W.B., Plumbridge, J.A. and Grunberg-Manago, M. (1984) Proc. Natl. Acad. Sci. USA 81, 7787–7791.
[39] Ponstingl, H., Krauhs, E., Little, M. and Kempf, T. (1981) Proc. Natl. Acad. Sci. USA 78, 2757–2761.
[40] Krauhs, E., Little, M., Kempf, T., Hofer-Warbinek, R., Ade, W. and Ponstingl, H. (1981) Proc. Natl. Acad. Sci. USA 78, 4156–4160.
[41] Rossmann, M.G., Moras, D. and Olsen, K.W. (1974) Nature 250, 194–199.
[42] Schulz, G.E. and Schirmer, R.H. (1979) Principles of Protein Structure, Springer, New York.
[43] Rossmann, M.G., Liljas, A., Brändén, C.-I. and Banaszak, L.J. (1975) The Enzymes 11, 61–102.
[44] Rossmann, M.G. and Argos, P. (1978) Mol. Cell. Biochem. 21, 161–182.
[45] Wierenga, R.K., Drenth, J. and Schulz, G.E. (1983) J. Mol. Biol. 167, 725–739.
[46] Hol, W.G.J., Van Duijnen, P.T. and Berendsen, H.J.C. (1978) Nature 273, 443–446.
[47] Rice, D.W., Schulz, G.E. and Guest, J.R. (1984) J. Mol. Biol. 174, 483–496.
[48] Eklund, H., Nordström, B., Zeppezauer, E., Söderlund, G., Ohlsson, I., Boiwe, T., Söderberg, B.O., Tapia, O. and Brändén, C.I. (1976) J. Mol. Biol. 102, 27–59.
[49] Untucht-Grau, R., Schirmer, R.H., Schirmer, I. and Krauth-Siegel, R.L. (1981) Eur. J. Biochem. 120, 407–419.
[50] Buehner, M., Ford, G.C., Moras, D., Olsen, K.W. and Rossmann, M.G. (1974) J. Mol. Biol. 90, 25–49.
[51] Davidson, B.E., Saigo, M., Noller, H.F. and Harris, J.I. (1967) Nature 216, 1183–1185.
[52] Krauth-Siegel, R.L., Blatterspiel, R., Saleh, M., Schiltz, E., Schirmer, R.H. and Untucht-Grau, R. (1982) Eur. J. Biochem. 121, 259–267.
[53] Hofsteenge, J., Weijer, W.J., Jekel, P.A. and Beintema, J.J. (1983) Eur. J. Biochem. 133, 91–108.
[54] Jörnvall, H. (1970) Eur. J. Biochem. 16, 25–49.
[55] Taylor, S.S. (1977) J. Biol. Chem. 252, 1799–1806.
[56] Kiltz, H.-H., Keil, W., Griesbach, M., Petry, K. and Meyer, H. (1977) Hoppe-Seyler's Z. Physiol. Chem. 358, 123–127.
[57] Ronchi, S., Minchiotti, L., Curti, B., Zopponi, M.C. and Bridgen, J. (1976) Biochim. Biophys. Acta 427, 634–643.
[58] Arscott, L.D., Williams, C.H. jr and Schulz, G.E. (1982) in: Flavins and Flavoproteins (Massey, V. and Williams, C.H. jr eds) vol.21, pp.44–48, Elsevier/North-Holland, Amsterdam, New York.
[59] Stephens, P.E., Levin, H.M., Darlison, M.G. and Guest, J.R. (1983) Eur. J. Biochem. 135, 519–527.
[60] Brown, N.L., Ford, S.J., Pridmore, R.D. and Fritzinger, D.A. (1983) Biochemistry 22, 4089–4094.
[61] Wills, C. and Jörnvall, H. (1977) Eur. J. Biochem. 99, 323–331.
[62] Dayhoff, M.O., Hunt, L.T., Barker, W.C., Schwartz, R.M. and Orcutt, B.C. (1978) Protein Segment Dictionary, Natl. Biomed. Res. Found., Washington.
[63] Leijonmarck, M., Eriksson, S. and Liljas, A. (1980) Nature 286, 824–826.
[64] Matheson, A.T., Möller, W., Amons, R. and Yaguchi, M. (1980) in: Ribosomes (Chambliss, G. et al. eds) pp.297–332, University Park Press, Baltimore.
[65] Amons, R. and Möller, W. (1980) in: RNA polymerase, tRNA and Ribosomes (Osawa, S. et al. eds) pp.601–608, University of Tokyo Press/Elsevier.
[66] Mamu, V., Bekesi, E. and King, H.F. (1985) Proc. Natl. Acad. Sci. USA 82, 376–380.
[67] Leberman, R. and Egner, U. (1984) EMBO J. 3, 339–341.