J Mol Evol (1982) 18:297–303

Journal of Molecular Evolution

Molecular Basis for the Genetic Code

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Summary. It was found by using the CPK molecular model that holes on the complexes of four nucleotides (C4N) on the tRNAs, namely complexes of the anticodon bases with the discriminator base at 4th position of 3' end, had lock and key relations to the corresponding protein amino acids. Various general features of the universal and mitochondrial genetic codes were easily explained in terms of the C4N model. The recognition mechanism of the tRNA by the aminoacyl-tRNA-synthetase is closely correlated with the formation of the C4N on the Rossmann fold on the synthetase. The meaning of the hypermodification of the tRNA base next to the third anticodon base and other phenomena were also discussed.

Key words: Genetic code – Protein synthesis – tRNA – Aminoacyl tRNA synthetase – Amino acid charging – Mitochondria – Hypermodified base – Rossmann fold

Introduction

The "universal" genetic code, which dictates the correspondence between three nucleic acid bases on a mRNA (codon) or those on a tRNA (anticodon) to a protein amino acid, was "deciphered" experimentally in the early 60's. However, the molecular basis for the correspondence or the reason why twenty kinds of protein amino acids were selected from more than hundreds kinds of amino acids have not yet been clarified. I shall point out here a clear and simple geometrical relation, a lock-and-key relation, behind the genetic code (including the recently found mitochondrial ones). This closely correlates with the charging mechanism of the amino acids to their corresponding tRNAs and with the recognition mechanism of the tRNAs by their corresponding aminoacyl-tRNA-synthetases.

Lock and Key Relation

On a tRNA, there are two sites specific to the corresponding amino acid, a set of three anticodon bases in the anticodon loop and a discriminator base at the 4th position from the 3' end (Crothers et al. 1971). Since both sites are exposed on the outside of the molecule, it is possible to combine them to form a complex under some conditions that I will discuss later. (I shall refer to this complex of four nucleotides as C4N.) The well known stacking conformation of the anticodon bases (Kim 1978) is important to guarantee the formation of the C4N. Otherwise, the discriminator base cannot combine with the three anticodon bases simultaneously.

I found by using the CPK molecular model that the pocket on the C4N had a lock-and-key relation to the corresponding amino acid as shown in Table 1 and 2. Hydrogen bonds (NHO or NHN) are always formed between the C4N bases and the NH_3^+ and COO^- radicals of the amino acid. The interaction between the bases and the side chain of the amino acid could be either by the hydrogen bonds or by the Van der Waals forces (see the Fig. 2). The lengths of the hydrogen bonds are always taken to be 2.9 Å. The angles of < N··HN and < O··HN are 180°. On the other hand, the angles of < CO··H are usually 120° (to fit the SP^2 electronic configulation), except some rare cases of 180° which are marked by * in the Table 2.

The conformation of the amino acids are taken from that observed by the electron scattering technique (Janis et al. 1978). The evidences for the possibilities of the interaction between the nucleic acid bases and the side chains of amino acids by the hydrogen bonding or stacking were already obtained by proton spin resonance method (Lancelot and Hèléne 1977).

The lock and key relation can hold only for the twenty kinds of protein amino acids and for no other non-protein amino acids. Figures 1 and 2 show the case of

0022–2844/82/0018/0297/$01.20

Table 1. The combination sites of three hydrogen bonds on the discriminator bases and on the anticodons in the case of the procaryote. A–N(6)H_2 indicates the amino radical in position 6 of adenine. For instance, in the case of alanine, a hydrogen bond NHN is formed between A–N(6)H_2 of the discriminator base and C–N(3) of the third anticodon base and so on. A, G, U, I, and C stand for adenine, guanine, uracyl, inosine, and cytosine, respectively

		Anticodon		
	Discriminator base	3rd	2nd	1st
	A	A–N(6)H_2	A–N(1)	A–N(3)
	G	G–C (6)O	G–N(1)H	G–N(2)H_2
	U	U–C(4)O	U–N(3)H	U–C(4)O
	C	C–N(4)H_2	C–N(3)	C–C(2)O
Amino acids				
Ala	A	C–N(3)	G–N(1)H	U–N(3)H
Arg_4	A	G–C(6)O	C–N(4)H_2	I–N(1)H
Arg_2	A	U–C(4)O	C–N(4)H_2	U–N(3)H
Asn	G	U–N(3)H	U–C(4)O	G–C(6)O
Asp	G	C–N(4)H_2	U–C(4)O	G–C(6)O
Cys	U	A–N(6)H_2	C–N(3)	G–N(1)H
Gln	G	G–N(1)H	U–C(4)O	U–C(4)O,C–N(3)
Glu	G	C–N(4)H_2	U–C(4)O	U–C(4)O
Gly	U	C–N(4)H_2	C–N(3)	G–N(2)H_2,U–N(3)H,C–N(4)H_2
His	C	G–C(6)O	U–N(3)H	G–N(3)H
Ile	A	U–C(4)O	A–N(6)H_2	G–N(2)H_2
Leu_4	A	G–C(6)O	A–N(6)H_2	G–N(2)H_2,C–N(4)H_2
Leu_2	A	A–N(1)	A–N(6)H_2	U–N(3)H,C–N(4)H_2
Lys	A	U–C(4)O	U–N(3)H	U–N(3)H
Met	A	U–C(4)O	A–N(6)H_2	C–N(4)H_2
Phe	A	A–N(1)	A–N(6)H_2	G–N(2)H_2
Pro	A	G–C(6)O	G–N(1)H	U–N(3)H
Ser_4	G	A–N(6)H_2	G–C(6)O	U–C(4)O,C–N(3)
Ser_2	G	U–N(3)H	C–N(4)H_2	G–C(6)O
Thr	A	U–C(4)O	G–N(1)H	G–N(2)H_2,U–N(3)H
Trp	G	A–N(6)H_2	C–N(3)	C–N(3)
Tyr	A	A–N(1)	U–N(3)H	G–N(2)H_2
Val	A	C–N(3)	A–N(6)H_2	G–N(2)H_2,U–N(3)H

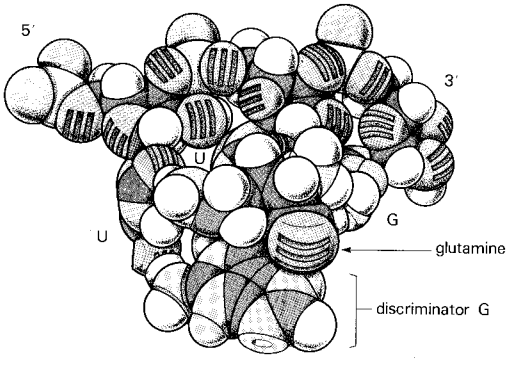

Fig. 1. CPK Molecular model of glutamine on its C4N, UUG=G. Only the anticodon in the anticodon loop of the tRNA (whose backbone chain is in the upper part of the figure) and the discriminator base (without the backbone chain) are shown. The attachment sites of the amino acid are determined from the energy minimum principle. The conformation of the ribose is taken in 3' endo form and the anticodon bases are in the anti form in relation to the ribose. The acceptor stem which continues to the discriminator base is located at the lower right side of the figure and the CCA chain covers the C4N from above. Consequently the other parts of the tRNA do not interfere with the formation of the C4N

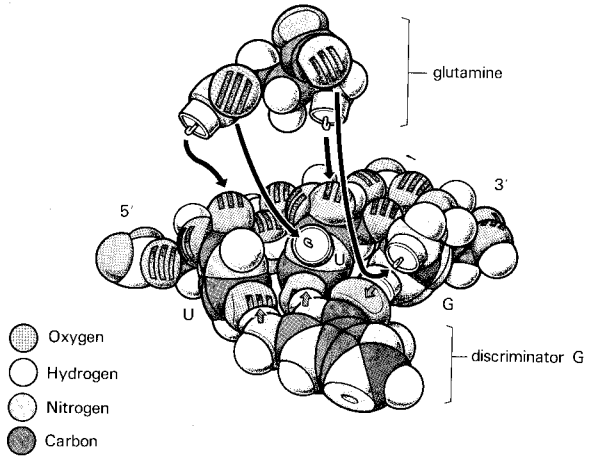

Fig. 2. Illustration for the hydrogen bond NHO formation between the anticodon bases and the discriminator bases (three ⇒) and between glutamine and its C4N (four ⇒)

Table 2. The combination sites of amino acids on the corresponding C4Ns in the case of the procaryote. 3C–C(2)O means that the attached site is the CO radical at the position 2 of the third anticodon base C. V.W. stands for the Van der Waals bonding. dA stands for the discriminator base A. It should be noted that one of the oxygen in the COO^- radical of the amino acid is always kept free without binding to combine with the adenosine of the CCA chain of the tRNA later. < COH is in most cases 120°, except the cases of 180° marked by *

	Discriminator base	NH_3^+	CO^-	Side chains
Amino acids				
Ala	A	3C–C(2)O	2G–N(2)H_2	V.W.
Arg_4	A	3G–N(3)	3G–N(2)H_2	*NH* *NH* 2C–C(2)O 2C–N(3)
Arg_2	A	3U–C(2)O	3U–N(3)H	*NH* *NH* 2C–N(3) 1U–C(2)O
Asn	G	3U–C(2)O	2U–N(3)H	*NH* 2U–C(2)O *CO* 1G–N(2)H_2
Asp	G	3C–C(2)O	2U–N(3)H	*CO* 1G–N(1)H
Cys	U	3A–N(1)	1G–N(2)H_2	*SH* 2C–C(2)O
Gln	G	2U–C(2)O	3G–N(2)H_2	*NH* 1C–C(2)O *CO* 2U–N(3)H
Glu	G	3C–C(2)O	2U–N(3)H	*CO* 1U–N(3)H
Gly	U	2C–C(2)O*	3C–N(4)H_2	
His	C	2U–C(2)O	3G–N(2)H_2	*N* 1G–N(2)H_2
Ile	A	2A–N(1)	dA–N(6)H_2	V.W.
Leu_4	A	2A–N(1)	dA–N(6)H_2	V.W.
Leu_2	A	2A–N(1)	dA–N(6)H_2	V.W.
Lys	A	3U–C(2)O	3U–N(3)H	*NH* 1U–C(2)O
Met	A	3U–C(2)O	3U–N(3)H	V.W.
Phe	A	2A–N(1)	dA–N(6)H_2	V.W.
Pro	A	3G–N(3)	2G–N(2)H_2	V.W.
Ser_4	G	3A–N(3)	2G–N(2)H_2	*OH* 2G–N(3)
Ser_2	G	2C–C(2)O	1G–N(2)H_2	*OH* 2C–N(3)
Thr	A	3U–C(2)O	2G–N(2)H_2	*OH* 2G–N(3)
Trp	G	2C–C(2)O*	3A–N(6)H_2	*NH* 1C–C(2)O
Tyr	A	2U–C(2)O	dA–N(6)H_2	*OH* 1G–N(3)
Val	A	2A–N(1)	dA–N(6)H_2	V.W.

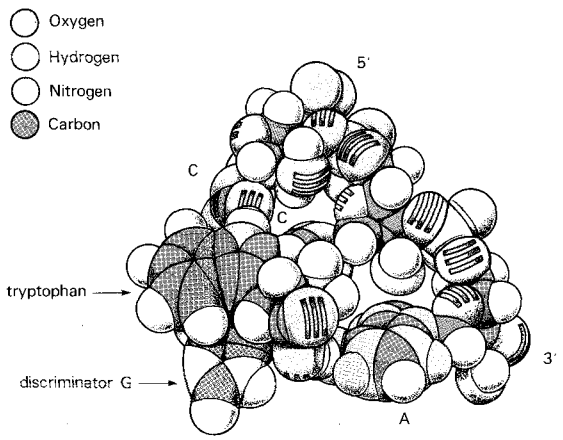

Fig. 3. CPK molecular model of tryptophan on its C4N CCA=G. The ring of tryptophan is well stacked with the discriminator base G. The NH in the tryptophan ring makes a hydrogen bond with one of the oxygen of the first anticodon base U

glutamine on its C4N. The number of hydrogen bonds between them reaches four in this case. Figure 3 shows the case of tryptophan. In this case the stacking of tryptophan ring with the discriminator base is strong.

Ornithine plays an important role in the pathway of metabolism, but it has not been used as a protein amino acid, in contrast to arginine or lysine, whose chemical structure is similar to that of ornithine. It has been found by using the molecular models that $N^{\varepsilon}H$ in the side chain of arginine cannot form a hydrogen bond with the corresponding C4N, while $N^{\eta_1}H_2$ and $N^{\eta_2}H_2$ can form hydrogen bonds with the C4N. This is consistent with the non usage of ornithine for protein amino acids, since the side chain of arginine will turn to be that of ornithine if the side chain terminates at the $N^{\varepsilon}H$. On the other hand, the side chain of ornithine, $-(CH_2)_3NH_2$, is shorter than that of lysine, $-(CH_2)_4NH_2$. With this number of CH_2, $N^{\zeta}H_2$ of lysine can reach the oxygen on the first anticodon base U to form a hydrogen bond. Amino acids which have shorter side chains than ornithine such as α–β diamino propionic acid and α–γ diamino butyric acid do not qualify as protein amino acid as well as ornithine. Homoserine and homocystein which

play the similar role as ornithine in the metabolic pathway can be shown to be rejected from the group of protein amino acids by similar geometrical reason.

The role of the discriminator base is threefold:

(1) Structural Role

The conformation of a C4N (or the mutual position of the anticodon bases) is uniquely determined by combining the anticodon bases with the discriminator base by use of three hydrogen bonds at one side and by using two 2'OH of riboses in the phosphodiester bond as wedges at the other side. (Arabinose or xylose has no 2'OH of this type and so can not be used for RNA (Shimizu 1981).)

(2) Informational Role

If the side chains of the anticodon bases such as NH_2, N, NH, or CO to form hydrogen bonds with the corresponding amino acid are too many, the discrimination of the amino acid by the anticodon cannot be unambiguously obtained. Three hydrogen bonds between the discriminator base with the anticodon bases reduce the number of the information containing side chains by three to result in an increase of the capability of the anticodon bases for the discrimination of the amino acid.

(3) Role as a CCA Chain Carrier

The CCA chain locates next to the discriminator base and, at the formation of a C4N-amino acid complex, the amino acid comes necessarily to the neighbour of the CCA chain to be charged with.

Consequently, as far as the formation of the C4N is concerned, the discriminator base can be any of four bases, if the above conditions are satisfied. Indeed, Ohtsuka et al. (1981) succeeded to charge methionine to all $tRNA^{Met}_f$ whose discriminator base was replaced from A to G, U, or C. (In general, however, purine is preferred to pyrimidine as a discriminator base due to the restriction come from the charging mechanism of an amino acid on a tRNA as I shall discuss later.)

Although the discriminator base of the procaryote is in most cases uniquely specific to each amino acid, the discriminator base of the eucaryote is sometimes different from that of the procaryote (Wetzel 1978). It can be shown, however, that the C4N can still form by using the new eucaryotic discriminator base and that the C4N can recognize the same amino acid in spite of the difference of the discriminator base. Such "evolutional" processes of the discriminator bases could have occurred within the restriction come from the role of discriminator bases discussed above.

C4N and the Genetic Code

The above C4N model can explain the general features of the genetic code: The codon is usually a triplet of bases, since the C4N is formed by three hydrogen bonds between the anticodon bases and the discriminator base (Tables 1 and 2). Many codons are quadruply degenerate. In these cases, the pockets formed by the third and second anticodon bases and the discriminator bases can accept the corresponding amino acids. Therefore, the initial doublet is important. In this sense, it is strange that serine is specified by entirely different doublet codons, UC (quadruply degenerate) and AG (doubly degenerate). This could be interpreted in terms of the C4N model as follows: The quadruply degenerate serine uses a half of the pocket on the corresponding N*GA*≡G (N stands for any of A, G, U, and C. NGA≡G means that the first, second and third anticodon bases are N, G, and A, respectively, and that the discriminator basis is G.), while the doubly degenerate serine uses the other half of the pocket on *GC*U≡G. About a half of the codons are doubly degenerate. In this case, the size of the third codon base or the first anticodon base is important. For instance, in the case of aspartic acid (GUC≡G) and glutamic acid (UUC≡G), there is a common discriminator base G. Consequently, the sizes of the pockets on their C4Ns are almost the same. The side chain of the glutamic acid is longer by size of a CH_2 radical than that of the aspartic acid. Therefore, the size of the first anticodon base for glutamic acid (a pyrimidine) is shorter than that for the aspartic acid (a purine).

The amino acids which have a common second anticodon base A in the corresponding anticodon have in general large and hydrophobic side chains. However, Met differs from other amino acids (Phe, Leu, Ile, and Val) in the point that it has a straight side chain, in particular when S in the side chain is interpreted as CH_2 due to the similarity of their sizes. (This means the similarity of Met to n-Leu). The second anticodon base A has an amino acid radical at the position of 6, which has two hydrogen atoms, say up and down H named from their positions, to combine with the discriminator base for all the above amino acids. If the discriminator A' combines with the down H from down side to form a hydrogen bond by using N at the position of 1 of A', the resulted C4N has a convex conformation, while the up H makes a concave C4N by combining with the N of A' approaching from up side.

The pocket between the third and second anticodon bases of the convex C4N is suitable to accept the amino acids with globular side chains such as Val, Leu, and Ile. In the case of the anticodon IAA or GAA, the above pocket is especially narrow and deep, particularly suitable to accept the benzene ring of Phe. This is because the first anticodon bases are purine (larger than pyrimidine for the case of Leu_2) to push the second anticodon base to the third one more closely than the case of Leu_2.

On the other hand, the long side chain of Met cannot be accepted in the pockets of the above type. However, the concave form for CAU and UAU can be shown by use of the CPK molecular model to accept the long Met (and n-Leu) side chain by using the whole pocket over the C4N. It can also be shown that the concave pockets for Phe etc. cannot accept Met and that the convex form of Met cannot accept other amino acids. It is interesting that ethionine is also shown experimentally to be acceptable in the pocket of Met (Wilson et al. 1981). It appears, on the other hand, homocysteine and n-valine cannot be accepted in this pocket. The length of methionine side chain may be the minimum one for the Van der Waals force to work effectively. These 'interpretation' may be confirmed by a detailed molecular theoretical computation and such a calculation is now in progress.

The essential feature of the mitochondrial genetic code is the minimum number of tRNAs, 23 or 24, in this system. Hence the first anticodon base is often irrelevant to amino acid recognition. The charged tRNA then recognises the codon through its first and second bases even if there is a mismatch with the third base (Barrel et al. 1980; Bonitz et al. 1980; Heckman et al. 1980). One of the interpretations of this phenomenon is the two out of three reading mechanism (Lagerkvist 1978). A molecular basis of the mechanism can easily be supplied if we assume that the pocket on the "C3N" composed of the third and second anticodon bases with the discriminator base can sufficiently discriminate the corresponding amino acid (,which is, in most cases, a small amino acid, since it should be received in the small pocket formed by the C3N). In the case of the yeast mitochondria, the codon of leucine (CUN) was found to be translated as threonine (Barrell et al. 1980) It is easily shown by using the CPK molecular model that the C4N of leucine (quartet) can accidently accept threonine by using the N on the second anticodon base A to catch the OH of the side chain of threonine.

Recognition of tRNA by Aminoacyl-tRNA-Synthetase

It is possible to form two C4Ns on an aminoacyl-tRNA-synthetase by using two tRNAs with the L letter form in a head to tail conformation (Shimizu 1979). Rich and Schimmel (1977) proposed a model based on various evidences that the L letter type tRNA used its inner side, in particular the D stem, the anticodon loop, and the acceptor stem, to recognize the synthetase. The D stems of all tRNAs are of the same size, since the order of purines and pyrimidines in them is the same. Consequently the D stems can be a common sticking point of the tRNAs to the synthetase (It is known that all tRNAs can temporarily stick to all synthetases before the recognition process), but cannot be specific to the amino acids. These evidences suggest that the formation of the C4N on the synthetase from the two same tRNAs in the head to tail conformation eventually results in the recognition of the synthetase by the tRNA.

The three dimensional structure of the synthetase is known for the cases of tyrosine and methionine. On the tyrosyl synthetase (Irwin et al. 1976), there are two holes in the antisymmetric position, which are sometimes called the Rossmann fold (Risler et al 1981). The distance between the holes can be estimated about 70 Å from the Fig. 3 and 5 of Irwin et al. (1976), just the distance between the anticodon bases and the discriminator base. Furthermore, the tyrosine in the tyrosyladenylate attached to the tyrosyl tRNA synthetase was found by the X ray analysis (Rubin and Blow 1981) to locate over the position of the C4N hole. Consequently the Rossmann fold may be the location of the C4N formation. In the case of the methionyl synthetase the three dimensional structure of an active monomer has been constructed (Zelwer et al. 1976). The distance of a hole on it from the end of the monomer can be estimated from the Fig. 3, of Zelwer et al. (1976) to be about 35 Å. If the total synthetase is a dimer composed of the two active monomers (plus small inactive pieces, to be axact) combined in an antisymmetric way, the synthetase would accept two tRNAs to form the C4Ns on it. Recently, Ebel et al. (1981) succeeded in crystalizing the tRNA-synthetase complex in the case of aspartic acid. The number of tRNAs on the synthetase is shown to be two by the fluorescence and neutron scattering experiments. The X ray data suggested that the form of the synthetase was dimeric and antisymmetric. These evidences are again in good agreement with our discussion.

There were some claims that the tRNA could make an U letter type structure in vivo (Reid 1977, Olson et al. 1976). A clover form with two leaves was found recently for the secondary structure of the human and rat mitochondrial serine tRNA (Koike 1980, Tsagoloff 1981). In these cases, the tRNA could have the U structure. It is known that the number of the loops of the tRNA could have gradually increased by the duplication of the gene. This suggests that the simple U structure might have been adopted by the primitive tRNA in the early biological system, which might have composed of the anticodon loop and the acceptor stem alone (Shimizu 1981) and charged the amino acid without the synthetase. In this scheme of the evolution of the tRNA, the rule of continuity is satisfied: The C4N has always used to recognize the amino acid throughout the history.

Other Evidences for the C4N

There are some indirect evidences to suggest the formation of the C4N. Hayashi and Miura (1963, 1966) found an inhibitory effect on the aminoacyl tRNA synthetase by the obligonucleotides simillar to the anticodon of the tRNA, in particular when the number of the nu-

cleotides was four or more. This may be interpreted in terms of the occupation of the C4N sites on the synthetase by the obligonucleotides. It was found by Weber and Lacey (1978) by Jungck (1978) that there is a correlation between the hydrophobicities of amino acids and those of the corresponding nucleotide dimers. This can be explained in terms of the C4N model as "The larger the size of the pocket on a C4N, the larger the size of the corresponding amino acid", since hydrophobicity of a substance is correlated with its bulkiness.

The charging mechanism of an amino acid to the acceptor stem of the tRNA may be described as follows: After the formation of the C4N and the attachment of the corresponding amino acid to it, the CCA chain comes over the amino acid and a homopolar bonding between the adenosine and the amino acid is formed. On the other hand, the strong Coulomb repulsion between the backbone of the anticodon and that of the CCA chain works to break the weaker hydrogen bonds and Van der Waals forces between the anticodon bases and the discriminator base and between the amino acid and the C4N. The anticodon now becomes free to look for its codon partner on the ribosome and the 3' end of tRNA charges the amino acid. The geometrical relation between the CCA chain and one of oxygens in the carboxyl radical of the amino acid, which does not bind with the C4N, would determine the 2' or 3' OH specificity (Hecht 1977) of the adenylate. Another restriction from this amino acid charging mechanism is that purine are in general more favorable for the discriminator base than pyrimidine, since the distance between the phosphodiester bond of the anticodon and that of the CCA chain is larger in the purine case than in the case of pyrimidine. This is in accord with the observation that a purine has much more been used in nature as a discriminator base than a pyrimidine.

The base next at the 3' side of the third anticodon base is usually "hypermodified". The study of the meaning of the hypermodification gives also a good evidence for the presence of the amino acid-C4N complex: The mode of the hypermodification is specific to the kind of the third anticodon base, for instance, ms^2i^6A and t^6A to the third anticodon base A and U, respectively. I found by using the CPK model that the 2-methylthio and N-isopentenyl groups of ms^2i^6A, namely $-SCH_3$ and $-NHCH_2\ CH{=}C(CH_3)_2$ respectively, geometrically match to the side of the, say, tyrosine-C4N complex to make a wall to stabilize the complex. Similarly, the side chain of the t^6A,-NH-CO-NH-CHCOOH-CHOH-CH_3, combines by using its two OH with two oxygens on the third anticodon base U to form a wall to the, say, isoleucine – C4N complex. Consequently, although the hypermodification appears to be random at a first glance, it has a deep geometrical meaning when we take into account the presence of the amino acid-C4N complex. Recently Weissenbach and Grosjean (1981) found an interaction between the third anticodon base and the hypermodified base experimentally.

At last, we hope to comment that an elaborative molecular theoretical computation has already carried out in our group to show the stability of some C4N conformations successfully. The result will be published later.

Acknowledgements The author appreciates the continuous encouragements of Dr. F. Egami and Prof. M. Kotani throughout this work. For the fruitful discussions on various aspects of this paper, he also thanks Drs. K. Miura, S. Nishimura, K. Koike, T. Oshima, Profs. A. Kornberg and A. Rich and many other scientists.

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Received April 24, 1982