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Alteration of the DNA double helix conformation upon incorporation of mispairs as revealed by energy computations and pathways of point mutations

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ABSTRACT

To explain biochemical and genetic data on spontaneous nucleotide replacements in nucleic acid biosynthesis all the 8 mispairs in normal tautomeric forms have been considered. Possible B-conformations of DNA fragments containing each of such mispairs incorporated between Watson-Crick pairs have been found using computations of the energy of non-bonded interactions via classical potential functions. These conformations have no reduced interatomic contacts. The values of each dihedral angle of the sugar-phosphate backbone fall within the limits of those of double-helical fragments of B-DNA in crystals. These values differ from those of the corresponding angles for the low-energy polynucleotide conformations consisting of canonical pairs by no more than 30° (except for the fragment with the U:U pair for which the $C_4'-C_3'-O-P$ angle differs by about 50°). The difference in experimentally observed frequencies of various nucleotide replacements in DNA biosynthesis correlates with the difference in the energy of non-bonded interactions and with the extent of the sugar-phosphate backbone distortion for the fragments containing the mispairs which serve as intermediates for the replacements.

INTRODUCTION

Almost exclusively complementary (i.e. those forming A:U (T) or G:C pairs) nucleotides are incorporated into the newly synthesized chain in nucleic acid biosynthesis. The formation of any other pair is an error leading to a nucleotide replacement: transition, if a purine-pyrimidine mispair is formed, or transversion, if a purine-purine or pyrimidine-pyrimidine mispair is formed. Errors in DNA biosynthesis *in vivo* occur with a probability of $10^{-8}-10^{-11}$ per base pair per replication (1). Complex enzyme systems ensure extremely high accuracy *in vitro*, too (2). To understand the processes of replication, repair and transcription and to be able to influence these processes (e.g. in chemeotherapy) it is important to elucidate what mechanisms ensure high accuracy of nucleic acid biosynthesis, to what extent accuracy is ensured by nucleic acid components, what is the role of synthesis enzymes and what are the pathways of infidelity.

Two types of mispairs have been suggested as pathways of spontaneous mutations (3-9). Mispairs of the first type (3-5) have practically the same

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dimensions as the correct pairs but one base is in a rare tautomeric form. Such pairs could be incorporated into an undistorted DNA double helix. Though some experimental data do not contradict such a mechanism, there are many facts which cannot be explained within its limits. Among these facts are: first, nucleotide replacements having pyrimidine-pyrimidine pairs as intermediate stages and the formation of such pairs in biosynthesis in vitro; second, the error frequency in some systems is higher than the probability of the rare tautomers (frequencies of different errors for a number of systems are summarized in reviews (10,11)) and third, incorporation into DNA and RNA of base analogs with no plausible pairs of this type (e.g. benzimidazol and some alkylated derivatives).

Another way of nucleotide mispairing assumes that the bases are in their normal tautomeric forms (5-9). Calculations of the interaction energy of nitrogen bases have shown that for each coplanar pair there are energy minima in which the mutual position of glycosyl bonds differs from that in A:T and G:C pairs by no more than 3 A and 30°. These minima correspond to the formation of two or one N-H...N and (or) N-H...O hydrogen bonds. In some pairs the base is in syn-orientation relative to sugar. Consideration of base pairs in normal tautomeric forms as intermediate stages of spontaneous mutations (6,7) suggests a qualitative explanation of all experimental data on spontaneous mutations involving replacements of base pairs and on errors of nucleic acid synthesis in vitro. Such mispairs are characterized by a displacement of bases relative to the position occupied by complementary bases in Watson-Crick pairs and the displacement of bases requires distortion of the sugar-phosphate backbone. It is not evident a priori that each mispair can be incorporated into the double helix without such a strong increase of energy that makes the incorporation of wrong nucleotides by this mechanism practically impossible.

In previous papers (12-14) we have demonstrated that different types of mispairs containing bases in normal tautomeric forms can be incorporated into the double helix without the appearance of reduced interatomic contacts and without a change of the sugar-phosphate backbone dihedral angles beyond the limits characteristic of double helices consisting of A:T and G:C pairs. We have considered the incorporation into the B-conformation and A-conformation double helices of purine-pyrimidine (G:U, G:T), purine-purine (I:A, G:A), purine-purine (syn) (I:A syn, G:A syn) and pyrimidine-pyrimidine (C:U, C:T) pairs. Each of these pairs has two hydrogen bonds and the energy of base interaction is close to that in the A:U pair or differs by 1÷2 kcal/mole.

Later Rein et al. (9) have demonstrated the possibility of G:T, A syn:G and A:C incorporation into the double helix. The only experimental data preceding our studies (see e.g. (15)) were those indicating the existence of a G:U wobble pair in double-helical RNA fragments, i.e. in the A-conformation double helices. Later NMR has been used to show that G:T pairs (16) and G:A pairs (17) can be formed in DNA fragments. The geometry of the G:A pair within the DNA fragment is similar to that of the I:A pair considered by us earlier (12-14).

In nucleic acid biosynthesis there is a small but finite probability of all possible nucleotide replacements and all possible base oppositions. To explain this fact we have calculated the energy of non-bonded interactions and have shown that for each nucleotide pair there is a mutual position of bases corresponding to a minimum of energy of base-base interaction and alloweing incorporation of this pair into the double helix. Such incorporation does not result in the appearance of reduced interatomic contacts, the energy of the sugar-phosphate backbone increases by no more than 3 kcal/mole and its dihedral angles deviate from the values characteristic of low-energy conformations of polynucleotides consisting of canonical pairs by no more than 30^{o} (for the fragment with a U:U pair one angle deviates by 55^{o}). Bases are connected by two or one N-H...N and (or) N-H...O hydrogen bond. In the case of such single H-bond the position of bases in the minimum is also stabilized by a C-H...O or C-H...N weak hydrogen bond. In some pairs one of the bases has a syn-orientation relative to sugar. Though the possibility of other base pairs and other polynucleotide chain conformations upon wrong nucleotide incorporation cannot be excluded, the nucleotide pairs considered by us are sufficient for explanation of all experimental data on spontaneous point nucleotide replacements in nucleic acid biosynthesis.

METHODS

To search for possible conformations of fragments of the DNA double helix containing mispairs we used the same methods of calculations as in our previous paper (14). Therefore we shall describe here only the essential features of the method.

The energy of non-bonded interactions was calculated as a sum of atom-atom interactions, torsional energy of rotation about single bonds and energy of distortion of variable bond angles. Bond lengths and bonded angles (except for internal angles of the sugar ring and C_3'-O-P angles) were assumed to be fixed. The parameters for energy calculations as well as bond lengths and

bond angles were assumed to be the same as in our paper (18) dealing with regular double-helical polynucleotide. The search for minimum energy values was performed by the method of parallel tangents. The found low-energy conformations were examined for reduced interatomic contacts and were visualized with the help of a plotter.

For each incorrect X:Y pair we considered two fragments dApdApdX:dYpdUpdU and dXpdApdA:dUpdUpdY containing the incorrect pair on one or the other side of the successive correct pairs. While searching for low-energy conformations we considered the fragment energy as a function of the following variables: parameters determining the mutual position of bases in mispairs (all base pairs were assumed to be planar) and the position of pairs relative to the helix axis, helix parameters, sugar ring conformations and glycosyl dihedral angles χ. It has been assumed that the parameters of nucleosides of the mispair and of the neighbouring correct pair can differ while the parameters of two nucleosides of the terminal correct pair are equal. The search was performed gradually shifting bases in the mispair to the position of the minimal interaction energy of two isolated bases and minimizing by other conformational variables. When the bases had reached this position, minimization was done by all independent variables.

For low-energy conformations of fragments dApdApdX:dYpdUpdU and dXpdApdA:dUpdUpdY the difference in conformational parameters of the nucleoside X:Y pair is a few degrees by the angle variables and some tenths of A by the variables characterizing shifts. Then the conformational parameters of nucleoside mispairs of the two fragments were made equivalent by shifting them gradually towards each other and minimizing by other variables at each step. The energy of non-bonded interactions of each fragment somewhat (by no more than 4 kcal/mole) increases but no reduced interatomic contacts appear. Thus we have found sterically allowed conformations of fragments dApdApdXpdApdA:dUpdUpdYpdUpdU containing a X:Y mispair incorporated between correct pairs.

RESULTS AND DISCUSSION

Mutual Position of Bases in the Pairs Incorporated into the Double Helix

To explain all nucleotide replacement we should consider all the 8 possible incorrect base pairs among which there are two purine-pyrimidine pairs (G:T and A:C), three purine-purine pairs (A:G, A:A and G:G) and three pyrimidine-pyrimidine pairs (U:C, U:U and C:C). In biosynthesis a mispair could be incorporated into DNA helix if it does not strongly distort the

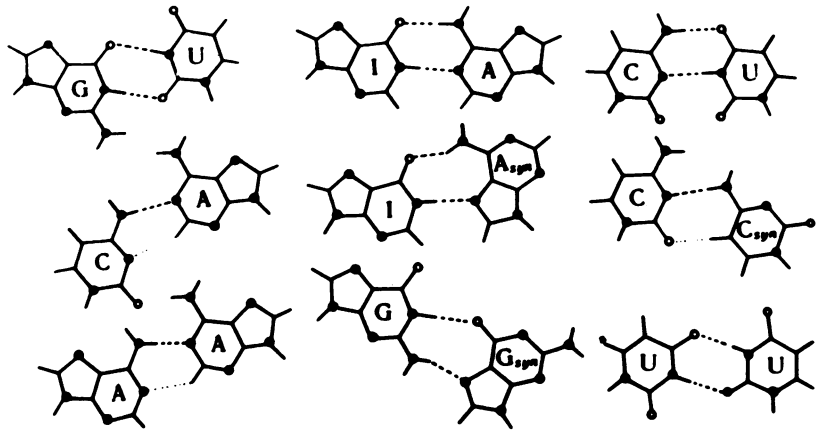


Fig. 1. Mutual positions of bases in mispairs corresponding to the energy minima of intermolecular interactions.

double helix conformation. We can assume that the enzyme systems performing template-directed synthesis of nucleic acids would impede incorporation of an incorrect nucleotide if this implies a considerable change of the sugar-phosphate backbone conformation and a transition of dihedral angles into other ranges. To avoid such changes, mutual position of glycosyl bonds in mispairs should not differ much from that in A:T and G:C pairs. For all base pairs there are minima of base interaction energy satisfying this requirement. The positions of bases in such minima chosen for incorporation into the double helix are given in Fig. 1 (including the minima for G:U, I:A and C:U pairs considered in our previous paper). For convenience, we have replaced in some pairs guanine by hypoxantine and thymine by uracil; this practically does not affect either the position of the minimum or the energy of base interactions and the replacement of hypoxantine by guanine and uracil by thymine in the found conformations of double-helical fragments does not create reduced interatomic contacts. For each pair we have chosen only one configuration which seems at the first glance the most suitable for incorporation into the double helix. The exception was made for the G:A (I:A) pair for which we have considered two configurations (I:A and I:A syn) in the preceding paper (14) as it is difficult to discriminate a priori the best one. For some other pairs there are also two or more energy minima in which the position of glycosyl bonds differs from that in A:T and G:C pairs by no more than 3 A and 30^{o}. Some of these pairs are given in papers (6,7,19). However even the base positions considered here are sufficient for explaining

all nucleotide replacements. Among the incorrect pairs whose incorporation into the double helix has been shown in this paper are those with two hydrogen bonds of the N-H...O and (or) N-H...N type (U:U and G:G). For the G:G pair the minimum of the base interaction energy slopes almost perpendicularly to the direction of hydrogen bonds so that there can be a 1÷2 A shift of bases in this direction upon a 1-2 kcal/mole energy increase. Besides, there are pairs with one N-H...N and one weak C-H...N bond (C:A and A:A) or a C-H...O (C:C) hydrogen bond. The consideration of such pairs (as well as those with a base in syn-orientation relative to sugar) is important for explaining all possible nucleotide replacements. The positions of bases in A:C, A:A and C:C pairs corresponding to the minima with two hydrogen bonds N-H...N and (or) N-H...O differs so much from the position in A:T and G:C pairs that it is difficult to imagine their incorporation into the double helix without a considerable change of the sugar-phosphate backbone conformation. The considered C:C pair has a base in syn-orientation. Though the syn-conformation of pyrimidine nucleosides requires additional energy, this energy expense in the C:C pair can be largely compensated by the interaction energy of bases in the pair similar to the energy in the A:U pair.

Conformation of the Fragments Containing Mispairs

For low-energy conformations of both fragments (dApdApdX:dYpdUpdU and dXpdApdA:dUpdUpdY) containing G:U, A:C, I:A, A:A and C:C pairs the mutual position of bases in mispairs differs from that in the base interaction minimum by only a few degrees in the angle variables, by some tenths of A in the variables characterizing the shifts and by 0.2÷0.7 kcal/mole in energy. For these pairs, constructing a 5-pair fragment with an incorrect pair incorporated between two correct pairs requires a rather small change in the parameters of the incorrect nucleotide pair and a 2÷3 kcal/mole energy increase. Low-energy conformations of fragments containing a G:G pair are charcterized by a shift of the position of bases in the mispair by 1÷2 A from that of the minimum energy for the isolated pair. In this case such a shift does not result in a considerable increase of the energy of interaction between the bases (see the preceding secion). For one of the fragments with the U:U pair the low-energy conformation corresponds to the base position close to the minimum for the isolated pair and for the other fragment the mutual position of glycosyl bonds in the U:U pair is closer to their position in the A:U pair than in the isolated U:U pair. When the position of bases in the incorrect pair of this fragment approaches the minimum for the isolated pair, the energy of the sugar-phosphate backbone increases by almost 8 kcal/mole and

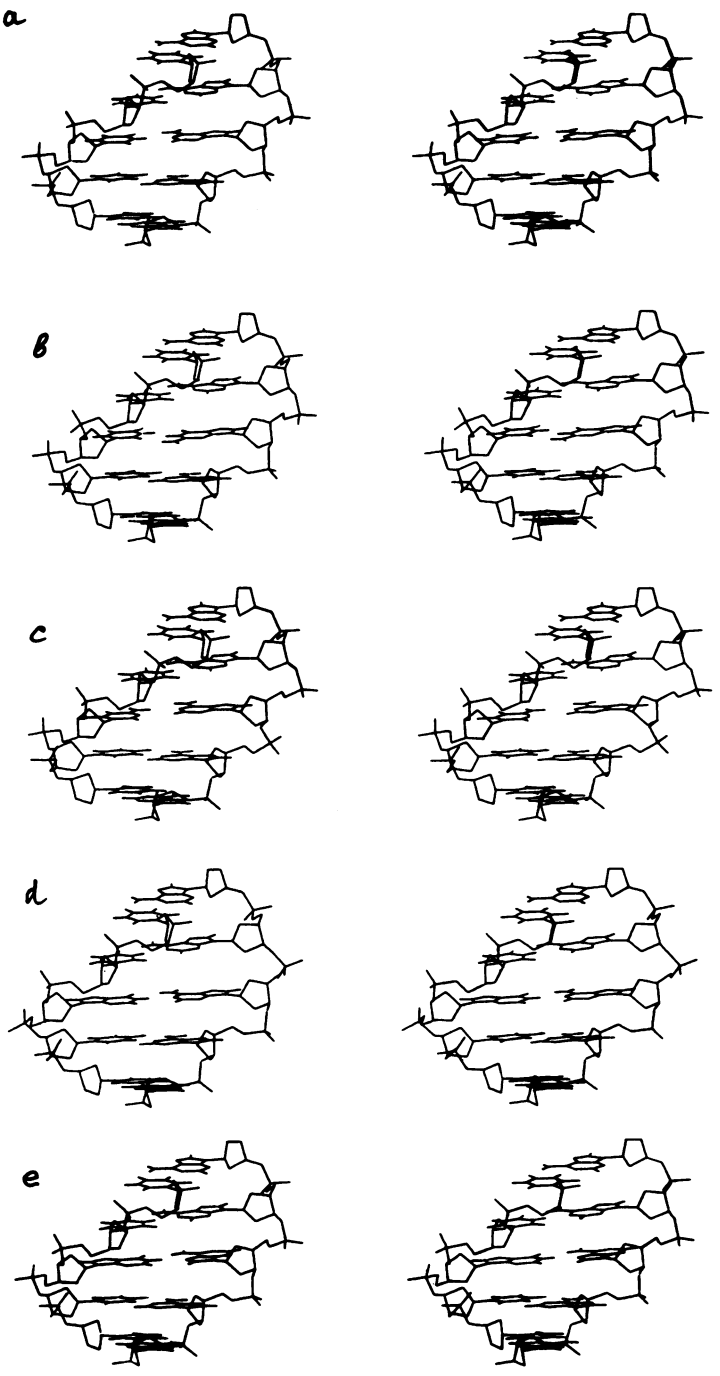
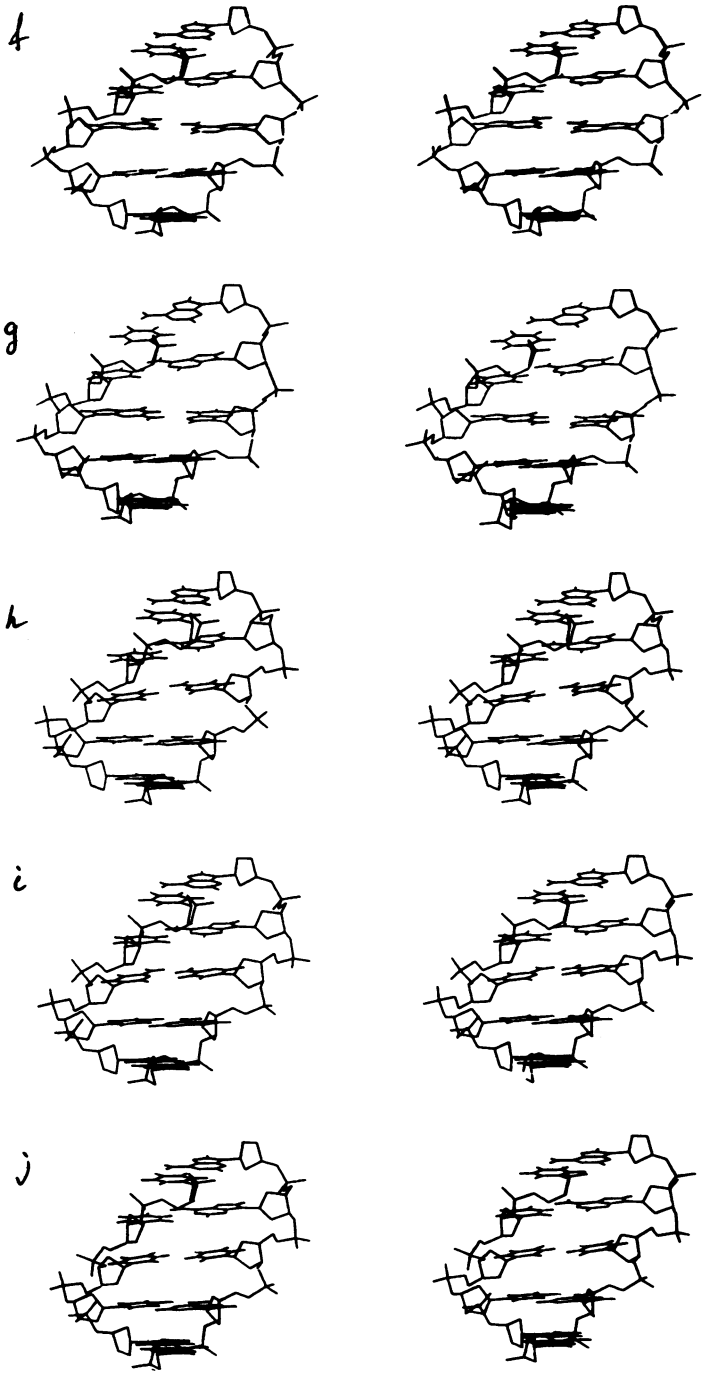


Fig. 2.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one of the dihedral angles shifts by 50° from its value for low-energy conformations of polynucleotides consisting of Watson-Crick pairs. For the same fragment we observed the highest increase of the energy of non-bonded interactions when the parameters of the incorrect nucleotide pair are shifted to find a possible conformation of the 5-pair fragment. It has been noted in our previous paper (14) that the energy minima for the conformations of fragments containing a C:U pair do not exactly correspond to the energy minimum of base interaction in the pair. Our preliminary data show, however, that if the calculation are performed without some simplifying assumptions (planarity of pairs, fixation of many bond angles) the mutual position of bases in low-energy conformations of fragments with U:U and C:U pairs become closer to the position of bases in isolated pairs.

Fig. 2 represents stereodrawings of DNA fragments containing each of the incorrect nucleotide pairs, including those considered in our previous paper. The values of the conformational parameters for the fragments considered here are given in Tables 1 and 2. It should be noted that for each pair we have found only one conformation, one point in the wide range of minimum energy values. The dihedral angles for all fragments are within the limits or differ slightly from those characteristic of double-helical B-conformations of DNA fragments in crystal (20,21). Calculations show that a shift of bases in a pair relative to each other along the dyad axis involves less changes of angles and a smaller increase of the sugar-phosphate backbone energy than a shift in the perpendicular direction. The conclusion that the sugar-phosphate backbone of the double helix permits rather large local changes of the DNA conformation due to a shift of the mutual position of bases is also important for the understanding of the nucleic acid dynamics. A 2A shift of one base relative to another along the line connecting C_1' atoms of the Watson-Crick pair, a 3 A shift along the dyad axis of this pair and shifts in both these mutually perpendicular directions are possible without the appearance of reduced interatomic contacts in the sugar-phosphate backbone. These shifts can be achieved through rather small helix distortions involving only the nearest and next-to-nearest nucleotide pairs. This permitted us to evaluate which modifications of the bases are possible without disruption of the double helix. Since the pairs with 2-aminopurine, 2,6-di-

Fig. 2. Stereoview of revealed B-conformations of double-helical fragment consisting of A:U pairs (a) and containing mispairs. (b, G:U; c, A:C; d, I:A; e, I:A syn; f, A:A; g, G:G; h, C:U; i, C:C; j, U:U). C-H bonds in the sugar-phosphate backbone are not shown. Projections on the planes forming an angle of 10° with helix axes permit a better view of base pairs.

Table 1. Conformational Parameters of Revealed B-Conformations of DNA Fragments Containing Mispairs

Fragment \ Angle	$C_4'-C_3'-O_3'-P$		$C_3'-O_3'-P-O_5'$		$O_3'-P-O_5'-C_5'$		$P-O_5'-C_5'-C_4'$		$O_5'-C_5'-C_4'-C_3'$	
U:A	180	180	252	253	295	292	186	187	54	56
U:A	178	179	256	265	294	291	190	181	52	61
C:A	182	221	250	214	289	284	184	159	59	58
U:A	180	179	252	253	293	291	186	187	56	57
U:A										
U:A	190	191	246	244	285	285	177	177	64	65
U:A	191	215	231	225	292	275	178	158	59	72
A:A	215	165	241	275	274	284	151	204	83	54
U:A	189	190	245	239	287	298	178	173	63	58
U:A										
U:A	182	186	245	248	290	288	180	180	62	61
U:A	243	166	219	266	254	290	142	205	82	49
U:U	170	202	275	243	281	296	197	164	61	61
U:A	188	184	246	242	287	295	176	176	65	61
U:A										
U:A	186	190	243	247	294	289	176	179	60	60
U:A	210	186	224	253	283	305	157	192	68	45
C:C	192	162	265	260	293	293	190	176	53	59
U:A	186	192	247	245	292	295	178	179	61	59
U:A										
U:A	186	190	248	252	291	284	176	186	63	60
U:A	213	174	216	234	291	271	163	183	60	81
G:G	178	190	255	281	291	286	168	191	67	65
U:A	186	183	245	246	291	282	183	178	61	69
U:A										
I	162 ÷ 242		214 ÷ 275		254 ÷ 298		142 ÷ 205		45 ÷ 83	
II	181 ÷ 187		239 ÷ 253		286 ÷ 293		169 ÷ 186		55 ÷ 73	
III	170 ÷ 260		150 ÷ 274		278 ÷ 309		139 ÷ 190		40 ÷ 66	

Arrows indicate the direction of the C_3'-O-P-O-C_5' sugar-phosphate backbone. For each angle the left values correspond to the sequence dUpdUpdYpdUpdU while the right ones to the sequence dApdApdXpdApdA. The two last lines give the ranges of angles found (I) for the fragments containing all 9 pairs (fig. 1) including those considered in our previous paper (14); (II) for low-energy poly-dA:poly-dU conformations according to the data of paper (18); (III) for double-helical B-DNA fragments in crystals (20-21). Note correlation between angles $C_4'-C_3'-O_3'-P$ and $C_3'-O_3'-P-O_5'$ similar to that observed in double-helical B-DNA fragments (21).

aminopurine (22) and some alkylated purines and pyrimidines (23,24) differ in dimensions and mutual position of bases no more than the mispairs considered here, their formation in template synthesis of nucleic acids is quite probable.

Table 2. Conformational Parameters of Revealed B-Conformations of DNA Fragments Containing Mispairs

Fragment	χ		P		δ	
U:A	128.0	128.0	152.2	152.2	139.1	139.1
U:A	128.1	128.2	151.9	152.9	138.1	138.8
C:A	128.0	128.4	155.2	151.0	140.6	137.7
U:A	127.4	127.8	154.4	155.0	139.7	140.4
U:A	127.9	127.9	153.3	153.3	139.3	139.3
U:A	127.5	127.5	157.5	157.5	142.1	142.1
U:A	127.2	129.3	162.2	156.8	144.8	140.9
A:A	129.2	127.5	149.6	156.2	136.7	141.4
U:A	129.5	127.4	155.5	146.4	140.5	134.7
U:A	127.8	127.8	159.7	159.7	143.3	143.3
U:A	126.8	126.8	156.4	156.4	141.9	141.9
U:A	130.1	127.3	153.0	156.8	139.0	142.2
U:U	130.0	127.4	151.1	154.2	137.0	140.0
U:A	125.6	130.0	157.3	147.8	142.6	135.3
U:A	127.3	127.3	158.0	158.0	142.2	142.2
U:A	125.8	125.8	155.4	155.4	140.1	140.1
U:A	130.7	129.1	155.4	155.3	140.5	141.0
C:C	129.0	301.0	149.3	150.7	135.9	137.0
U:A	126.0	129.0	155.8	147.8	141.5	135.5
U:A	127.3	127.3	156.1	156.1	140.8	140.8
U:A	120.8	120.8	153.9	153.9	139.7	139.7
U:A	127.7	133.7	163.0	154.4	145.5	139.5
G:G	131.7	309.4	148.3	145.1	135.8	133.6
U:A	129.9	117.2	162.7	140.5	141.7	130.6
U:A	126.9	126.9	161.1	161.1	143.6	143.6

Glycosyl dihedral angles χ (C_8(Pu) or C_6(Py)-N-C_1'-C_2'), phase angles (P) of sugar pseudorotation and angles δ (O_3'-C_3'-C_4'-C_5') are given for each nucleoside of all fragments. The conformations are the same as in Table 1. The angles of complementary nucleosides in terminal pairs are equal as a result of the assumptions made for calculations.

Incorporation of Mispairs into the Double Helix and the Mechanisms of Errors in Nucleic Acid Biosynthesis

Our calculations have shown that any base opposition can be incorporated into the DNA double helix, i.e. any nucleotide replacement can be explained by the formation of base pairs in normal tautomeric forms considered by us. The frequencies of mispair formation during biosynthesis *in vitro* observed experimentally (25-28) correlate qualitatively with double helix distortions and the increase of the energy of non-bonded interactions obtained in our calculations. Here we do not consider in detail energetics of the mispair incorporation into the double helix, we have restricted ourselves to noting only qualitative regularities. A quantitative comparison of experi-

mentally observed frequencies of errors with theoretical predictions requires the absence of simplifying assumptions used in this work, such as minimum fragment dimensions, planarity of pairs, fixation of many bond angles. The values of dihedral angles presented here can be used as the starting points in the process of energy minimization. An analysis of the contribution made by interactions of individual structural components into the total energy allows an evaluation of the limits of energy change upon incorporation of different mispairs instead of one or another correct pair. An energy increase caused by strains in the sugar-phosphate backbone can be considered as the lower limit of the energy change upon incorporation of a mispair (for most pairs our estimates give an increase of no more than 3 kcal/mole of the fragment). A contribution to the change of the fragment total energy upon replacement of the correct nucleotide by an incorrect one is also made by a change of the sugar-base interactions upon incorporation of the nucleotide into the double helix. This change is essential for the pairs containing a nucleotide in syn-conformation. As for the changes of base interactions, especially those in coplanar pairs, these changes cannot be used directly for evaluation of error frequency. This is due to the fact that our calculations practically do not take into account the solvent while the difference in interations energies in pairs considerably decreases when the base pairs are placed in a solvent. A quantitative account of the solvent is practically impossible at present in calculations performed within the limits of the same approximations as for the interaction energy of nucleic acid components. Besides, the contribution of enzymes which increase accuracy of template synthesis (29) cannot be calculated now.

At the same time, a qualitative consideration permits an interesting comparison of the results of calculations with the experimental data. The calculations show that the incorporation of some pairs (G:U, I:A) leads to a change of the non-bonded interaction energy by no more than 3 kcal/mole as compared to the energy of the fragment consisting of A:U pairs (14). This gives the error frequency of 10^{-2}÷10^{-3} observed in some enzyme systems. Such a value cannot be explained with the assumption of rare tautomeric forms. A high level of incorporation of non-complementary nucleotides (10^{-2}÷10^{-3}) is also observed in non-enzymatic template synthesis (30). A considerably lower error frequency observed usually in template synthesis is due to the action of enzymes which increase accuracy of synthesis and to the interaction of the enzyme recognition site with structural invariants of correct nucleotide pairs (29).

Our calculations show that the G:U pair considered in our previous paper (14) is most easily incorporated into the double helix. Incorporation of this pair results in a small energy increase and the least (among other mispairs) change of the dihedral angles of the sugar-phosphate backbone as compared to the angles for poly-dA:poly-dU. This result can explain a higher frequency of transitions than transversions (31) and the indication that the transitions mainly proceed through the formation of the G:T pair (25-28). Another pair through which transitions can occur is the A:C pair, but its formation is considerably rarer as its incorporation into the double helix is connected with a larger energy increase and larger changes of dihedral angles. The incorporation of any purine-purine pair leads to greater distortions of the sugar-phosphate backbone than for the G:U pair. The probability of formation of pyrimidine-pyrimidine pairs is the least according to our calculations. These results explain the experimental data that transversions proceed mainly through the formation of purine-purine pairs (25-28). The formation of pyrimidine-pyrimidine pairs occurs extremely rarely in DNA biosynthesis (25-28) or is not revealed at all as the frequencies of the corresponding nucleotide replacements are lower than sensitivity of the method.

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