Enzyme-Bound Conformations of Nucleotide Substrates. X-ray Structure and Absolute Configuration of 8,5′-Cycloadenosine Monohydrate†

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ABSTRACT: Irradiation of adenosine 5′-monophosphate (AMP) stereospecifically produces only the C(5′) epimer of 8,5′-cycloadenosine 5′-monophosphate (8,5′-cAMP) which is inactive as a substrate for various AMP utilizing enzymes, while the other C(5′) epimer, from chemical synthesis, is active. The present X-ray study of the nucleoside corresponding to the inactive irradiation product has established the absolute configuration to be C(5′)-*S*; thus, the active epimer is C(5′)-*R*. Crystals of 8,5′-cycloadenosine monohydrate are orthorhombic, space group $P2_12_12_1$ ($Z = 4$), with unit cell dimensions of 4.675 (2), 14.605 (2), and 17.583 (2) Å for *a*, *b*, and *c*, respectively. The structure was solved by the multisolution technique and refined by the least-squares method to a disagreement index of 0.055 using 1319 intensities. The C(3′)–C(4′)–C(5′)–O(5′) torsion angle is gauche$^-$ (−51.5°) indicating that the active C(5′)-*R* epimer has to be trans. This result indicates that the trans conformer of AMP is selectively bound to snake venom 5′-nucleotidase and pig muscle AMP kinase and that the trans conformer of adenosine 5′-diphosphate is bound to rabbit muscle pyruvate kinase. Cyclization constrains the ribose ring to the rare C(1′)-endo O(4′)-exo (${}^1_0T$) pucker with pseudorotation parameters $P = 288.6°$ and $\tau_m = 47.7°$. The fused six-membered ring C(5′)–C(8)–N(9)–C(1′)–O(4′)–C(4′) assumes a half-chair conformation with the O(4′) atom puckered. The N(6) and N(7) atoms of the adenine base form a pair of hydrogen bonds to the O(2′) and O(3′) atoms of a symmetry-related ribose. The water of hydration forms a zigzag scheme of hydrogen bonds around a 2_1 screw axis.

Structural studies of fused nucleotides and nucleosides can contribute valuable information regarding the substrate conformation and the stereospecificity of enzyme active sites. If enzymatic activity can be demonstrated for one configuration of a given fused substrate molecule, then the substrate binding site on the enzyme would be expected to also demand a similar conformation for free, noncyclized, substrate molecules.

In the case of 8,5′-cAMP, the fused C(8)–C(5′) linkage prevents any substantial conformational changes during enzyme binding. Also, only one of two possible C(5′) epimers (Figure 1) of chemically synthesized 8,5′-cAMP will act as a substrate for such enzymes as snake venom 5′-nucleotidase and pig muscle AMP kinase, while the same C(5′) epimer of 8,5′-cycloadenosine 5′-diphosphate also acts as a substrate for rabbit muscle pyruvate kinase. In earlier work Hampton et al. (1972) hypothesized that the active form was epimer a in Figure 1 since for epimer b they reasoned that there would be an unfavorable oxygen–oxygen repulsion between the furanoid ring O(4′) atom and the O(5′) atom. 8,5′-cAMP can also be produced by irradiation of an aqueous solution of adenosine 5′-monophosphate by X-rays or γ radiation in the absence of molecular oxygen. This cyclization, which is proposed to occur via a free-radical mechanism involving a hydroxyl radical, is stereospecific resulting in only the epimer of 8,5′-cAMP which is not hydrolyzable by snake venon 5′-nucleotidase (Keck, 1968; Raleigh & Kremers, 1975; Raleigh et al., 1976). The inactive epimer was shown to correspond to epimer a in Figure 1, based on evidence derived from nuclear magnetic resonance spectroscopy (Raleigh & Blackburn, 1978), thereby indicating that epimer b in Figure 1 corresponds to the enzymatically active form.

This paper unequivocally establishes the absolute configuration of 8,5′-cycloadenosine, the nucleoside corresponding to the inactive radiation product, to be (a) in Figure 1 by using single-crystal X-ray diffraction analysis. Apparently the oxygen–oxygen repulsion predicted by Hampton et al. (1972) for the active epimer b in Figure 1 is not serious.

Experimental Procedures

White needles of 8,5′-cycloadenosine monohydrate ($C_{10}H_{13}N_5O_5$) elongated along the *a* axis were obtained by slow cooling of a solution containing 8,5′-cycloadenosine dissolved in hot water. Intensity data were collected with a crystal having dimensions 0.6 × 0.05 × 0.05 mm on an Enraf-Nonius CAD4 diffractometer using Ni-filtered Cu Kα radiation (λ = 1.5418 Å). Unit-cell parameters were refined by a least-squares algorithm using 25 automatically centered reflections. The crystal had an observed and calculated density of 1.57 and 1.567 g/cm^3, respectively. Of a total of 1515 unique reflections measured up to a 2θ limit of 155°, 1319 with intensities greater than $2\sigma(I)$ were used for the structure analysis. Four reflections were monitored throughout the data collection to correct for crystal decay, which was approximately 7% for the duration of the crystal exposure. The data were also corrected for Lorentz and polarization effects. An empirical absorption correction was also applied with a maximum difference of 12% in intensity for the same reflection counted at points of both minimum and maximum absorption.

Structure Determination and Refinement. The structure was solved by application of the multisolution tangent formula technique using the computer program MULTAN (Main et al., 1970). A total of 128 solutions were generated and submitted to tangent refinement. The correct solution had the second lowest NQEST figure of merit (DeTitta et al., 1975). A three-dimensional Fourier synthesis (*E* map) using the phases from the correct solution revealed all the nonhydrogen atoms except the water. These atoms were refined by the full-matrix least-squares method, and subsequent difference Fourier syntheses yielded electron densities corresponding to the water oxygen and all the hydrogen atoms. Refinement of all atoms to convergence, nonhydrogen atoms with anisotropic temperature factors and hydrogen atoms with isotropic temper-

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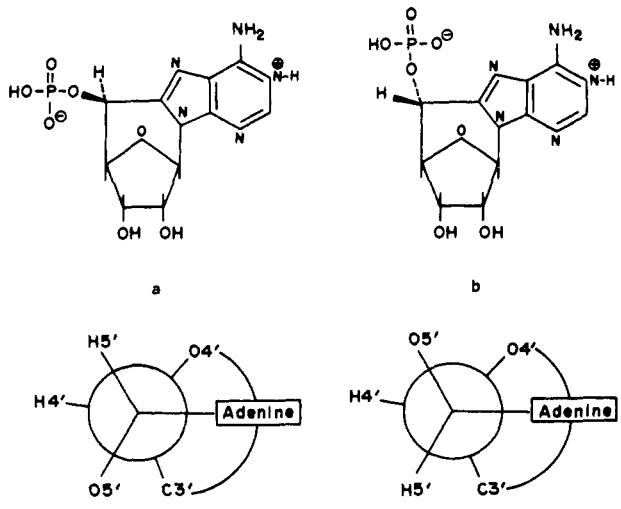

FIGURE 1: C(5′)-*S* configuration (a), ψ = gauche$^-$ (top left), and C(5′)-*R* configuration (b), ψ = trans (top right), of 8,5′-cycloadenosine monophosphate and their respective Newman projections (bottom) viewed down the C(5′)–C(4′) bond.

Table I: Fractional Positional Parameters for All Atoms of 8, 5′-Cycloadenosine Monohydrate[a]

atom	*x/a*	*y/b*	*z/c*
N(1)	671 (7)	736 (2)	4925 (2)
C(2)	2111 (8)	−51 (2)	4919 (2)
N(3)	4090 (6)	−339 (2)	4433 (1)
C(4)	4566 (6)	292 (2)	3885 (2)
C(5)	3238 (7)	1129 (2)	3810 (2)
C(6)	1186 (7)	1363 (2)	4367 (2)
N(6)	−221 (6)	2159 (2)	4385 (2)
N(7)	4084 (6)	1565 (2)	3150 (1)
C(8)	5896 (6)	993 (2)	2844 (2)
N(9)	6340 (6)	222 (2)	3269 (1)
C(1′)	8316 (6)	−515 (2)	3044 (2)
C(2′)	6898 (7)	−1193 (2)	2517 (2)
O(2′)	8701 (6)	−1958 (1)	2489 (1)
C(3′)	6804 (7)	−644 (2)	1764 (2)
O(3′)	7729 (6)	−1197 (2)	1148 (1)
C(4′)	8859 (7)	158 (2)	1906 (2)
O(4′)	10416 (5)	−87 (2)	2587 (1)
C(5′)	7369 (7)	1076 (2)	2073 (2)
O(5′)	5316 (6)	1258 (2)	1501 (1)
O(W)	5265 (7)	2718 (2)	436 (2)
H(2)	171 (9)	−51 (3)	537 (2)
H(1N6)	14 (12)	258 (3)	406 (3)
H(2N6)	−154 (12)	233 (3)	483 (2)
H(1′)	917 (10)	−88 (3)	354 (2)
H(2′)	513 (10)	−134 (2)	277 (2)
H(O2′)	782 (10)	−243 (3)	228 (2)
H(3′)	471 (10)	−38 (2)	169 (2)
H(O3′)	687 (12)	−99 (3)	75 (2)
H(4′)	1024 (8)	26 (2)	142 (2)
H(5′)	882 (7)	163 (2)	209 (2)
H(O5′)	595 (11)	175 (3)	132 (3)
H(1W)	509 (16)	351 (5)	44 (4)
H(2W)	379 (15)	244 (4)	18 (3)

[a] All values are multiplied by 10^4 for nonhydrogen atoms and 10^3 for hydrogen atoms.

ature factors (see paragraph at end of paper regarding supplementary material) gave an *R* index $[=\sum(||F_o| - |F_c||)/\sum|F_o|]$ of 0.055. A modified counting statistics weighting scheme with the weight of each reflection proportional to $1/(\sigma F + 0.05F_o)$ was used (Stout & Jensen, 1968). Six reflections with very low F_o and unusually large disagreement with F_c were eliminated from the final refinement. The average and maximum values of the shift/error ratios for the atomic parameters after refinement were 0.10 and 0.38 for nonhydrogen atoms, respectively, and 0.12 and 0.51, respectively, for the hydrogen atoms. The scattering factors used for the oxygen, nitrogen, and carbon atoms were taken from Cromer & Waber (1965), and those for the hydrogen atoms were from Stewart et al. (1965).

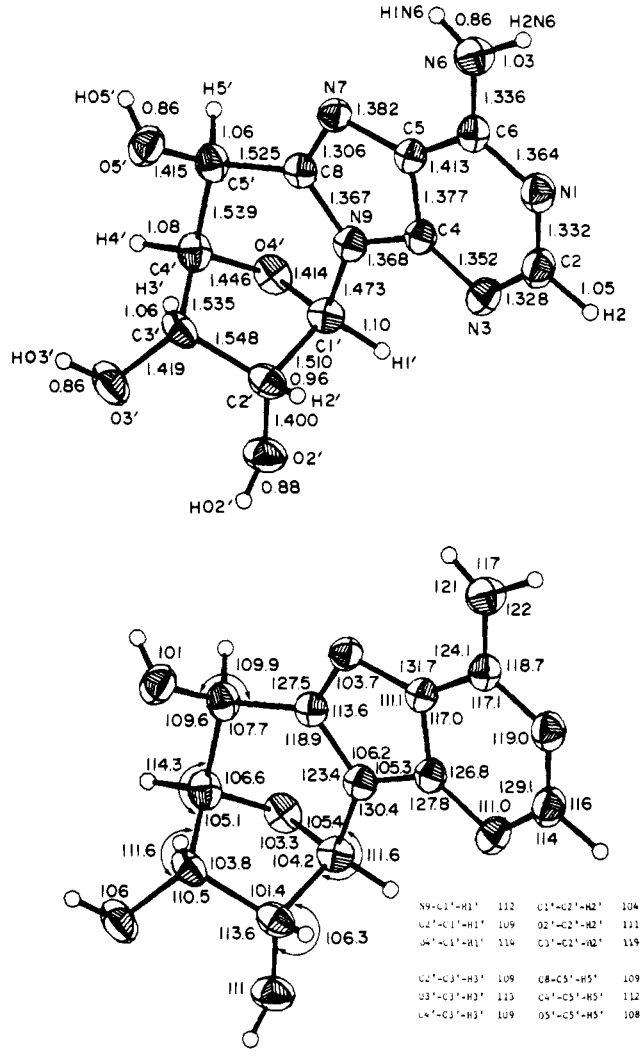

FIGURE 2: ORTEP drawings of 8,5′-cycloadenosine showing 50% probability ellipsoids for nonhydrogen atoms. The atom numbering scheme and all bond lengths and bond angles are indicated.

Results and Discussion

The final positional parameters are presented in Table I. Figure 2 shows ORTEP drawings (Johnson, 1965) of 8,5′-cycloadenosine with 50% probability ellipsoids for the nonhydrogen atoms and equisized spheres for the hydrogen atoms with the bond lengths and bond angles indicated. Unlike the nucleotide, which is indicated in Figure 1 in its usual zwitterionic form, the nucleoside lacks the acidic phosphate group and is, therefore, not protonated on the base.

The absolute configuration of 8,5′-cycloadenosine at the C(5′) atom was determined to be the C(5′)-*S* epimer with respect to the absolute configuration of the known D-ribofuranose moiety.

Molecular Conformation and Dimensions. The relevant torsion angles for the nucleoside including the endocyclic torsion angles and pseudorotation parameters (Altona & Sundaralingam, 1972) are given in Table II. Due to the covalent 8,5′ linkage, the 8,5′-cycloadenosine molecule must adopt the anti conformation (Figure 3a). The ribofuranoid

Table II: Conformational Parameters of 8,5′-Cycloadenosine Monohydrate

χ	O(4′)-C(1′)-N(9)-C(8)	27.4°
τ_0	C(4′)-O(4′)-C(1′)-C(2′)	48.6°
τ_1	O(4′)-C(1′)-C(2′)-C(3′)	−38.5°
τ_2	C(1′)-C(2′)-C(3′)-C(4′)	14.4°
τ_3	C(2′)-C(3′)-C(4′)-O(4′)	13.3°
τ_4	C(3′)-C(4′)-O(4′)-C(1′)	−38.1°
P	phase angle of pseudorotation	288.6°
τ_m	max amplitude of pseudorotation	47.7
	mode of ring pucker	${}^1_0T$, C(1′)-endo O(4′)-exo
ψ	C(3′)-C(4′)-C(5′)-O(5′)	−51.5 (gauche⁻)
	O(4′)-C(4′)-C(5′)-O(5′)	−167.2
	O(2′)-C(2′)-C(3′)-O(3′)	20.5

Conformational Parameters of the Six-Membered Fused Ring

endocyclic torsion angles (deg)

C(8)-N(9)-C(1′)-O(4′)	27.4	O(4′)-C(4′)-C(5′)-C(8)	−47.6
N(9)-C(1′)-O(4′)-C(4′)	−69.1	C(4′)-C(5′)-C(8)-N(9)	6.5
C(1′)-O(4′)-C(4′)-C(5′)	83.6	C(5′)-C(8)-N(9)-C(1′)	3.9

Cremer and Pople ring-puckering parameters

Q	0.644 A	q_2	0.520 A
θ	53.8°	q_3	0.381 A
ϕ_2	−165.2°		

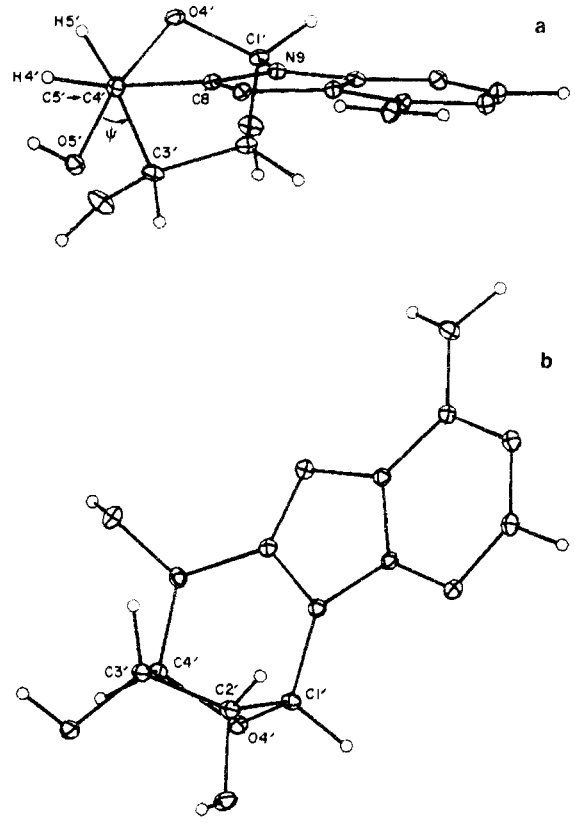

FIGURE 3: (a) 8,5′-Cycloadenosine viewed down the C(5′)–C(4′) bond (analogous to Figure 1) showing the gauche⁻ conformation for ψ and the anti conformation for the base. (b) Structure demonstrating the C(1′)-endo O(4′)-exo pucker of the ribofuranose ring.

ring is in the symmetric twist conformation C(1′)-endo O(4′)-exo (${}^1_0T$) which is illustrated in Figure 3b. This unusual mode of pucker is imposed upon the ribofuranose ring by the presence of the C(8)–C(5′) bond. This contrasts to the noncyclized adenosine molecule which assumes a C(3′)-endo conformation (Lai & Marsh, 1972) and deoxyadenosine which assumes a C(3′)-exo conformation (Watson et al., 1965; Sundaralingam, 1965). The torsion angle ψ [C(3′)–C(4′)–C(5′)–O(5′)] is gauche⁻ (Figure 3a), which corresponds to the inactive *S* epimer as found for the corresponding nucleotide (Figure 1a) from nuclear magnetic resonance studies by Raleigh & Blackburn (1978).

The fused C(8)–C(5′) linkage, as well as the N(9)–C(1′) linkage, is in the plane of the adenine base (Figure 3a). The least-squares plane through the nine atoms of the adenine ring including N(6), C(1′), and C(5′) is described by the equation $0.7363X + 0.4356Y + 0.5178Z = 5.247$ where X, Y, and Z are measured in angstroms along the crystallographic a, b, and c axes, respectively. The greatest deviation from this plane is shown by C(5′) which lies 0.138 Å off the plane. The dihedral angle between the above plane and the least-squares plane through the ribofuranose ring, described by the equation $0.7162X - 0.6363Y - 0.2866Z = 1.998$, is 84.2°.

The ring puckering parameters for the six-membered fused ring C(8)–N(9)–C(1′)–O(4′)–C(4′)–C(5′) are given in Table II (Cremer & Pople, 1975). This ring assumes the half-chair conformation (Figure 3a) with the O(4′) atom lying 0.825 Å off the least-squares plane through the other five atoms described by the equation $0.8090X + 0.4412Y + 0.3884Z = 4.826$. This plane makes a dihedral angle of 68.9° with the plane through C(1′)–O(4′)–C(4′) and a dihedral angle of 8.5° with the 12-atom plane through the adenine base described earlier.

The C(8)–C(5′) bond length is 1.525 Å and is within the same range of values found for normal carbon–carbon single bonds. In the ribofuranose moiety the C–C bonds range from 1.510 to 1.548 Å. The C(4′)–C(5′) bond of 1.539 Å is significantly longer than 1.509 Å observed for noncyclized adenosine (Lai & Marsh, 1972; Sundaralingam, 1965). The endocyclic C(2′)–C(3′) and C(3′)–C(4′) bond lengths of 1.548 and 1.535 Å, respectively, are also significantly longer than the corresponding values 1.528 and 1.522 Å observed for adenosine. The bond lengthenings result to relieve the strain imposed by the fused ring system where the furanoid ring assumes the ${}^1_0T$ pucker with the endocyclic torsion angles τ_2 and τ_3 about the C(2′)–C(3′) and C(3′)–C(4′) bonds being the smallest. The N(9)–C(1′)–O(4′) and O(4′)–C(4′)–C(5′) bond angles of 105.4 and 106.6°, respectively, are significantly

Table III: Hydrogen Bond Lengths in 8,5′-Cycloadenosine Monohydrate

bond A-H···B	sym no.[a] for B	translation for B			distances (A)			angle A-H···B (deg)
		x	y	z	A-H	H···B	A···B	
N(6)-H(1N6)···O(3′)	4	1	0	0	0.86	2.08	2.829	146
O(2′)-H(O2′)···N(7)	4	1	−1	0	0.88	1.88	2.759	179
O(3′)-H(O3′)···N(1)	2	0	0	−1	0.86	1.91	2.758	167
O(W)-H(1W)···N(3)	4	1	0	0	1.16	1.74	2.863	162
O(W)-H(2W)···O(W)	3	−1	0	0	0.92	1.99	2.867	160

[a] Symmetry numbers: (1) x, y, z; (2) $1/2 - x, -y, 1/2 + z$; (3) $1/2 + x, 1/2 - y, -z$; (4) $-x, 1/2 + y, 1/2 - z$.

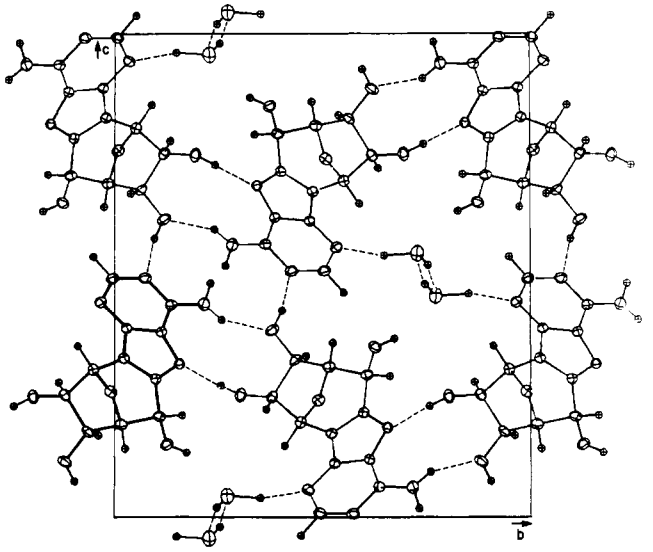

FIGURE 4: Packing diagram of 8,5′-cycloadenosine monohydrate viewed down the crystallographic *a* axis with the origin in the lower left-hand corner. The reference molecule (corresponding to the coordinates in Table I) is shown with darker bonds, and all hydrogen bonds are indicated by dashed lines.

smaller than the more nearly tetrahedral angles of 109.3 and 109.0° observed for the equivalent angles in adenosine (Lai & Marsh, 1972), which is probably due to the constraint imposed by the fused ring system. The endocyclic angle of 103.3° of the furanoid ring at O(4′) shows the greatest compression when compared to adenosine (Lai & Marsh, 1972) due to the O(4′)-exo puckering.

The bond distances and bond angles between nonhydrogen atoms of the base agree well with the usual values for known structures (Voet & Rich, 1970; Rao & Sundaralingam, 1973). However, those bond angles involving the C(1′) atom differ significantly from the average values; the C(4)–N(9)–C(1′) bond angle of 130.4° is significantly greater than the average of 126.1° for other neutral adenosine derivatives, and the C(8)–N(9)–C(1′) bond angle of 123.4° is significantly smaller than the reported average of 128.4° (Voet & Rich, 1970). The differences are yet more significant when compared to adenosine which has a C(4)–N(9)–C(1′) bond angle of 124.3° and a C(8)–N(9)–C(1′) bond angle of 130.0° (Lai & Marsh, 1972). This rather significant deviation is clearly due to the bond strain at the N(9) atom due to the C(8)–C(5′) bond which compresses the C(8)–N(9)–C(1′) bond angle at the expense of enlarging the C(4)–N(9)–C(1′) bond angle.

Hydrogen Bonding and Molecular Packing. The hydrogen bond lengths are presented in Table III. The hydrogen-bonding scheme can best be visualized as a network of 8,5′-adenosine molecules self-paired through the base N(6) and N(7) sites and the ribose hydroxyl groups O(2′) and O(3′) of the symmetry-related molecule to form ribbons parallel to the *b* axis (Figure 4). These ribbons are in turn linked by a hydrogen bond from N(1) to O(2′) parallel to the *c* axis. Self-hydrogen-bonded water molecules related by the 2_1 screw axis bridge the gaps between the adenosine molecules forming a zigzag chain parallel to the *a* axis, while making available the second proton of each water molecule to hydrogen bond to N(3) of the adenine moiety. The water oxygen bond angle is 113°. One of the amino hydrogen atoms is not involved in hydrogen bonding.

Base Sugar Contacts. The pucker of the O(4′) atom out of the plane of the adenine moiety brings the O(4′) atom unusually close to all of the atoms in the C(4)–C(5)–N(7)–C(8)–N(9) ring of the equivalent molecule translated one unit cell length along the *a* axis, the nearest contact being to C(8) (3.043 Å) and the farthest to N(7) (3.121 Å) with C(4), C(5), and N(9) having similar contact distances of 3.046, 3.085, and 3.052 Å, respectively.

Enzyme-Bound Conformations of Nucleotide Substrates. Several X-ray crystallographic studies of enzyme–nucleotide substrate complexes have been reported (Sundaralingam, 1975). While these structures have not been determined to the level of resolution required to clearly distinguish individual

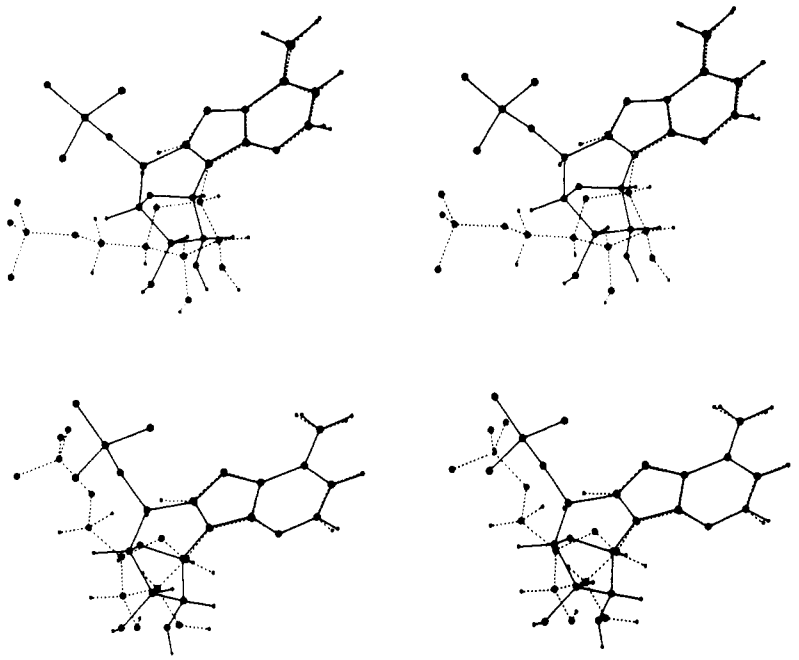

FIGURE 5: Two stereo overlays of 8,5′-cAMP (solid lines) and 5′-AMP (dotted lines) displaying the enzymatically active trans conformation for the ψ torsion angle. The upper stereopair depicts 5′-AMP in the C(3′)-endo anti conformation, and the lower pair depicts the C(2′)-endo anti conformation of 5′-AMP.

atoms and precisely determine the conformational parameters, they have, nevertheless, provided significant information regarding the conformation of enzyme-bound substrates. In none of these enzyme–substrate complexes does the nucleotide exhibit the gauche$^+$ conformation for the ψ torsion angle, in contrast to free nucleotides which prefer the gauche$^+$ conformation both in the solid state and in solution (Sundaralingam, 1975). Instead, either the trans or gauche$^-$ conformation for the ψ torsion angle is exhibited by the enzyme-bound nucleotides, which indicates that the enzyme binds its substrate in a less preferred conformation. Substrate activation from its most stable (gauche$^+$) "ground" state to a less preferred (trans or gauche$^-$) "excited" conformational state probably helps to decrease the activation barrier remaining to be overcome for the catalytic step of the enzymatic reaction.

The active epimer of 8,5′-cAMP was shown to react with pig muscle AMP kinase approximately twice as fast as noncyclized AMP (Hampton et al., 1972). This observation can be rationalized in terms of the fact that the active epimer is always in the normally less preferred trans conformation, and thus no time is lost in either forcing the conformational change upon the substrate during enzyme binding or in waiting for a substrate molecule which happens to be in the less preferred trans conformation.

Since, in the case of 8,5′-cAMP, very little conformational change is possible during enzyme binding, the enzyme presumably interacts with the base of AMP in the anti conformation, while the ribofuranose moiety probably assumes a pucker different from C(1′)-endo O(4′)-exo (^1_0T) since this puckering would result in steric conflict between the base and the C(5′) atom (Yathindra & Sundaralingam, 1974). In Figure 5, the *trans*-8,5′-cAMP model (*R* epimer) is shown overlaid on models for both trans-C(2′)-endo and trans-C(3′)-endo 5′-AMP with anti χ. The coordinates for the C(3′)-endo model are based on the monoclinic structure of 5′-AMP (Kraut & Jensen, 1963) with the ψ torsion angle set to 130° (trans range), and the C(2′)-endo model is based on the orthorhombic structure of 5′-AMP (Neidle et al., 1976) with the ψ torsion angle similarly adjusted. When the bases are brought into coincidence, the phosphate groups are separated by ~5 Å in both cases. Part of this disparity may be relieved by the ribofuranose ring adopting a conformation different from the most preferred C(2′)-endo or C(3′)-endo conformations; also, small changes in the other backbone torsion angles may further help to minimize the discrepancy.

In light of the fact that irradiation produces only the inactive epimer of 8,5′-cAMP, an interesting consideration is the possible presence of hydroxyl radical induced cyclic nucleotides in vivo. Fortunately, like most other types of radiation damage to nucleotides (Myers, 1973), the gauche$^-$ epimer is probably not further metabolized in anabolic pathways leading to macromolecular synthesis. On the other hand, if the radiation-induced 8,5′-cyclic nucleotides were active, their incorporation into essential macromolecules may pose a serious threat to the survival of the organism; thus in the course of evolution, those organisms whose enzymes were unable to process the hydroxyl radical induced gauche$^-$ cyclic nucleotides might have been favored for survival.

Supplementary Material Available

Tables showing the anisotropic thermal parameters for all nonhydrogen atoms and the isotropic thermal parameters for the hydrogen atoms and a list of all observed and calculated structure factors (6 pages). Ordering information is given on any current masthead page.

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