The Crystal and Molecular Structure of Cyclic Adenosine 3′,5′-Monophosphate Sodium Salt, Monoclinic Form[1]

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Abstract: The monosodium salt of adenosine 3′,5′-monophosphate (cAMP) crystallizes in space group $P2_1$ with a = 13.949 (2), b = 21.406 (2), and c = 5.825 Å, (1) β = 95.47 (1), and Z = 4. The crystal and molecular structure has been determined by X-ray diffraction methods and refined to an R factor of 0.037 by using 3279 observed intensities. The two cAMP molecules in the asymmetric unit form a dimer through two O(2′)H···H(3) hydrogen bonds between them. Conformation about the C(1′)–N(9) bond is anti for both molecules, with χ_{CN} values of 31° and 11°. The conformation of the furanose ring in one of the molecules is C(3′)endo C(4′)exo while the other is in the C(3′)endo C(2′)exo conformation. An analysis of the conformation of the furanose rings in cAMP molecules shows that the ring is more flexible than previously assumed. The crystal packing is strongly influenced by the cations, and both sodium ions in the asymmetric unit exhibit 6-fold coordination.

The early studies[2] of Sutherland and co-workers suggested that adenosine 3′,5′-monophosphate (cAMP) acts as a "second messenger" in the action of some hormones. Now it is well established that cAMP plays diverse roles in many metabolic processes. A preliminary crystallographic report[3] on cAMP appeared about 13 years ago, and X-ray crystallographic results have also been reported on some cAMP analogues.[4-7]

We have been studing cAMP sturctures[6-9] to see the influence of substitution and environment on molecular conformation. As a part of this program, we carried out the X-ray crystallographic studies on a trigonal[8] and a monoclinic form of cAMP sodium salt, and here we report the crystal structure of the monoclinic form.

Experimental Section

The crystals were grown by diffusing acetone into an aqueous solution with the use of materials purchased from the Sigma Chemical Co. The crystals became disordered on exposure to air. Therefore, a crystal enclosed in a capillary was used for diffraction data collection. The crystal data are as follows: mol formula $C_{10}H_{11}N_5O_6P{\cdot}Na{\cdot}4H_2O$; M_n 423.3; space group $P2_1$; a = 13.949 (2) Å; b = 21.406 (2) Å; c = 5.825 (1) Å; β = 95.47° (1); Z = 4; ρ(calcd) 1.558 gm/cm^3; crystal size 0.6 × 0.4 × 0.2 mm, and mass abs coeff, 22.

The X-ray intensity data were measured with an automatic diffractometer CAD-4 to a 2θ limit of 154° by using Cu Kα (λ = 1.5418 Å) radiation. Three axial reflections were used to monitor the intensity data, and the intensity of the control reflections showed an average drop of 6.4%, the maximum decrease being 8.3% for *800* reflections during the data measurements. A total of 4146 reflections were measured by using $\omega/2\theta$ scan techniques, and they were corrected for decay as a function of time. Empirical ϕ absorption correction[10] was also carried out by using 3 reflections with χ angles close to 90°. The maximum and minimum absorption correction factors differed by about 12%. Out of the 3741 unique reflections measured, 3278 had intensities greater than $2\sigma(I)$, and these were considered observed and used in structure determination and refinement.

The structure was solved by multisolution methods using the program MULTAN.[11] All the hydrogens, except five belonging to water molecules, were located from difference electron density map. All of the nonhydrogen atoms were refined with anisotropic thermal parameters, while the hydrogens were refined with isotropic thermal parameters using full matrix least-squares techniques to a discrepancy index $R(\sum[|F_o| - |F_c|]/\sum|F_o|$ of 0.037 for 3272 observed reflections. Atomic scattering factors[12] and anomalous dispersion coefficients[13] were taken from International Tables of X-ray Crystallography. The secondary extinction parameter[14] was also included in the structure factor calculations and the calculated structure amplitudes were modified to $F_c(1 + gI_c)^{-1}$. The final refined value of the extinction parameter g is 2.69×10^{-6}. The quantity minimized in the least-squares refinement was $\omega(|F_o| - |F_c|)^2$, where $\omega = 1/\sigma^2(F)$. In Tables I and II are given the final fractional coordinates of the atoms. A list of structure factors and anisotropic thermal parameters are provided as supplementary material.

Discussion

Bond Lengths and Angles. The bond lengths and angles are shown in Figure 1. There are no significant differences in bond lengths between the two molecules in the asymmetric unit of the crystal; the maximum deviation (0.015 Å) for the C(4)–C(5) bond is at the 3σ level. The lengths of C(1′)–O(1′) and C(4′)–O(1′) are equal within 2σ for both molecules, as is found to be the case[4,15] for the 3′,5′ cyclonucleotides. However, when no cyclization is involved, the average C(1′)–O(1′) bond (1.427 Å) is found to be[16] significantly shorter than the C(4′)–O(1′) bond (1.450 Å) length. In the present crystal form, since it is a salt, the cAMP molecules exist as negative ions. Hence, the two exocyclic P–O bonds are partial double bonds, and the lengths of these two bonds are equal within experimental error for both molecules.

The exocyclic C(1′)–N(9)–C(8) angles are about 4° larger than the C(1′)–N(9)–C(4) angles usually found[4] for molecules in the anti conformation. When the bond angles between the two molecules are compared, it is seen that bond angles in the furanose ring (other than the one involving C(1′)) show deviations of 1 to 2°. For the furanose ring, the torsion angles and bond angles are interrelated, and as the ring conformations of the molecules are different, the observed deviations in bond angles are not surprising. The largest difference in bond angles between the two molecules, however, is for the N(9)–C(1′)–C(2′) bond angles, which have values of 115.1° and 111.7° for the A and B molecules, respectively. This rather large difference appears to be related to differences in the sugar pucker as well as conformational differences about the glycosidic bond, C(1′)–N(9). The O(2′)–C-

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Table I. Positional and Thermal Parameters of Nonhydrogen Atoms

atom	x	y	z	B_{eq},[a] Å^2
P(A)	0.63770 (6)	0.14158 (5)	0.2668 (2)	2.7
O(1'A)	0.7332 (2)	−0.0406 (1)	0.5003 (5)	2.9
O(2'A)	0.8760 (2)	0.0667 (1)	0.6935 (5)	3.1
O(3'A)	0.7461 (2)	0.1224 (1)	0.3633 (5)	2.7
O(5'A)	0.5710 (2)	0.0933 (1)	0.3890 (5)	2.9
O(6A)	0.6202 (2)	0.2047 (1)	0.3548 (6)	3.5
O(7A)	0.6256 (2)	0.1319 (2)	0.0145 (5)	3.6
N(1A)	1.1205 (2)	−0.1764 (2)	0.3906 (5)	2.6
N(3A)	1.0287 (2)	−0.0999 (2)	0.5820 (5)	2.6
N(6A)	1.0662 (2)	−0.2218 (2)	0.0424 (6)	3.2
N(7A)	0.8866 (2)	−0.1397 (2)	0.0567 (5)	2.7
N(9A)	0.8746 (2)	−0.0772 (1)	0.3642 (5)	2.4
C(1'A)	0.8365 (2)	−0.0333 (2)	0.5240 (6)	2.6
C(2'A)	0.8588 (2)	0.0358 (2)	0.4809 (7)	2.6
C(3'A)	0.7631 (2)	0.0565 (2)	0.3579 (7)	2.4
C(4'A)	0.6936 (2)	0.0211 (2)	0.4977 (7)	2.5
C(5'A)	0.5914 (2)	0.0264 (2)	0.3873 (8)	2.8
C(2A)	1.1049 (3)	−0.1371 (2)	0.5598 (7)	2.8
C(4A)	0.9633 (2)	−0.1064 (2)	0.3990 (6)	2.4
C(5A)	0.9688 (2)	−0.1445 (2)	0.2114 (6)	2.3
C(6A)	1.0519 (2)	−0.1821 (2)	0.2092 (6)	2.4
C(8A)	0.8330 (2)	−0.0989 (2)	0.1535 (7)	2.8
P(B)	0.66211 (7)	0.42241 (5)	0.9232 (2)	2.9
O(1'B)	0.8393 (2)	0.5748 (1)	0.7281 (4)	2.9
O(2'B)	0.9629 (2)	0.4825 (1)	1.0285 (5)	3.2
O(3'B)	0.7675 (2)	0.4410 (1)	1.0416 (4)	2.9
O(5'B)	0.6635 (2)	0.4465 (1)	0.6623 (5)	3.4
O(6B)	0.6583 (2)	0.3531 (1)	0.9195 (5)	3.7
O(7B)	0.5878 (2)	0.4572 (1)	1.0385 (6)	4.1
N(1B)	0.9488 (2)	0.7320 (2)	1.6330 (6)	2.9
N(3B)	0.9859 (2)	0.6512 (2)	1.3704 (6)	2.9
N(6B)	0.8095 (2)	0.7902 (2)	1.5979 (6)	3.2
N(7B)	0.7585 (2)	0.7143 (2)	1.1465 (5)	2.9
N(9B)	0.8598 (2)	0.6385 (1)	1.0549 (5)	2.5
C(1'B)	0.8978 (2)	0.5844 (2)	0.9417 (6)	2.6
C(2'B)	0.8919 (2)	0.5245 (2)	1.0872 (6)	2.5
C(3'B)	0.7914 (2)	0.5044 (2)	0.9959 (6)	2.4
C(4'B)	0.7942 (3)	0.6147 (2)	0.7393 (6)	2.7
C(5'B)	0.6940 (3)	0.5095 (2)	0.6163 (7)	3.2
C(2B)	1.0035 (3)	0.6878 (2)	1.5550 (7)	2.9
C(4B)	0.9013 (2)	0.6662 (2)	1.2537 (6)	2.4
C(5B)	0.8380 (2)	0.7125 (2)	1.3087 (6)	2.5
C(6B)	0.8633 (2)	0.7461 (2)	1.5132 (6)	2.6
C(8B)	0.7744 (3)	0.6697 (2)	0.9994 (6)	2.8
Na(1)	0.4811 (1)	0.26061 (7)	0.4427 (2)	3.2
Na(2)	0.7144 (1)	0.27426 (8)	0.6057 (3)	3.8
O(W1)	0.3844 (2)	0.3460 (1)	0.5677 (5)	4.4
O(W2)	0.4020 (2)	0.2796 (2)	0.0695 (5)	4.2
O(W3)	0.7801 (2)	0.1873 (1)	0.8274 (5)	3.5
O(W4)	0.6051 (2)	0.3386 (1)	0.3818 (5)	3.7
O(W5)	0.5542 (2)	0.2488 (1)	0.8253 (5)	3.9
O(W6)	0.3885 (2)	0.1677 (2)	0.4871 (6)	5.0
O(W7)	0.4006 (2)	0.4088 (2)	0.0477 (8)	5.8
O(W8)	0.4377 (3)	0.0831 (2)	0.8534 (7)	6.8

[a] B_{eq} is the isotropic equivalent of anisotropic thermal parameters and is calculated as $8\pi^2(U_{11} + U_{22} + U_{33})^{1/3}$. The average standard deviation in B_{eq} is 0.1 Å^2.

Table II. Positional and Thermal Parameters and Bond Lengths of Hydrogen Atoms

atom	x	y	z	B	bond length,[a] Å
H1N6A	1.116 (3)	−0.242 (2)	0.033 (7)	2.8 (9)	0.82
H2N6A	1.037 (4)	−0.226 (3)	−0.068 (9)	5.9 (14)	0.74
HC1'A	0.864 (3)	−0.045 (2)	0.688 (7)	2.6 (8)	1.02
HC2'A	0.913 (3)	0.045 (2)	0.378 (8)	4.0 (11)	1.03
HC3'A	0.746 (4)	0.047 (2)	0.189 (8)	4.3 (11)	1.01
HC4'A	0.693 (4)	0.035 (3)	0.670 (9)	5.0 (12)	1.05
H1C5'A	0.544 (3)	0.007 (2)	0.465 (8)	4.0 (11)	0.93
H2C5'A	0.579 (3)	0.011 (2)	0.216 (8)	3.4 (10)	1.05
HC2A	1.139 (3)	−0.142 (2)	0.697 (7)	4.0 (10)	0.90
HC8A	0.771 (4)	−0.092 (3)	0.074 (10)	6.9 (16)	0.95
HO2'A	0.926 (3)	0.101 (2)	0.657 (7)	3.6 (10)	1.04
HC2'B	0.895 (3)	0.538 (2)	1.260 (7)	2.5 (8)	1.04
HC3'B	0.741 (4)	0.531 (3)	1.048 (9)	5.4 (13)	0.97
HC4'B	0.836 (3)	0.481 (2)	0.665 (7)	3.0 (9)	1.05
H1C5'B	0.695 (3)	0.512 (2)	0.448 (6)	2.1 (7)	1.05
H2C5'B	0.655 (4)	0.543 (3)	0.673 (9)	5.2 (12)	0.98
HC2B	1.055 (3)	0.680 (2)	1.634 (7)	3.4 (9)	0.84
HC8B	0.737 (3)	0.661 (2)	0.855 (6)	2.2 (8)	0.96
H1N6B	0.820 (4)	0.809 (2)	1.742 (7)	3.4 (10)	0.94
H2N6B	0.761 (4)	0.799 (3)	1.521 (9)	5.6 (13)	0.80
HO2'B	0.970 (3)	0.453 (3)	1.147 (9)	5.7 (13)	0.94
HC1'B	0.968 (5)	0.591 (2)	0.920 (8)	4.0 (10)	1.01
H1W1	0.391 (6)	0.385 (3)	0.443 (12)	9.3 (18)	1.11
H2W1	0.438 (3)	0.359 (4)	0.731 (13)	16.8 (26)	1.18
H1W2	0.448 (4)	0.264 (2)	−0.043 (6)	2.7 (8)	1.01
H2W2	0.354 (4)	0.265 (3)	−0.001 (9)	6.7 (14)	0.81
H1W3	0.727 (4)	0.169 (3)	0.869 (9)	6.7 (14)	0.89
H2W3	0.782 (3)	0.170 (3)	0.714 (9)	6.9 (14)	0.76
H1W4	0.604 (3)	0.340 (2)	0.208 (7)	5.0 (11)	1.01
H2W4	0.641 (4)	0.358 (3)	0.379 (11)	10.1 (19)	0.65
H1W6	0.349 (5)	0.171 (4)	0.578 (12)	13.1 (27)	0.80
H1W7	0.465 (3)	0.412 (2)	0.057 (7)	3.3 (9)	0.90
H1W8	0.514 (5)	0.086 (4)	0.849 (12)	12.8 (26)	1.07

[a] The standard deviations in the bond lengths involving hydrogen atoms range from 0.04 to 0.08 Å.

Table III. Conformation about the Glycosidic Bond C(1')-N(9) and the Conformation of the Furanose Ring in 3',5' Cyclic Nucleotides

molecule	χ_{CN}, deg	P, deg	τ_m, deg	ref
cAMPNa, monoclinic form	31 (anti)	33 ($^3T_4$)	49	present work
	11 (anti)	15 ($^3T_2$)	47	present work
cAMPNa, trigonal form	32 (anti)	27 ($^3T_4$)	49	8
cAMP, free acid A	62 (anti)	38 ($_4T^3$)	50	9
B	−90 (syn)	50 ($_4T^3$)	48	9
8-bromo-cAMP	−71 (syn)	19 (^3E)	50	6
5'-methylene-cAMP	−126 (syn)	37 ($_4T^3$)	46	4
8-[(2-aminoethyl)amino]-cAMP	−107 (syn)	51 ($_4T^3$)	49	5
cGMPNa	−102 (syn)	43 ($_4T^3$)	44	15
cGMP, free acid	−98 (syn)	44 ($_4T^3$)	44[a]	19
cUMPEt$_3$NH A	77 (anti)	42 ($_4T^3$)	48	20
B	58 (anti)	48 ($_4T^3$)	47	
cCMP[b]	12 (anti)	($^3T_2$)		21

[a] The reported value is 314° (with the convention that O(1')endo envelop is 0°). [b] P and T_m for this structure are not reported.

(2')–C(3') angle also shows a difference of 2.3°.

Conformation of the Molecule. The main conformation variation cAMP can exhibit is the rotation about the glycosidic bond C(1')–N(9). The χ_{CN}[17] angles [O(1')–C(1')–N(9)–C(8)] are 31° and 11° for molecules A and B, respectively. Energy calculations[18] on 3',5' cyclic nucleotides show that cAMP has a conformational preference for anti over syn in the ratio 7:3, while cGMP prefers syn conformation. The pyrimidine bases U, T, and C all have strong preferences for anti conformation. In Table III are listed the χ_{CN} angles and pseudorotation parameters[22] for 3',5' cyclonucleotides. It is seen that both syn and anti conformations are

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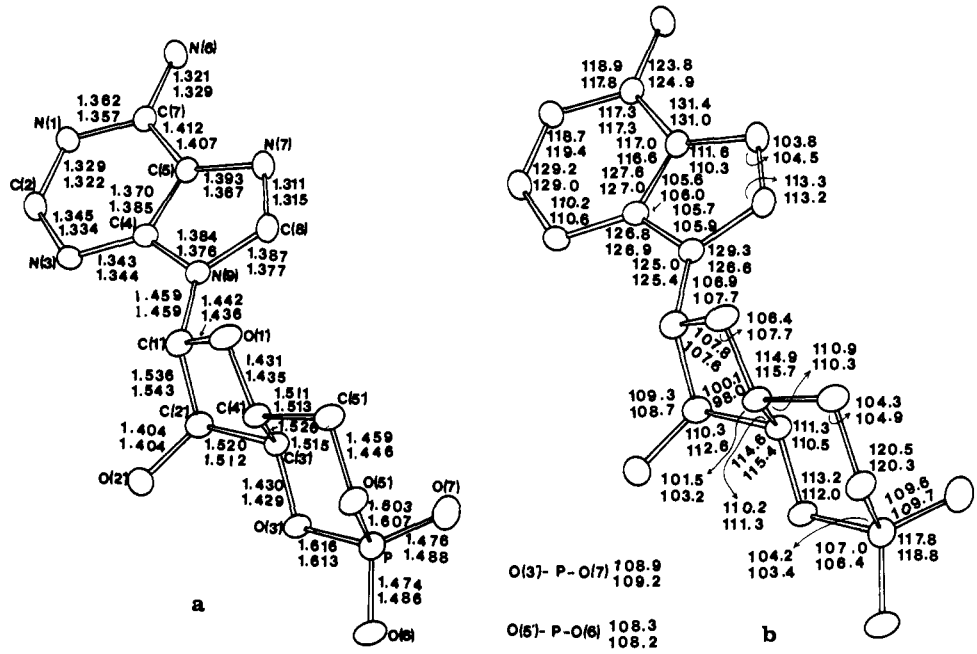

Figure 1. (a) Bond lengths. Upper and lower values are for molecule A and molecule B, respectively. The standard deviations in the bond lengths are in the range of 0.003–0.005 Å. (b) Bond angles. Standard deviations in bond angles are about 0.25°.

Table IV. Endocyclic Torsion Angles[a]

			(a) Furanose Ring		
τ_0	C(2')	C(1')	O(1')	C(4')	−12.7, 3.0
τ_1	O(1')	C(1')	C(2')	C(3')	−18.1, −29.9
τ_2	C(1')	C(2')	C(3')	C(4')	39.7, 44.1
τ_3	C(2')	C(3')	C(4')	O(1')	−49.1, −44.8
τ_4	C(3')	C(4')	O(1')	C(1')	38.2, 25.6
			(b) Phosphate Ring		
	O(3')	C(3')	C(4')	C(5')	66.6, 68.3
	C(3')	C(4')	C(5')	O(5')	−61.1, −60.8
	C(4')	C(5')	O(5')	P	57.2, 56.6
	C(5')	O(5')	P	O(3')	−49.0, −49.9
	O(5')	P	O(3')	C(3')	46.0, 48.9
	P	O(3')	C(3')	C(4')	−58.1, −61.9

[a] The first and second values are for molecule A and molecule B, respectively; values in degrees.

observed in cAMP crystal structures. The χ_{CN} value of 11° reported here for molecule B is the smallest that has so far been observed in cAMP structures. The cCMP[21] is the only other cyclic nucleotide in this series for which a similar low χ_{CN} value has been observed. It is also seen in Table II that for molecules in the anti conformation lower χ_{CN} values are usually accompanied by lower P values. The existence of an interrelationship between the χ angle and the sugar pucker as well as between the χ angle and the back-bone torsion angles has been pointed out by some investigators.[17,23-27]

The internal torsion angles of the furanose rings are listed in Table IV, which shows the differences in conformations. The furanose ring in molecule A is in the C(3')endo C(4')exo($^3T_4$)[22] conformation with a P value of 33°. The sugar ring in B is in C(3')endo C(2')exo ($^3T_2$) conformation with a P value of 15°. In molecule B the deviation of C(2') from the plane of O(1'), C(1'), and C(4') is only 0.078 Å, which indicates that the sugar ring is very close to the C(3')endo envelope (^3E) conformation.

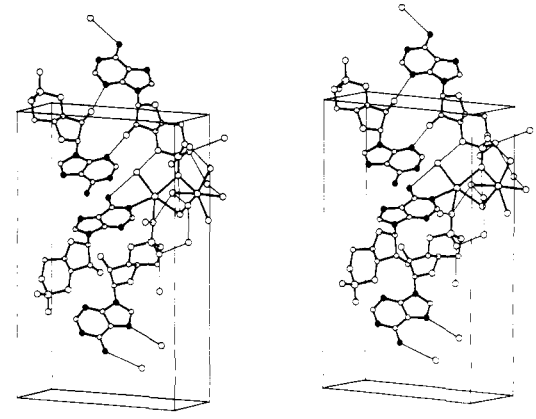

Figure 2. Stereo view of the crystal packing. Both the crystallographically independent sodium ions in the unit cell have sixfold coordination. Two N-H···O hydrogen bonds between molecule A and molecule B result in the formation of the dimer.

Table V. Hydrogen Bond Distances and Angles[a,b]

molecule	A···B, Å	H···B, Å	A-H···B, deg
O(2'A)-H···N(3B)	2.694	1.73	172
N(6A)-H···O(W3)	2.940	2.00	150
O(2'B)-H···N(3A)	2.868	1.91	170
N(6B)-H···O(W1)	3.030	2.06	154
O(W2)-H···O(W5)	2.746	1.81	162
O(W2)-H···N(7B)	2.831	1.87	169
O(W3)-H···(O(3'A)	3.037	2.09	163
O(W3)-H···O(7A)	2.773	1.82	168
O(W4)-H···O(6B)	2.878	1.94	162
O(W5)···O(6B)	2.690		
O(W5)···O(7A)	2.875		
O(W6)···O(W8)	2.833		
O(W7)···O(7B)	2.815	1.92	153
O(W7)···O(W2)	2.769		
O(W8)···O(7B)	2.797		
O(W8)-H···O(7A)	2.890	2.08	140

[a] A and B are nonhydrogen atoms. [b] H···B and the A-H···B correspond to the idealized lengths of 1.04 and 0.97 Å for N-H and O-H lengths, respectively.

The 3',5' cyclization imposes conformational restraints on the furanose ring, and it was pointed out that the sugar conformations

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in such cases are restricted[15,18] to ${}_4T^3$ or to a small range[4] of conformations, ${}_4T^3 \leftrightarrow {}^3T_4$. The pseudorotation parameter, P, of initially known structures fell into a narrow range (37–48°). However, in Table III it is seen that the phase angles (P) can have values over a much wider range (15–57°).

The six-membered phosphate rings are in the chair conformation and are slightly flattened at the phosphate end, probably because the P–O bonds are longer than the other bonds in the ring.

Hydrogen Bonding and Dimer Formation. A striking feature of the structure is the formation of the dimer seen in Figure 2. The two molecules are oriented in an antiparallel fashion and O(2′) of molecule A is hydrogen bonded to N(3) of molecule B with an H···N distance of 1.73 Å. The O(2′) of B is in turn hydrogen bonded to N(3) of A with an H···N distance of 1.91 Å. Hydrogen-bond parameters are listed in Table V. The phosphate oxygens are heavily hydrated, and O(7A) accepts three hydrogen bonds from water molecules while O(7B) is an acceptor for two hydrogen bonds. In both molecules, N(6) has only one hydrogen bond.

Sodium Coordination. Na(1) is octahedrally coordinated to five water molecules and O(6A), with coordination distances varying from 2.377 to 2.454 Å. The number of angles made by the six coordinating atoms at the central ion is 15, and in a regular octahedron, 12 of these are 90° and 3 are 180°. At Na(1) the maximum deviation from these ideal values is 21°. For Na(2) the coordination distances vary from 2.354 to 2.734 Å and for the angles the maximum deviation from the ideal values is 51°, which indicates a much larger deviation from ideal octahedral geometry. This deviation may reflect the fact that, while for Na(1), 5 of the coordinating atoms are water oxygens, in the case of the Na(2) atom three of the coordinating oxygens belong to water molecules and the other three are parts of the cAMP molecule.

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Supplementary Material Available: Listing of the structure factor amplitudes and anisotropic thermal parameters and a table giving the coordination geometry around sodium ions (18 pages). Ordering information is given on any current masthead page.

Crystal and Molecular Structure of the Quinoxaline Antibiotic Analogue TANDEM (Des-*N*-tetramethyltriostin A)

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Abstract: The crystal structure of TANDEM (des-*N*-tetramethyltriostin A), a synthetic analogue of the quinoxaline antibiotic triostin A, has been determined independently at −135 and 7 °C and refined to R values of 0.088 and 0.147, respectively. The molecule has approximate 2-fold symmetry, with the quinoxaline chromophores and the disulfide cross-bridge projecting from opposite sides of the peptide ring. The quinoxaline groups are nearly parallel to each other and separated by about 6.5 Å. The peptide backbone resembles a distorted antiparallel β ribbon joined by intramolecular hydrogen bonds N–H(L-Val)--O(L-Ala). At low temperatures, the TANDEM molecule is surrounded by a regular first- and second-order hydration sphere containing 14 independent water molecules. At room temperature, only the first-order hydration shell is maintained. Calculations of the interplanar separation of the quinoxaline groups as a function of their orientation with respect to the peptide ring support the viability of TANDEM to intercalate bifunctionally into DNA.

Des-*N*-tetramethyltriostin A (TANDEM), a synthetic analogue in the triostin family of quinoxaline antibiotics, was synthesized by Ciardelli, Chakravarty, and Olsen.[2a] The natural antibiotic, triostin A,[2b] is a symmetrical bicyclic octadepsipeptide composed of two units each of D-serine, L-alanine, *N*-methyl-L-cysteine, and *N*-methyl-L-valine. The depsipeptide bond occurs between the hydroxyl group of D-serine and the carboxyl group of *N*-methyl-L-valine, while a disulfide cross-bridge connects the two *N*-methyl-L-cysteine units. A 2-quinoxaline carbonyl (Qxc) moiety is attached to the amino group of each D-Ser unit. The title compound (Figure 1) differs from triostin A by the lack of *N*-methyl groups on the L-Cys and L-Val residues.

The quinoxaline antibiotics are active against Gram-positive bacteria[3] and against certain animal tumors.[4] The triostin an-

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