Structural Chemistry of Cyclic Nucleotides. 5. Methyl α-D-Glucopyranoside Cyclic 4,6-Phosphate[1]

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Abstract: Methyl α-D-glucopyranoside cyclic 4,6-phosphate has an enthalpy of hydrolysis 5 kcal/mol less exothermic than that of methyl β-D-ribofuranoside cyclic 3,5-phosphate or of cyclic nucleoside 3′,5′-phosphates. Crystals of the cyclohexylammonium salt of the glucoside cyclic phosphate ($C_{13}H_{26}NO_8P$) are monoclinic, space group $C2$, with a = 17.96 (1), b = 7.961 (4), and c = 12.491 (7) Å, β = 100.2 (1)°, and four molecules per cell. X-Ray diffraction data were collected using Mo radiation, and the intensity data were corrected for absorption. The structure was solved by Patterson methods and refined to an R value of 3.5% for the 1233 data. The axial glycosidic bond distance [1.387 (8) Å] in the glucoside is shorter than the expected 1.43 Å and comparable to values observed for equatorial glycosidic bonds. The main conformational change from the methyl α-D-glucopyranoside structure is a 120° rotation about the equatorial C(5)–C(6) bond to form the cyclic 4,6-phosphodiester. In cyclic nucleoside 3′,5′-phosphates the normally axial substituent on C(4′) is changed to an equatorial orientation to make the diester linkage. This leads to an unusual sugar conformation and a restricted pseudorotation angle range, suggesting rigidity in the normally flexible ribose ring. This rigidity would be a source of hydrolysis energy and may be responsible for the differences in the enthalpies of hydrolysis of ribonucleoside and glucoside cyclic phosphates.

In contrast to simple phosphate esters, cyclic adenosine 3′,5′-monophosphate (cyclic 3′,5′-AMP) has a large free energy[2] and enthalpy[2-4] of hydrolysis, both values being at least 3 kcal/mol more negative than the values for the hydrolysis of ATP to ADP and inorganic phosphate under the same conditions.[5] Cyclic 3′,5′-AMP is involved in the regulation of numerous cellular processes,[6,7] and its high energy nature may be a functional determinant for some of the regulatory uses of this small molecule. To investigate this possibility and to develop our understanding of the chemistry of cyclic nucleotides, structural studies of monocyclic[1] and bicyclic[8,9] phosphodiesters have been carried out and the results correlated with previously reported structural, thermochemical, and kinetic data on phosphate esters and their hydrolysis reactions. The heat of hydrolysis of trimethylene phosphate is 8 kcal/mol less exothermic than that observed for cyclic 3′,5′-AMP.[4] The geometry of the six-membered 3′,5′-phosphodiester rings of nucleotides differs slightly from that of cyclic alkyl phosphates, but the structural features suggesting strain, which might explain the enthalpy differences, are poorly defined and clearly involve the sugar as well as the phosphate rings. Replacement of the adenine in cyclic 3′,5′-AMP by a methoxyl group to give methyl β-D-ribofuranoside cyclic 3,5-phosphate does not change the heat of hydrolysis of the phosphate ring;[4] thus the fused ribose–phosphate ring system is responsible for the high-energy nature of these esters. Changing from a furanose ring to a pyranose ring does alter the energetics of hydrolysis, and the enthalpy of hydrolysis of methyl α-D-glucopyranoside cyclic 4,6-phosphate is 5 kcal/mol less exothermic than that of the corresponding β-ribonucleoside cyclic phosphate or of cyclic 3′,5′-AMP.[4] Comparison of the structures of ribonucleoside and glucoside cyclic phosphates is needed to determine whether the structural features of these sugar–phosphate ring systems can explain the large differences in the enthalpies of hydrolysis. Hence, a crystal structure study of the cyclohexylammonium salt of methyl α-D-glucopyranoside cyclic 4,6-phosphate was undertaken, the results of which are reported here.

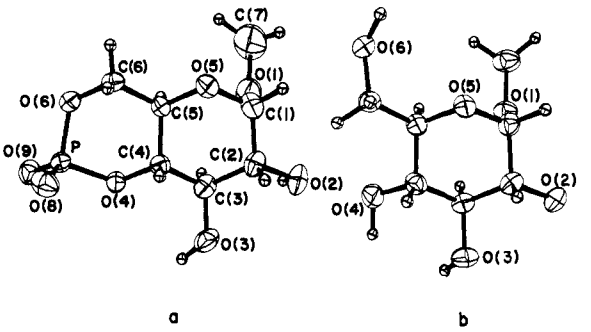
Experimental Section

The cyclohexylammonium salt of methyl α-D-glucopyranoside cyclic 4,6-phosphate was prepared by Gerlt[4] by phosphorylation of methyl α-D-glucopyranoside.[10] Crystals were obtained by diffusing ethyl ether into a solution of the salt in ethanol; the crystal data are given in Table I. A crystal of dimensions 0.40 × 0.13 × 0.45 mm was used to collect intensity data to 2θ = 55° using monochromated molybdenum x-radiation and a Picker FACS-I diffractometer. The cell dimensions in Table I were derived by least-squares fit to the $\pm 2\theta$ values for 15 reflections. Three quadrants of data were collected using θ–2θ scans (2°/min) with 20-s background measurements at each end of the scan. Three reference peaks were monitored every 100 reflections, and these intensities remained constant (±1%) throughout the data collection. The intensities were corrected for absorption on the basis of a normalized plot of scan count vs. φ for two ($00l$) reflections (χ = 90°) and the equations of North et al.[11] The maximum correction was approximately 8%. After correcting for Lorentz and polarization effects, the symmetry-related reflections were averaged; the average deviation from the mean intensity of equivalent reflections was below 2%. The final observational data consisted of 1233 intensities above 2 $\sigma(I)$ where $\sigma(I)$ was the standard deviation derived from counting statistics. All calculations were done on the IBM 370/168 system at the University of Chicago using programs cited in earlier publications.[1,9] Scattering factors were taken from the International Tables.[12]

Solution and Refinement. The six atoms in the phosphate ring and the two other phosphate oxygens were placed in the unit cell by inspection of a sharpened Patterson synthesis. A Fourier synthesis using phase angles based upon the positions of these eight atoms contained peaks for the remainder of the nonhydrogen atoms. The structure was refined by isotropic least-squares methods, and a difference Fourier synthesis was calculated. This map contained peaks of height 0.3–0.7 e/Å^3 for most of the glycoside hydrogens and some of the hydrogen atoms in the cyclohexylammonium counterion. The remainder of the hydrogen atoms were placed from a second difference Fourier map, calculated after two cycles of anisotropic refinement. The least-squares refinement minimized $\Sigma w(|F_o| - k|F_c|)^2$, and the weights, w, were derived from $\sigma(I)$. The final refinement cycles included positional parameters for most of the hydrogen atoms; the two hydroxyl hydrogens and the three ammonium ion hydrogens were kept fixed for space reasons in the computer program. The final R value for the 1233 data was 3.5%, where $R = \Sigma||F_o| - |F_c||/\Sigma|F_o|$, and the weighted R was 4.4%. The final shifts in parameters were less than 0.3 of the estimated error in the parameter, and the goodness of fit (1.0 for optimum weighting[12]) was 2.9.

Results and Discussion

The positional parameters for the 23 nonhydrogen atoms in the asymmetric unit are given in Table II and the hydrogen atom positional parameters in Table III. The atom numbering is given in Figure 1 (a), which also gives an idea of the variation in the thermal motion of the atoms. Figure 1 (b) is a view of methyl α-D-glucopyranoside[13] in the same orientation. The conformational similarity of the two structures, with and



a b

Figure 1. Equivalent views of (a) methyl α-D-glucopyranoside cyclic 4,6-phosphate and (b) methyl α-D-glucopyranoside. The thermal ellipsoids are at 50% probability.

Table I. Crystal Data for the Cyclohexylammonium Salt of Methyl α-D-Glucopyranoside Cyclic 4,6-Phosphate

Crystal system, monoclinic
Space group, $C2$
$a = 17.959 \pm 0.01$ Å
$b = 7.961 \pm 0.004$ Å
$c = 12.491 \pm 0.007$ Å
$\beta = 100.2 \pm 0.05°$
$d_{obsd} = 1.35$ g/cm^3; $d_{calcd} = 1.34$ g/cm^3
$Z = 4$
$\lambda = 0.71069$ Å (Mo Kα)

Table II. Positional Parameters (×10^4) and Their Estimated Standard Deviations[a]

Atom	x/a	y/b	z/c
P	2775 (0.7)	0	3506 (1)
O(8)	3406 (2)	1137 (5)	3972 (3)
O(9)	2015 (2)	236 (6)	3770 (3)
O(4)	3013 (2)	−1922 (5)	3831 (3)
O(6)	2695 (2)	−33 (6)	2202 (2)
C(4)	3640 (3)	−2602 (7)	3397 (4)
C(5)	3467 (3)	−2468 (7)	2160 (4)
C(6)	3341 (4)	−669 (8)	1791 (5)
O(5)	4084 (2)	−3129 (6)	1721 (3)
C(1)	4210 (3)	−4886 (10)	1990 (5)
C(2)	4383 (3)	−5145 (9)	3219 (4)
C(3)	3768 (3)	−4385 (8)	3774 (4)
O(1)	3586 (3)	−5866 (7)	1579 (4)
O(2)	4532 (2)	−6867 (6)	3471 (3)
O(3)	4005 (2)	−4456 (6)	4919 (3)
C(7)	3412 (7)	−5814 (17)	400 (8)
N	3877 (2)	2278 (6)	6057 (3)
CH(1)	3743 (4)	1023 (8)	6898 (5)
CH(2)	4022 (5)	1738 (10)	8034 (6)
CH(3)	3868 (6)	469 (10)	8910 (6)
CH(4)	4231 (6)	−1183 (11)	8755 (7)
CH(5)	3950 (6)	−1854 (10)	7637 (7)
CH(6)	4119 (5)	−627 (9)	6757 (6)

[a] Thermal parameters are included with the supplementary material.

Table III. Positional (×10^3) Parameters for the Hydrogen Atoms[a]

Atom	x/a	y/b	z/c
HC1	461	−524	164
HC2	480	−478	354
HC3	324	−499	348
HC4	404	−190	369
HC5	298	−314	186
HC6A	382	8	204
HC6B	323	−46	104
HC7A	322	−453	−1
HC7B	388	−615	22
HC7C	299	−674	36
HCH1	327	61	668
HCH2A	375	271	808
HCH2B	463	204	802
HCH3A	407	123	981
HCH3B	329	21	877
HCH4A	422	−189	929
HCH4B	487	−74	894
HCH5A	329	−199	738
HCH5B	413	−265	751
HCH6A	399	−93	591
HCH6B	470	−33	679
HNA	425	250	615
HNB	374	170	560
HNC	360	320	620
HO2	400	−740	350
HO3	360	−430	540

[a] Each hydrogen atom is given the number of the atom to which it is bound. The hydrogens were given an isotropic B of 5 Å^2.

Table IV. Final Bond Distances (Å) and Estimated Standard Deviations (×10^{-3})

P-O(4)	1.621 (4)	C(4)-O(4)	1.440 (6)
P-O(6)	1.610 (3)	C(5)-O(5)	1.422 (6)
P-O(9)	1.472 (4)	C(1)-O(5)	1.447 (9)
P-O(8)	1.486 (4)	C(6)-O(6)	1.441 (6)
C(1)-C(2)	1.525 (8)	C(7)-O(1)	1.451 (11)
C(2)-C(3)	1.528 (8)	N-CH(1)	1.500 (7)
C(3)-C(4)	1.500 (8)	CH(1)-CH(2)	1.528 (10)
C(4)-C(5)	1.526 (6)	CH(1)-CH(6)	1.502 (9)
C(5)-C(6)	1.509 (8)	CH(2)-CH(3)	1.549 (10)
C(1)-O(1)	1.387 (8)	CH(3)-CH(4)	1.495 (11)
C(2)-O(2)	1.422 (8)	CH(4)-CH(5)	1.497 (12)
C(3)-O(3)	1.420 (7)	CH(5)-CH(6)	1.541 (12)

Table V. Bond Angles (Deg) and Estimated Standard Deviations

O(9)-P-O(8)	120.5 (2)	C(2)-C(1)-O(1)	107.7 (5)
O(9)-P-O(6)	108.0 (2)	C(2)-C(1)-O(5)	111.1 (5)
O(9)-P-O(4)	106.2 (2)	C(1)-C(2)-O(2)	110.4 (5)
O(8)-P-O(6)	109.3 (2)	C(3)-C(2)-O(2)	113.9 (5)
O(8)-P-O(4)	109.1 (2)	C(1)-C(2)-C (3)	111.6 (5)
O(4)-P-O(6)	102.1 (2)	C(2)-C(3)-O(3)	109.2 (4)
P-O(4)-C(4)	116.8 (3)	C(4)-C(3)-O(3)	110.8 (5)
P-O(6)-C(6)	115.7 (3)	C(2)-C(3)-C(4)	108.4 (4)
O(4)-C(4)-C(3)	108.9 (4)	C(1)-O(1)-C(7)	112.0 (7)
O(4)-C(4)-C(5)	108.8 (4)	N-CH(1)-CH(6)	111.6 (5)
O(6)-C(6)-C(5)	108.1 (5)	N-CH(1)-CH(2)	109.6 (5)
C(3)-C(4)-C(5)	112.1 (4)	CH(1)-CH(2)-CH(3)	110.0 (6)
C(4)-C(5)-C(6)	111.6 (5)	CH(2)-CH(3)-CH(4)	110.3 (6)
C(4)-C(5)-O(5)	109.3 (4)	CH(3)-CH(4)-CH(5)	110.6 (7)
C(6)-C(5)-O(5)	108.6 (4)	CH(4)-CH(5)-CH(6)	111.3 (7)
C(5)-O(5)-C(1)	111.6 (4)	CH(5)-CH(6)-CH(1)	108.7 (6)
O(5)-C(1)-O(1)	112.0 (5)	CH(6)-CH(1)-CH(2)	110.8 (6)

without the phosphate, is evident. The bond lengths and bond angles for the pyranoside cyclic phosphate are given in Tables IV and V, along with those for the cyclohexylammonium cation. The C-C bond lengths in the sugar average 1.518 Å, and none differ significantly from this average value. Similar C-C bond lengths and a similar range of values were observed in methyl α-D-glucopyranoside,[13] α-D-glucose,[14] β-D-glucose,[15] and methyl β-maltopyranoside.[16] The C-O bond lengths, excluding C(1)-O(1), range from 1.420 to 1.451 Å, with the mean value 1.435 Å. The bond length of C(1)-O(1) is 1.387 Å which is shorter than the mean value by 6 σ. Equatorial glycosidic C(1)-O(1) bonds are normally significantly

Table VI. Dihedral Angles and Least-Squares Plane Data for the Phosphodiester Ring

Bond	Angle,[a] deg	Atom[b]	Deviation from best plane, Å
O(4)-P-O(6)-C(6)	−53.2	O(4)	0.013
P-O(6)-C(6)-C(5)	61.4	C(4)	−0.013
O(6)-C(6)-C(5)-C(4)	−61.8	O(6)	−0.013
C(6)-C(5)-C(4)-O(4)	59.7	C(6)	0.013
C(5)-C(4)-O(4)-P	−56.9	P	0.72
C(4)-O(4)-P-O(6)	51.3	C(5)	−0.71

[a] Positive angles correspond to clockwise rotation of the far atoms about the central bond. [b] The first four atoms were used to define the plane. Equation of the plane: $9.062x + 5.614y + 4.908z = 3.518$ Å, where x, y, and z are from Table II.

shorter than the expected 1.43 Å, but axial glycosidic bonds have previously been found short only when the hydrogen atom on O(1) is unsubstituted.[16,17] The 1.387-Å distance observed for this axial bond agrees with the values found for the equatorial bonds in β-D-glucose[15] (1.384 Å), methyl β-maltopyranoside[16] (1.375 Å), and cellobiose[18] (1.373 and 1.389 Å). The C(1)-O(1) bond length in methyl α-D-glucopyranoside was 1.411 Å, midway between the short and normal values.[13] Variations in these distances are of interest because the C(1)-O(1), C(1)-O(5), and C(5)-O(5) bonds form the hemiacetal (or acetal in this case) group of the pyranose ring, the properties of which give rise to much of the variety in carbohydrate chemistry in aqueous solution. The C(1)-O(5) and C(5)-O(5) bond distances (Table IV) are both within 2 σ of the mean value, as expected for pyranose rings with short glycosidic bonds.[16] The torsion angles about the C(1)-O(1) and C(1)-O(5) are 62.4 and 60.7°, which correspond to the most stable (+ synclinal, + synclinal) conformation for α-D anomers.[17]

In the phosphate ring the P-O bond lengths are normal and the bond angles are the same, within error, as the angles observed in the six-membered phosphodiester rings of cyclic uridine 3′,5′-monophosphate, reported in paper 1 of this series.[8] The valence angles in the sugar lie within the range normally observed for pyranose rings.[19] The C-C distances in the cyclohexylammonium ion average 1.52 ± 0.02 Å, and the mean ring angle is 110.3 ± 0.7°. The average C-H distance is 1.02 Å, and the N-H and O-H distances average 0.89 Å, both ±0.07 Å. The pyranose sugar is in the standard C1 chair conformation, and the torsion angles range from 51.4 to 61.3°; the range for the nonphosphorylated glucoside[14] was 54.2-60.2° and for β-D-glucose[16] 51.3-62.2°. The cyclohexane ring is also in the chair conformation with a narrower range of torsion angles (56.5-59.1°) because of the equal bond distances. Torsion angles and least-squares plane data for the phosphodiester ring are given in Table VI. The conformation is chair, with the P and C(5) puckered on opposite sides of the best four-atom plane. The same conformation with similar degrees of puckering has been observed in other six-membered phosphodiester rings.[1]

The packing is shown in Figure 2. The ions are linked through a system of hydrogen bonds about the symmetry axes. The cyclohexylammonium nitrogen forms three hydrogen bonds, two to phosphate oxygens and one to O(2) of the pyranoside; O(2), in turn, donates a hydrogen bond to phosphate oxygen O(8) of the anion one unit cell below in b, and O(9) is linked to O(3) across the 2_1 screw axis. The geometry of these hydrogen bonds is given in Table VII. The nitrogen is also quite close to O(3), but since the N already donates three hydrogen bonds and O(3) one hydrogen bond, it is difficult to see this as anything other than a close contact.

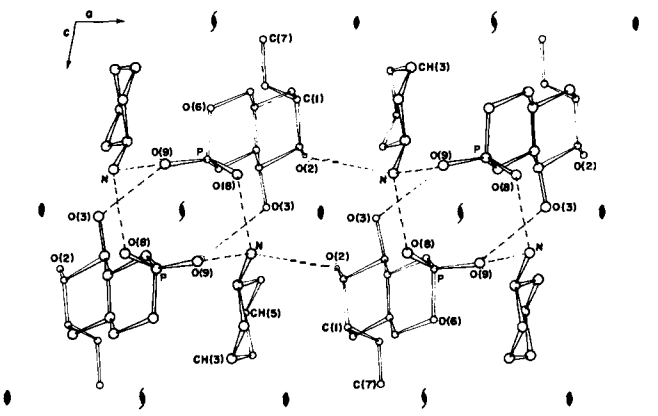


Figure 2. The crystal structure viewed down b. Hydrogen atoms are not shown. Hydrogen bonds appear as dashed lines.

Table VII. Hydrogen Bond Distances and Angles

Atom A	Atom B	B coordinates	d(A,B), Å	∠R-A···B, deg
N	O(8)	(x,y,z)	2.746	112.6
N	O(9)	$(\frac{1}{2}-x,\frac{1}{2}+y,1-z)$	2.863	109.4
N	O(2)	$(1-x,1+y,1-z)$	2.895	106.8
O(2)	O(8)	$(1-x,-1+y,1-z)$	2.730	93.8
O(3)	O(9)	$(\frac{1}{2}-x,-\frac{1}{2}+y,1-z)$	2.675	92.2
O(3)	N	$(x,-1+y,z)$	2.991[a]	118.6

[a] This is a close contact, but not a hydrogen bond; the H-N distance is 2.86 Å.

Furanose Rings. The purpose of this study was to examine the structural differences arising from the fusion of a six-membered phosphodiester ring to a furanose or pyranose sugar ring. Five-membered rings are puckered in their lowest energy conformations, and the angle of maximum puckering can rotate around the ring—a motion described as pseudorotation.[20,21] The pseudorotation angles for the heterocyclic sugar rings of nucleotides and nucleosides cluster in two regions corresponding to conformations with C(2′) or C(3′) of the ribose showing maximum pucker,[22,23] and NMR studies[24-26] suggest that both conformers are present in dynamic equilibrium in solution. Cremer and Pople[27] have recently proposed a general definition of ring puckering coordinates which can be applied without approximation to any cyclic molecule, and Table VIII gives puckering parameters, calculated using Cremer's program,[27] for a number of five- and six-membered rings for which crystal structure studies have been reported. In the five-membered sugars, 5-chlorouridine[28] shows a C(2′)-endo conformation and cytidine[29] a C(3′)-endo conformation. These are analogous to Altona and Sundaralingam's type S and type N conformations and have pseudorotation angles near the mean values found by these authors,[23] i.e., 80° for type S and 280° for type N. Cyclic 3′,5′-nucleotides have pseudorotation angles for the sugars outside the range of values reported for C(3′)-endo conformations (273-304°, with a preference for the lower part of the range[23]), and the three examples fall in a very narrow range. The exocyclic $-CH_2OH$ group is axial in ribofuranosides; the same group is equatorial in cyclic 3′,5′-nucleotides, apparently because of the geometrical requirements for formation of the trans-fused bicyclic ring system. This leads to an unusual sugar conformation, with C(4′) usually puckered, and a restricted pseudorotation angle range suggesting rigidity.[31] Rigidity alone would be a potential source of energy for ribofuranosyl phosphates and may be a significant source of hydrolysis energy for cyclic 3′,5′-nucleotides.

Table VIII. Puckering Parameters for Five- and Six-Membered Rings from the Equations of Cremer and Pople[a]

Compound	q, Å	φ, deg	Conformation[c]	Ref
(1) Furanose Rings[b]				
5-Chlorouridine	0.35	80.1	$^2T_3$	28
Cytidine	0.38	278.7	$^3T_2$	29
3′,5′-UMP (A)	0.45	309.5	$_4T^3$	8
3′,5′-UMP (B)	0.44	315.4	$_4T^3$	8
3′,5′-GMP	0.41	310.2	$_4T^3$	33

Compound	Q, Å	θ, deg	φ, deg	Ref
(2) Pyranose Rings				
α-Methyl glucoside cyclic phosphate	0.57	3.7	312.7	
α-Methyl glucoside	0.57	2.8	116.9	13
β-D-Glucose	0.58	6.9	324.0	15
Cyclohexyl ring[d]	0.59	1.2	301.2	
(3) Six-Membered Phosphate Rings				
α-Methyl glucoside cyclic phosphate	0.58	4.4	146.4	
$(CH_2)_3PO_4H$	0.54	7.6	179.0	34
3′,5′-UMP (A)	0.60	5.0	167.4	8
3′,5′-UMP (B)	0.58	6.6	201.8	8
3′,5′-GMP	0.57	13.6	195.9	33

[a] Parameters for the five-membered rings are defined by $z_j = (\frac{2}{5})^{1/2} q \cos(\varphi + 4\pi(j-1)/5)$ where q is a puckering amplitude and φ a phase angle; for the general equation for six-membered rings, see Cremer and Pople.[27] [b] The oxygen is taken as atom 1 in both the furanoid and pyranoid rings and the carbon atom with the glycosidic linkage as atom 2, in accordance with IUPAC rules. The φ values will thus differ from those of Altona and Sundaralingam[23] by about 270°. [c] Sundaralingam's nomenclature.[30] [d] This entry was included for reference; the coordinates used were those from Table II.

Pyranose Rings. In pyranose sugars, pseudorotation from one chair conformation to the other involves passing through a higher energy[32] boat or twist-boat conformation and is thus less likely. In methyl α-D-glucopyranoside, the $-CH_2OH$ group on C(5) is equatorial in the most stable C1 chair conformation, and phosphorylation to give the cyclic 4,6-phosphodiester does not require changes in the ring orientation of the exocyclic substituent. The main conformational difference between methyl α-D-glucopyranoside cyclic 4,6-phosphate and the nonphosphorylated glucoside reported by Berman and Kim[13] is a rotation of ~120° about the C(5)-C(6) bond to make the ester linkage (Figure 1); the O(5)-C(5)-C(6)-O(6) and C(4)-C(5)-C(6)-O(6) dihedral angles are 73.4 and 165.1° for the glucoside[13] and 177.7 and 61.8° for the glucoside cyclic phosphate. The less negative heat of hydrolysis of the methyl α-D-glucopyranoside cyclic 4,6-phosphate compared to ribonucleoside cyclic phosphates is thus not unexpected. Theoretical estimates of the strain energy induced by the fusion of the phosphate ring to the ribofuranoside sugar have not been made, but the thermochemical data[4] suggest that about 5 kcal/mol of additional hydrolysis energy for the ribonucleoside cyclic phosphates comes from the trans fusion of the rings.

Quantitatively, six-membered rings have three puckering degrees of freedom. These can be described[27] in terms of a spherical polar set of coordinates, (Q, θ, φ), where Q is the total puckering amplitude, θ an angle measuring deviation from the polar positions which correspond to chair conformations, and φ a phase angle showing the direction of deviation of the six-membered ring from a chair conformation. The pyranose sugar rings in Table VIII are all quite close to the chair conformation. The distortions are given[27] by the tan θ values, which are very small, and correspond to a slight flattening of the rings at C(2) or, for the glucoside, at C(5) with corresponding torsion angle differences of 3-5°. The six-membered phosphodiester rings are also in chair conformations, with cyclic guanosine 3′,5′-monophosphate[33] showing the maximum deviation (13.6°) in a direction which corresponds to a flattening of the chair at the phosphorus atom. This flattening is also reflected in the torsion angles about the P-O ester bonds which are smaller than the other ring torsion angles in all cases, as can be seen in Table VI for the glucoside cyclic phosphate.

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Supplementary Material Available: thermal parameters and a listing of observed and calculated structure factors (3 pages). Ordering information is given on any current masthead page.

References and Notes

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