Solid-State Conformations of Nucleoside Cyclic 3′,5′-Monophosphate Derivatives. Effects of Substituents on Phosphorus on Ring Geometries and n/σ* Orbital Interactions

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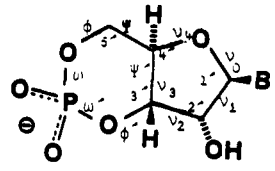
Published X-ray crystal structure data for seven nucleotide cyclic 3′,5′-monophosphates, nine neutral cyclic nucleotide-based phosphate triesters, phosphonates, and phosphoramidates, and X-ray results for one new neutral, cyclic nucleotide-based phosphate triester were compared. Clearly evident is the pronounced flattening of the phosphate ring about phosphorus. This effect is greater for the neutral derivatives and assigned in part to an increased degree of stabilization arising from overlap of the *p*-like lone pair orbitals on O(3′) and O(5′) with the σ* orbital of the axial substituent on phosphorus. Support for this interpretation is seen in shorter P–O(3′) and P–O (5′) bonds noted for the neutral derivatives. The degree of flattening also is enhanced by steric repulsions involving axial substituents on phosphorus. Most of the structural features of these phosphate ring-based systems were successfully modeled by MNDO calculation on monocyclic analogues. Comparisons of these findings were made to those summarized earlier for the X-ray structures of the analogous monocyclic rings, for which ab initio calculations on systems that modeled those rings had been carried out. Similarities and differences between the cyclic nucleotide-based derivatives and the monocyclic systems were noted.

Introduction

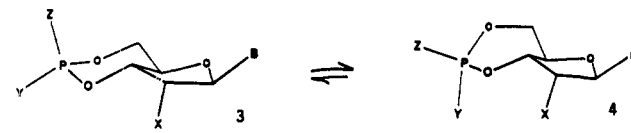
The cyclic nucleotides cAMP (adenosine cyclic 3′,5′-monophosphate, **1**) and cGMP (guanosine cyclic 3′,5′-monophosphate, **2**) are extremely important bioregulator



1, B = Adenyl

2, B = Guanyl

molecules. The actions of many hormones and other first messengers are mediated intracellularly by second messenger cAMP.[2] The effects of cAMP occur primarily through its activation of protein kinases I and II (PKI and PKII).[3] The concentration of cAMP in living cells is in part controlled by its hydrolysis to 5′-AMP under the influence of several isozymic phosphodiesterases (PDE).[4] There has been a considerable interest in cyclic nucleotides derivatized at phosphorus, for example, as phosphate triesters, phosphoramidates, and alkylphosphonates. Such derivatives have potential as agonists or antagonists of the natural diesters,[5] as storage forms of the natural diester,[6] and when based on antiviral and antitumor nucleosides, as prodrugs.[7] Moreover, they have proved to be useful in probing the conformational properties of the phosphate ring. Thus, the equilibrium **3** ⇄ **4** can be directed to favor the twist conformation, **4**, under the influence of an axial dialkylamino group (e.g., Z = Me_2N, Y = O)[8d] or an equatorial phenoxy substituent (Z = O, Y = PhO).[8c]



3 ⇌ **4**

Stereoelectronic (equatorial PhO) or steric (axial Me_2N) driving forces destabilize the *normally* more stable chair conformation in these cases. The free energy change for the chair to twist conversion of the phosphate ring of cAMP is estimated to be 1–3 kcal/mol on the basis of the equilibria for such derivatives, measured by proton NMR methods.[8a,c,e]

Knowledge of the molecular structure of cyclic nucleotide diesters and their derivatives should prove to be very important to the full understanding of the molecular details of the binding of cAMP to phosphodiesterases and protein kinases, its hydrolysis by phosphodiesters, and its activation of protein kinases. While NMR techniques reveal the conformational properties of such a ring system, only X-ray crystallography provides details concerning variations in bond lengths and dihedral (torsion) angles that may reveal the origins of the steric and stereoelectronic effects which control conformational equilibrium **3** ⇄ **4**.

Numerous X-ray structures of nucleoside cyclic 3′,5′-monophosphates and their derivatives have been published including several from this laboratory. Successful correlations of changes in structural details determined by X-ray crystallography with concomitant variations in steric and stereoelectronic factors have been made for *symmetrical*, monocyclic, four-coordinate 1,3,2-dioxaphosphorinanes.[9]

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(2) See, for example the review series: *Advances in Cyclic Nucleotide Research* **1971–1983**, *1–15*. *Advances in Cyclic Nucleotide Research and Protein Phosphorylation Research*, **1983–1987**, *16–20*. *Advances in Second Messenger and Phosphoprotein Research*, **1988–1990**, *21–24*.

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(5) An example of a neutral derivative of cAMP that retains biological activity is the *N,N*-dimethyl compound. The R_P and S_P diastereomers both bind in the surface receptors of *Dictyostelium discoideum* cells with similar affinities. However, only the S_P diasteromer elicites an intracellular cGMP response and chemotactic response. Van Haastert, P. J. M.; Kien, E. *J. Biol. Chem.* **1983**, *258*, 9636. Van Haastert, P. J. M. *Ibid.* **1983**, *258*, 9643.

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(9) For summaries see: (a) Van Nuffel, P.; Van Alsenoy, C.; Lenstra, A. T. H.; Geise, H. J. *J. Mol. Struct.* **1984**, *125*, 1. (b) Warrent, R. W.; Caughlan, C. N.; Hargis, J. H.; Yee K. C.; Bentrude, W. G. *J. Org. Chem.* **1987**, *43*, 4266.

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By contrast for nucleoside cyclic 3',5'-monophosphates and their derivatives, no systematic correlation of structural details from X-ray crystallography with stereoelectronic or steric factors has been attempted. Unlike the monocylics, these molecules feature distorted, *unsymmetrical* 1,3,2-dioxaphosphorinane rings. This is most readily seen in the unequal C(3')–O(3')–P and C(5')–O(5')–P bond angles to be discussed below in connection with the data of Table I. Furthermore, the transoid fusion of the five- and six-membered rings imparts approximately 5 kcal/mol of strain to the phosphate ring of cAMP itself.[10] These features potentially change both steric and stereoelectronic interactions within the cyclic 3',5'-monophosphates and their derivatives with respect to the monocyclic cases which may lead to different structural patterns. Indeed, similarities but also some *differences* between the two systems will be noted.

The purpose of this paper is to examine for the first time in a systematic way the geometrical features, determined by X-ray crystallography, of cAMP and related diesters, as well as their derivatives in which the functional groups attached to phosphorus have been changed to form uncharged phosphonates, phosphates, and phosphoramidates. Variations in structural parameters will be shown to be related to specific *steric* and *stereoelectronic* interactions within molecules. Especially important appears to be n/σ^* stabilization of the anomeric-effect type involving electron lone pairs on O(3') and O(5') and axial substituents on phosphorus. In addition, MNDO calculations will be successfully used to correlate and predict certain of the structural features observed.

X-ray structures for molecules 1–18 (Table I) had been reported previously, while that of **19** was only recently determined in this laboratory. However, for a number of 1–18, only selected data appeared in the literature. In those cases, we calculated the required parameters from the published X-ray coordinates and crystal data.

Results and Discussion

Phosphate Ring Conformations. X-ray Crystal Structures. A comparison of geometrical parameters from X-ray crystal structures of a number of nucleoside cyclic 3',5'-monophosphates and their derivatives is presented in Table I. (All diesters were examined as the phosphate salt.) The chair-form phosphate rings of the phosphate diesters **1**, **2**, and **5–9** are flattened at the phosphorus end of the ring, as seen most clearly from the dihedral angles ω and ω', which average −49.8° and 49.1°, respectively, relative to the expected 60° value for those of a perfect chair conformation. (See structure **1** as well as Table I for designation of torsion (dihedral) angles.) Derivatives **10–14** with substituents on phosphorus cis to the heterocyclic base ring (**3**, Z = R, R_2N, RO, etc; Y = O) show an even greater degree of flattening. Dihedral angles ω and ω' average −39.2° and 38.8°, respectively, and cover a relatively narrow range of values. Most of the trans derivatives **15–19** display much less flattening than do the cis compounds. If the values for the unusually flattened molecule **18** are not included, averages for ω and ω' of −43.7° and 46.5°, respectively, are found. These rings are still somewhat more flattened than those of the diesters. Although torsion angles ω and ω' show changes in ring geometry about phosphorus most dramatically, the same conclusions result from comparing ϕ and ϕ' throughout the series **1**, **2**, and **5–19**.

The degree of flattening of the phosphate ring of *trans*-thymidine cyclic phenyl 3',5'-phosphate **18**, is most notable. The ring adopts a conformation approaching a half-chair with ω = −15.4° and ω' = 27.8°. The conformation looks to approach that of a barrier structure for the chair to twist conversion (**3** → **4**). This flattening was first interpreted to be the result of the propensity of the phenoxy group to be pseudoaxial in a twist conformation (**4**) as evidenced by the major population of **4** by **18** in acetone-d_6.[8c] However, we recently prepared **19** and showed that it populates **4** to a greater degree than does **18**.[26] Yet its X-ray structure, not previously published, reveals flattening normal for a trans derivative (Table I).[26] The degree of flattening in **18**, therefore, is considered to be the exception.

Examination of the data for **14** and **17** (not previously compared)[14,25] is most instructive since the only difference between the two molecules is in configuration at phosphorus. For **14** the average values for ω and ω' (two crystallographic forms) are −37.9° and 39.5°, respectively, while those for the trans diastereomer **17** are −44.3° and 48.3°, respectively.

The greater flattening observed with the cis derivatives is most probably in part related to greater syn axial steric repulsions involving the various axial substituents (Z) on phosphorus and axial protons H(3') and H(5') (**3**, Z = substituent, Y = O). Indeed for **13** (axial Z = Me), the interatomic distances between the methyl carbon and axial H(3') and H(5') are 2.89 and 3.30 Å, respectively.[21] The van der Waals radius of a methyl group is about 2.0 Å.[27a] and that of a hydrogen atom is 1.25 Å.[27b] The axial methyl on phosphorus and axial H(3') are in fact closer than the van der Waals contact distance (3.75 Å), while the methyl and axial H(5') are very nearly in contact. Similarly, for **14** the distances between the amino nitrogen and axial H(3') in the two crystallographically independent molecules observed were 2.66 and 2.76 Å,[22] both at or closer than the van der Waals contact distance (1.5 + 1.75 = 2.75 Å[27b]). Between the axial dimethylamino nitrogen and the axial H(5'), distances of 3.00 and 3.07 Å were determined. Flattening of the 1,3,2-dioxaphosphorinane ring reduces

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Table I. Comparison of Phosphate Ring Geometrical Parameters in 3′,5′-Cyclic Nucleotides in Chair Conformation 3

compd no.	B	X	Y	Z	bond lengths (Å) P–O(3′)	bond lengths (Å) P–O(5′)	bond angles (deg) P–O-(3′)–C(3′)	bond angles (deg) P–O-(5′)–C(5′)	bond angles (deg) O(3′)–P–O-(5′)	torsion angles (deg) ψ C(3′)–C(4′)–C-(5′)–O(5′)	torsion angles (deg) ψ′ O(3′)–C(3′)–C-(4′)–C(5′)	torsion angles (deg) ϕ P–O(5′)–C(5′)–C(4′)	torsion angles (deg) ϕ′ P–O(3′)–C(3′)–C(4′)	torsion angles (deg) ω O(3′)–P–O(5′)–C(5′)	torsion angles (deg) ω′ O(5′)–P–C(3′)–C(3′)	ref
1	A	OH	O[b]	O	1.616	1.603	113.2	120.5	104.2	−61.1	66.6	57.2	−58.1	−49.0	46.0	11
					1.613	1.607	112.0	120.3	103.4	60.8	68.3	56.6	−61.9	−49.9	48.9	
2	G	OH	O	O	1.610	1.592	113.6	121.9	108.7	−60.5	68.5	53.6	−59.8	−44.3	44.2	12
5	U	OH	O	O	1.609	1.611	111.3	119.2	103.5	−61.4	69.1	60.5	−66.7	−56.7	57.4	13
					1.619	1.611	112.7	118.3	102.7	−59.5	67.1	56.5	−61.2	−50.5	49.3	
6	5-I-U	OH	O	O	1.599	1.602	112.9	121.4	104.3	−56.8	64.9	52.0	−59.9	−47.0	47.2	14
7	5-F-U	H	O	O	1.615	1.603	111.8	118.6	103.6	−61.0	67.4	57.1	−61.7	−51.5	51.0	15
8	I	OH	O	O	1.604	1.605	112.4	118.3	104.7	−64.5	69.1	59.8	−59.7	−51.0	47.8	16
9[d]	2-AE-A	OH	O	O	1.614	1.610	112.5	117.8	103.3	−62.9	67.4	60.5	−60.0	−53.6	50.1	17
			average, diesters		1.611	1.605	112.5	119.6	104.3	−60.9	67.6	57.0	−61.0	−50.4	49.1	
10	A	OH	O	OEt	1.57	1.53	113	122	108.8	−59.3	65.9	50.9	−54.1	−40.3	49.6	18
11	A	H	O	NHPh	1.596	1.590	114.8	120.1	106.2	−64.6	67.5	54.7	−53.3	−45.6	39.9	19
12	5-I-U	H	O	OMe	1.580	1.586	115.9	120.4	108.1	−66.0	69.4	52.1	−52.8	−37.4	36.1	20
13	T	H	O	Me	1.590	1.581	115.1	124.5	105.7	−60.3	69.3	48.0	−56.7	−36.4	38.2	21
14	T	H	O	NMe_2	1.58	1.57	114.5	123.0	106.2	−61.6	69.2	50.3	−57.1	−41.1	40.4	22
			average, cis compd		1.57	1.56	114.7	123.4	106.4	−62.3	71.4	46.1	−57.5	−34.6	38.6	
					1.581	1.570	114.7	122.2	106.9	−62.4	68.8	50.8	−55.3	−39.2	38.8	
15	U	OAc	OBz	O	1.579	1.568	111.0	120.0	106.3	−58.9	67.1	53.9	−60.9	−49.1	49.3	23
16	5-i-Pr-U	H	NHBz	O	1.579	1.585	112.9	124.0	103.7	−58.0	69.5	49.2	−63.1	−43.2	46.8	24
17	T	H	NMe_2	O	1.621	1.583	115.5	124.3	103.1	−59.8	73.5	49.4	−65.7	−44.3	48.3	25
18	T	H	OPh	O	1.577	1.559	115.5	129.8	107.6	−54.2	72.5	28.6	−56.5	−15.4	27.8	8[c]
19	T	H	$OC_6H_4NO_2$-*p*	O	1.59	1.56	112.4	127.0	106.5	60.7	74.7	46.4	−60.7	−38.1	41.5	26
			average, trans compd		1.592[c]	1.579[c]	113.0[c]	123.8[c]	104.9[c]	59.4[c]	71.2[c]	49.7[c]	−62.6[c]	−43.7[c]	46.5[c]	

[a] Data not published were obtained from data repository given in the references, from the authors, or by use of the published fractional atomic coordinates and cell parameters and the PC program ALCHEMY. [b] All structures of diesters were determined on sodium, NH_4^+, or Et_3NH^+ salts on zwitterions in which the P(O)OH proton had been transferred to the nucleobase. [c] Not including values for 18. [d] 8-[(2-Aminoethyl)amino]adenosine cyclic 3′,5′-monophosphate.

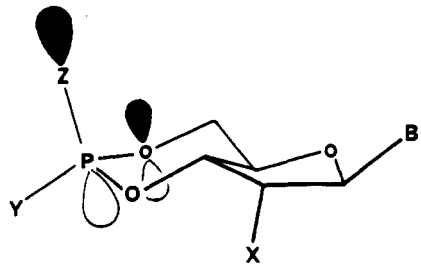

Figure 1. The anomeric effect in 3',5'-cyclic nucleotides depicted as an energetically favorable orbital interaction between the lone pair of an endocyclic ring oxygen and the P–Z antibonding orbital of an axial substituent on phosphorus.

such 1,3-syn axial repulsions and presumably has occurred to some energetically optimal extent in **10–14**.

The above results highlight an important distinction between the cyclic nucleotide-based systems and the symmetrical monocyclic 1,3,2-dioxaphosphorinane derivatives. The closer proximity between axial P–Z and H(3') means that the repulsive interactions between axial Z and H(3') are almost certainly greater than those between axial Z and H(5'). This introduces some uncertainty into the use[8] of chair–chair equilibria measurements for monocyclic rings to estimate the driving force for conversions of **3** to **4**. (See especially the discussion of this point in ref 8a.)

In addition to steric effects, electronic interactions very probably play a role in ring flattening of **10–14**. Thus, the sort of stereoelectronic interaction that is thought to be primarily responsible for the anomeric effect[28] is likely very important in these molecules. This stabilizing interaction, illustrated in Figure 1, involves overlap of the lone pair orbital on oxygen, optimally a p orbital, with the axial P–Z σ^* orbital. A similar n/σ^* interactions between the sp^2 lone pair on oxygen and the *equatorial* substituent, Y in Figure 1, would be comparatively less important *since the energy gap between the higher energy p orbital lone pair and the* σ^*_{P-Z} *orbital is less than that between the* sp^2 *oxygen lone pair and the* σ^*_{P-Y} *orbital.*[29] Dreiding models show that the favorable n/σ^* overlap of the O(3') and O(5') p orbitals is *increased* by ring flattening at phosphorus. Optimization of n/σ^* stabilization, therefore, *should lead to ring flattening.* Such influences on ring geometry have been suggested earlier for monocyclic four-coordinate 1,3,2-dioxaphosphorinanes.[9a] These effects should be greater for a neutral derivative than for a diester anion, since in the former case the substituent on phosphorus can better accomodate the increased electron density on Z that results from n/σ^* overlap. (This increase in n/σ^* stabilization is in fact throught to be the major factor in causing a methyl or phenyl triester to be more stable in chair conformation **3** when Z = MeO or PhO and to lead to large populations of conformation **4** if Y = MeO or PhO.[8c]) This stabilization, along with relief of 1,3-synaxial repulsions, leads to the flattening of the ring revealed by comparisons of angles ω and ω' noted above for **10–14** and also to an increase in angles P–O(3')–C(3') and P–O(5')–C(5'). (Increased p character in the lone pair will raise its energy and concomitantly maximize overlap stabilization.) These two angles average for the diesters of Table I, 112.5° and 119.6°, respectively, and for cis derivatives **8–14**, 114.7° and 122.2° (Table I).

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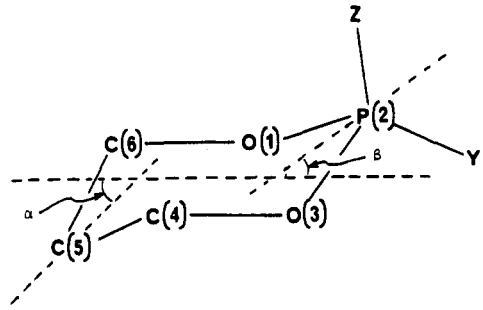


Figure 2. Schematic drawing of the 1,3,2-dioxaphosphorinane ring system showing the P flap angle β (the angle between the plane defined by O(1), P(2), and O(3) and the plane defined by O(1), O(3), and C(4), and C(6)), the C(5) flap angle, α (the angle between the plane defined by C(4), C(5), and C(6)), and the plane defined by (O(1), O(3), C(4), and C(6)).

The n/σ^* stabilization of Figure 1 would in theory result as well in shortened P–O(3') and P–O(5') bond distances. Indeed, averages for P–O(3') and P–O(5') for the diesters of 1.611 and 1.605 Å, respectively, are shortened to 1.581 and 1.570 Å for **10–14**.

For derivatives **15–19** with substituent Y trans (**3**, Z = O, Y = substituent), 1,3-syn axial repulsions resulting from the axial P=O should be very similar to those in the diesters themselves. Here, stereoelectronic interactions must account for the measured differences in geometries (ω, ω', bond angles) and bond lengths compared to the diesters. Thus, excluding the especially flattened ring of **16**, the average bond angles P–O(3')–C(3) and P–O(5')–C(5') are 113.0° and 123.8°, respectively. If the somewhat more puckered ring of **13** is excluded as well, the averages for the remaining compounds are 113.6° and 125.0°. Inspection of Table I shows the bond lengths P–O(3') and P–O(5') of **15–19** to be shorter than those for the diesters, as noted above for the cis derivatives **10–14**. Excluding those for **18**, they average 1.592 and 1.579 Å, respectively.

The extreme flattening of **18**, as expected, is accompanied by exceptionally large P–O(3')–C(3') and P–O(5')–C(5') angles, 115.5° and 129.8°, respectively. In addition, the bonds (P–O(3') = 1.577 Å, P–O(5') = 1.559 Å) are shorter than the average of those of the other trans compounds (P–O(3') = 1.592 Å; P–O(5') = 1.579 Å) *as expected if* n/σ^* *overlap is improved by ring flattening and vice versa.*

The *trans*-benzyl phosphate of 2'-acetyluridine cyclic 3',5'-monophosphate, **15**, surprisingly shows little ring flattening, even though its endocyclic P–O bonds are relatively short. Perhaps changes in intramolecular dipole–dipole repulsions arising from the acetylation of the 2'-OH play a role. The protection of the 2'-OH also may affect intermolecular, crystal-packing interactions leading to the anomalously low ring pucker about phosphorus. Interestingly, the trans isomers **15–19** show more variation in the key structural parameters than do the cis compounds **10–14**.

Similar correlations of the degree of ring flattening about phosphorus with phosphorus configuration were noted earlier for monocyclic 2-oxo-1,3,2-dioxaphosphorinanes.[9b] The interplane or flap angle β (defined in Figure 2) for those cases for which it was reported[9b] averaged 36° (range 31° to 40°) for rings with P=O equatorial and 47° (range 46–50°) when P=O is axial. The C(5) end of the ring was little affected by the configuration at phosphorus. Thus, angle α averaged 53° (50°–56°) and 51° (46°–56°) for the P=O equatorial and P=O axial compounds, respectively. The P–O–C bond angles for 1,3,2-dioxaphosphorinanes with equatorial P=O averaged 119°, while those with

P=O axial had an average P–O–C angle of 116°.

More recently, the X-ray crystal structures of a large number of simple, monocyclic 2-oxo- and 2-thio-1,3,2-dioxaphosphorinanes were compared.[9a] Correlations of torsion angles, valence angles, and bond distances with P=O or P=S orientation similar to those reported above were found. Endocyclic P–O–C angles for molecules with P=O axial averaged 115.1°, while an average of 118.8° was noted for those with P=O equatorial. Average endocyclic P–O bond lengths also correlated with P=O orientation: 1.583 Å (P=O axial) and 1.559 Å (P=O equatorial). The potential influence of C–O–P–O dihedral angle on n/σ^* interaction was emphasized and used to rationalize the trends in structural parameters noted. The increased shortening of the P–O bonds for the P=O equatorial compounds was ascribed to the more favorable dihedral angle (ω and ω' in our molecules) for n/σ^* overlap.[9a]

These effects are not seen in the cyclic 3′,5′-nucleotide data of Table I for average P–O(3′) and P–O(5′) bond lengths. There is no substantial difference in the *averages* for cis and trans derivatives. This may be because the axial Z substituents for **10–14** vary greatly in electronegativity and thus in their abilities to engage in C–O bond-shortening n/σ^* overlap. Also the average P–O(3′)–C(3′) and P–O(5′)–C(5′) angles do not differ in any systematic way. One angle, P–O(3′)–C(3′), is greater in **10–14** and the other, P–O(5′)–C(5′), in **15–19**. However, in the *only directly comparable* single set of diastereomers, **14** and **17**, the bond length correlation found for the monocyclic, 1,3,2-dioxaphosphorinanes[9a] is observed, (P–O(3′), cis) < (P–O(3′), trans) and P–O(5′), cis) < (P–O(5′), trans). Similarly, the exocyclic P–N bond lengths follow the order P–NMe_2 (axial, **14**, 1.64 Å) > P–NMe_2 (equatorial, **17**, 1.55 Å) to be expected if the axial P–N bond is involved with an anomeric-effect-like n–σ^* interaction with the p orbitals on O(3′) and O(5′). The P–N bond length differences also reflect the greater exo anomeric interaction of the equatorial Me_2N of **17**. The greater flattening of the ring of **17** (ω,ω'), however, is not reflected in the bond angles P–O(3′)–C(3′) and P–O(5′)–C(5′) for **14** and **17**.

The comparisons of the monocyclic 1,3,2-dioxaphosphorinanes revealed that the axially oriented P=O bonds were on the average longer than the equatorial ones.[9a] No correlation of this kind was seen for the P=O bonds for the structures of Table I. (P=O bond lengths not recorded in Table I).

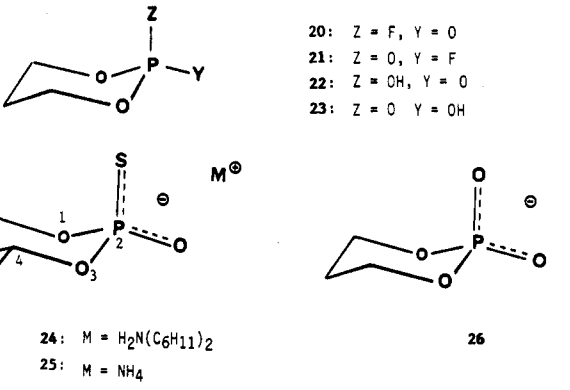
Interestingly, but perhaps not surprisingly, none of the phosphate rings of the cyclic nucleotide derivatives compared in the present study adopt a non-chair, boat, or twist conformation in the solid state. This is in spite of the fact that proton NMR unmistakeably assigns a range of equilibria **4/3** running as high as 60/40 for **18** in polar solvents[8c] and up to 72/28 for **14** in nonpolar solvents.[8d,26]

Phosphate Ring Conformations. Semiempirical Calculations. As emphasized above, the greater ring flattening of those compounds with axial substituents, **10–14** (**3**, Z = axial substituent, Y = phosphoryl oxygen, P=O, equatorial), is in part a result of greater repulsive steric interactions assignable to axial Z than to axial P=O. As also suggested above, stereoelectronic effects are very probably important as well, as flattening of the ring will increase the overlap involved in the stabilizing n/σ^*_{P-Z} amd $n/\sigma^*_{P=O}$ interactions. Results, recorded in Table II, of the application of MNDO calculation methods[30] to the 1,3,2-dioxaphosphorinane rings of **20–26** are in accord with these ideas.[31] Comparisons of **20** vs **21** and of **22** vs **23** show variations in bond lengths, endocyclic P–O–C angle, and torsion angle ϕ (C–O–P–C) that completely parallel what is observed experimentally for the monocyclic rings.[9] Steric repulsions should be similar for **22** and **23**. Therefore, the differences in parameters calculated appear to reflect the dominance of the greater anomeric stabilization present when OH is axial. Structures **22** and **23** also represent fairly reasonable models for alkyl phosphate triesters.

Table II. Final Geometrical Parameters from MNDO Calculations on 1,3,2-Dioxaphosphorinanes

compd	P–O (Å)	P–O–C (deg)	β^a (deg)
20	1.601	124.4	33.6
21	1.609	122.8	37.3
22	1.601	124.1	34.1
23	1.611	122.8	37.1
26	1.653	124.8	37.2

[a] As defined in Figure 2.



The X-ray structures of anionic dioxaphosphorinanes **24**[32] and **25**[33] display larger values of β (44.4° and 47.1° for **24**, and 45.3° for **25**) and decreased endocyclic P–O–C angles (117° and 116°, respectively) compared to these parameters for analogues derivatized at phosphorus to form uncharged molecules.[9] Again, this is not solely a steric phenomenon but reflects reduced n/σ^* stabilization with the negative charge present on oxygen or sulfur. These ideas are partially supported by the MNDO results for **26**, Table II. The endocyclic P–O bonds are significantly lengthened relative to those for **20–23**. However, angles β and P–O–C remain rather similar to those for **20–23**.

In previously published work,[9a] results of ab initio level calculations, utilizing $(HO)_2P(O)H$ and $(HO)_2P(S)H$ as models for the 1,3,2-dioxaphosphorinanes, were shown to mimic the experimentally determined variations of endocyclic P–O–C and O–P–O angles and P–O and C–O bond distances with phosphorus geometry (P=O, P=S equatorial or axial). In that work, the torsion angles O=P–OH and S=P–OH were fixed at values equal to the average of the O=P–OC and S=P–O–C angles determined by X-ray crystallography for the P=O(S) axial or P=O(S) equatorial conformers. The ability of calculations at the MNDO level in the present work to correctly mimic most of the experimental variations in the above parameters is gratifying considering the relative ease with which MNDO computations can be carried out.

(30) For a discussion of the MNDO computational technique see: (a) Dewar, M. J. S.; Thiel, W. *J. Am. Chem. Soc.* **1977**, *99*, 4899. (b) Clark, T. *A Handbook of Computational Chemistry*; Wiley: New York, 1985; Chapter 4.

(31) For our calculations we used the IBM-PC version available from the Quantum Chemistry Program Exchange, QCMP 002 (QCPE 353) by Walter Thiel (converted by Jannetta D. Bowen).

(32) Bartczak, T. J. *Acta Crystallogr., Sect. C* **1983**, *C39*, 1059.

(33) Bartczak, T. J.; Wolf, W.; Cameron, T. S. *Acta Crystallogr., Sect. C* **1983**, *C39*, 1467.

Cyclic 3′,5′-Monophosphate Derivatives vs Monocycles. It is important to note that consistent geometrical differences are found in comparing the structures of the cyclic nucleotides (Tables I) to those of simple, monocyclic 1,3,2-dioxaphosphorinanes.[9] With respect to the monocyclics, the P–O(3′)–C(3′) bond angles are compressed while the P–O(5′)–C(5′) angles are greatly expanded. This probably is in response to the distortions found at the C(3′)–C(4′)–C(5′) end of the cyclic nucleotide phosphate rings. Indeed, that end of the ring is severely puckered as evidenced by the angles Ψ and Ψ′ (Table I) which vary widely (−54.2° to −62.3° for Ψ, and 65.9° to 73.5° for Ψ′) and also demonstrate further the lack of symmetry in the phosphate rings. (By comparison, in a compilation of values for this dihedral angle for 37 monocyclic 2-oxo- and 2-thio-1,3,2-dioxaphosphorinanes of only 55.5° to 61.9° was noted with average values 57.3° and 58.8°[9a] for P=O or P=S axial or equatorial, respectively.) The X-ray structures of the cyclic nucleotide derivatives (Table I) have P–O(3′)–C(3′) angles (111.8°–115.5°) that are much less than the 120° geometry of an ideally hybridized sp^2 O(3′). The P–O(5′)–C(5′) geometries (118.6°–127.0°, mostly 119°–124°) are generally closer to 120°. The nearly uniformly shorter P–(O5′) bond distances compared to those for P–O(3′) (see the average for **10–14** and **15–19** in Table I) suggests that the n/σ^* stabilization involving the more nearly *p*-hybridized lone pair on O(5′) is the greater of the two.

The lack of symmetry in the 1,3,2-dioxaphosphorinane ring of course is responsible for the closer syn axial Z/H(5′) contacts, noted above, compared to those for Z/H(5′). The failure of average ring P–O bond lengths and average endocyclic P–O–C angles for the cyclic nucleotides to correlate with the cis or trans nature of the diastereomer (cis or trans) also was pointed out above as being in contrast to the findings for the corresponding monocyclic derivatives.

Ribose Ring Conformations. In Table III are found the dihedral angle data for the ribose rings of the cyclic nucleotides whose phosphate ring geometries were compared in Table I. The molecules are listed in the order of decreasingly less negative values of ν_o, i.e., from −30.8° to 3.0°. Those ribose rings with very large ν_o values (about −30°) and small values for ν_1 (1–2°) are in a conformation designated[34] $_4$E (C(4′)-exo) in which the heterocyclic base is attached to the envelope-form ribose ring in an essentially equatorial position. At the other extreme, the ribose ring approaches the ^{3}E envelope conformation (C(3′)endo). One of the two independent cAMP molecules (**1**), and no other in this list, is in the ^{3}E conformation. In solution, proton NMR studies of cyclic 3′,5′-monophosphates, the ribose rings of 2′-deoxy cases have been assigned the $_4$E–$_4$T^3 range of conformations, whereas 2′-deoxy compounds were found to have ribose rings with conformations in the ^{3}T$_4$–^{3}E range.[35,36] Perusal of Table II yields no discernible trends relating ribose conformation to the nature of the substitution on phosphorus, the presence or absence of the 2′-OH, or the particular heterocyclic base. Not even the diesters themselves follow any obvious trend, as ribose and 2′-deoxyribose compounds are all found to have ν_o values

Table III. Comparison of Ribose Ring Dihedral Angles in 3′,5′-Cyclic Nucleotides[a]

compd no.	B	X	Y	Z	C(4′)–O(1′)–C(1′)–C(2′) (ν_0)	O(1′)–C(1′)–C(2′)–C(3′) (ν_1)	C(1′)–C(2′)–C(3′)–C(4′) (ν_2)	C(2′)–C(3′)–C(4′)–O(1′) (ν_3)	C(3′)–C(4′)–O(1′)–C(1′) (ν_4)
16	5-*i*-Pr-U	H	NHBz	O	−30.8	1.9	25.8	−46.2	47.4
11	A	H	O	NHPh	−30.3	1.4	26.4	−46.6	48.3
14	T	H	O	NMe_2	−29.3	2.1	25.8	−45.8	47.0
					−27.2	1.0	24.8	−41.8	43.7
9	2-AE-A	OH	O	O	−26.4	−3.2	29.6	−47.5	45.6
15	U	OAc	OBz	O	−24.2	−5.1	30.3	−46.6	43.7
5	U	OH	O	O	−23.5	−5.5	30.8	−46.7	43.2
					−19.3	−10.4	34.6	−48.1	41.5
17	T	H	NMe_2	O	−23.0	−5.5	30.7	−46.8	43.6
10	A	OH	O	OEt	−22.5	−8.7	35.1	−49.4	44.5
12	5-I-U	H	O	OMe	−21.8	−7.0	31.1	−46.0	42.3
6	5-I-U	OH	O	O	−19.0	−10.0	33.1	−46.9	40.8
2	G	OH	O	O	−18.4	−9.3	31.7	−44.3	38.7
19	T	H	$OC_6H_4NO_2$-*p*	O	−17.4	−10.5	33.3	−43.9	38.3
18	T	H	OPh	O	−16.6	−11.3	33.1	−44.7	38.0
13	T	H	O	Me	−16.0	−13.0	35.3	−46.5	38.6
7	5-F-U	H	O	O	−15.8	−12.3	33.7	−45.0	37.8
1	A	OH	O	O	−12.7	−18.1	39.7	−49.1	38.2
					3.0	−29.9	44.1	−44.8	25.6
8	I	OH	O	O	−7.0	−20.1	37.2	−43.5	31.3

[a] Taken from same references which yielded data for Table I.

(34) The Greek designations for dihedral angles used in Tables I and III follow the IUPAC recommendations which also spell out the $_3$T^4,$_4$E, etc. designations. *Eur. J. Biochem.* **1983**, *131*, 9.

(35) (a) Blackburn, B. J.; Lapper, R. D.; Smith, I. C. P. *J. Am. Chem. Soc.* **1973**, *95*, 2873. (b) Kainosho, M.; Ajisaka, K. *J. Am. Chem. Soc.* **1975**, *97*, 6839. (c) Lee, C.-H.; Sarma, R. H. *J. Am. Chem. Soc.* **1976**, *98*, 3541.

(36) Robins, M. J.; MacCoss, M.; Wilson, J. S. *J. Am. Chem. Soc.* **1977**, *99*, 4660 and references cited therein.

in the range -18.4° to -12.7° with the exception of the cAMP case mentioned above. In the solid state, intermolecular association may play a role more important than the dipole–dipole interactions between the 2'-OH and the base proposed to be the factor that determines ribose ring conformation in solution.[36]

Conformation of Nucleobases and Intramolecular Association. Since the interest of this paper is in the conformations of the phosphate and ribose rings of nucleoside cyclic 3',5'-monophosphates and derivatives thereof, we have not complied available information on the conformations of the nucleobases with regard to C(1')–N rotation, i.e., the glycosyl torsion angle. Comparisons of glycosyl torsion angles for the diesters (**1**, **2**, **5**–**9**) of Table I can be found in refs 15 and 17. Glycosyl torsion angles for **10**–**19** show no evident systematic correlation with phosphorus configuration. The related question of the nature of intramolecular interactions in the solid state, which can involve H bonding between nucleobases and also nucleobase–phosphate oxyanion interactions, has not been addressed.

Conclusions

X-ray crystal structure data for nucleoside cyclic 3',5'-monophosphates and their derivatives with substituents on phosphorus either trans and cis to the heterocyclic base have been compared. The six-membered, phosphorus-containing, 1,3,2-dioxaphosphorinane rings lack the mirror symmetry of the simple, monocyclic analogues. This is clearly shown by certain dihedral and bond angles involving atoms endocyclic to the ring. The dihedral angles ω and ω' show that the 1,3,2-dioxaphosphorinane rings that are derivatized at phosphorus to form triesters, phosphoramidates, and methylphosphonates are more flattened about phosphorus than are the anionic, nucleoside cyclic 3',5'-monophosphate diesters. This is also revealed by comparisons of the bond angles P–O(3')–C(3') and P–O(5')–C(5'). Moreover, the neutral derivatives with substituents axial on phosphorus are more flattened about phosphorus than are those with equatorial substituents on phosphorus. This is most clearly revealed by the torsion angles ω and ω'. These findings, along with effects on the P–O(3') and P–O(5') bond distances seen in comparing all three types of 1,3,2-dioxaphosphorinanes can be understood in terms of two effects: (1) the greater repulsive steric interactions of axial P–Z compared to axial P=O and (2) variations in the degree of n/σ^* stabilization involving the higher energy, p-orbital electron lone pair on oxygen and the axial P–Z or P=O antibonding σ orbital. Both cis and trans neutral derivatives (**8**–**17**) display effects of a greater n/σ^*, anomeric-effect-like stabilization than do the negatively charged anionic diesters. Moreover, the n/σ^* stabilization involving the O(5') lone pair and the larger P–O–C angle (P–O(5')–C(5')) is greater than that for the O(3') lone pair. Furthermore, the repulsive 1,3-syn axial repulsions between axial P–Z are almost certainly greater for H(3') than for H(5') as the former is closer to Z in the distorted chair **3**. These two structural features are distinctive for the cyclic nucleotide-based derivatives as compared to the symmetrical monocyclic 1,3,2-dioxaphosphorinanes. The results in the cyclic nucleotide systems are generally consistent with what was delineated earlier for highly symmetrical, simple, monocyclic 2-oxo- and 2-thio-1,3,2-dioxaphosphorinanes.[9] However, not all of the well-correlated bond distance and bond angle differences between P=O axial and P=O equatorial isomers for the simple monocyclic neutral derivatives were found for the cyclic nucleotide based molecules. The majority of the bond length and angle correlations found for monocyclic 2-oxo-1,3,2-dioxaphosphorinanes, and predicted by the previously reported ab initio calculations,[9a] were also revealed in the present study by calculations at the semiempirical MNDO level.

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Photo-Arbuzov Rearrangement Route to Acyclic Nucleoside Benzylphosphonates

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The recently discovered photo-Arbuzov rearrangement was carried out with a series of *tert*-butyldimethylsilyl-protected dimethyl benzyl phosphites, **9**, **15**, **18**, **20**, and **22**, easily derived from alcohol precursors, to afford the corresponding dimethyl benzylphosphonates in 67–74% isolated yields. One of the phosphonates, **10**, was further converted to the primary bromide which underwent reaction with the sodium salts of adenine, cytosine, and 2-amino-6-chloropurine to give the desired N-alkylated acyclic nucleoside dimethyl benzylphosphonates. The 2-amino-6-chloro compound was further elaborated to the guaninyl and 2,6-diamino derivatives. Demethylation afforded the acyclic nucleoside-based benzylphosphonic acids **25**, **27**, **29**, **31**, and **32** in good overall yields. These molecules are closely related structurally to the active antiviral 9-[2-(phosphonomethoxy)ethyl]adenine (PMEA) and the potent human erythrocyte purine nucleoside phosphorylase (PNP) inhibitors 9-(5-phosphonopentyl)guanine and 9-(5,5-difluoro-5-phosphonopentyl)guanine.

Acyclic nucleosides have been shown in recent years to have considerable potential as antiviral agents.[1] Amongst key advances in this area has been the discovery of the potent, selective antiherpes activity of 9-[(2-hydroxyeth-

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