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Intramolecular Hydrogen Bonding (P=O--H) Stabilizes the Chair Conformation of Six-Membered Ring Phosphates

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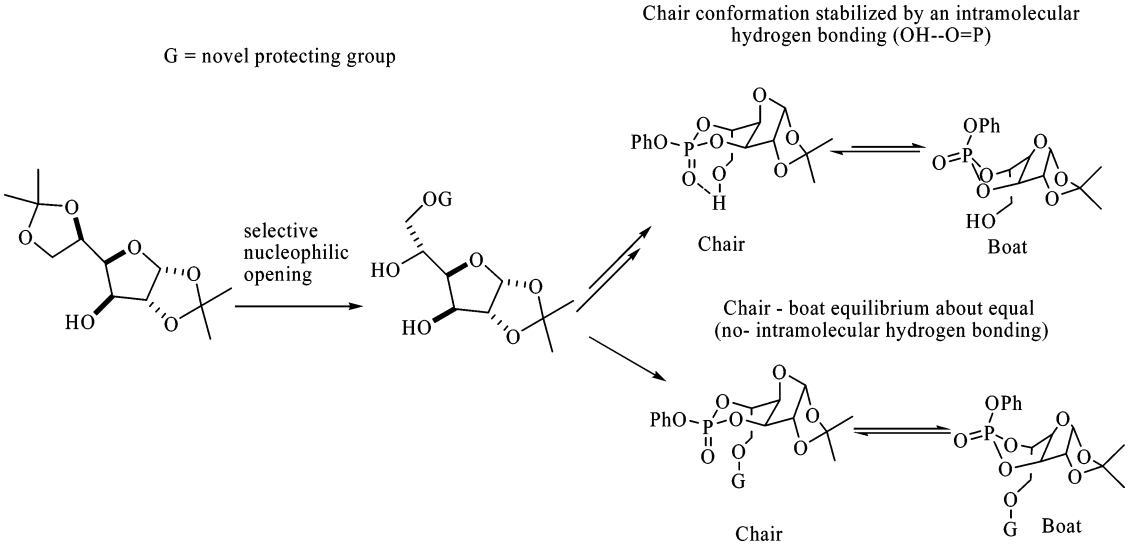

Six-membered cyclic phosphates (2-phenoxy-2-oxo-1,3,2-dioxaphosphorinanes) bearing an internal protected or unprotected hydroxyl group were designed, synthesized, and studied by NMR and computational methods. Selective opening of *O*-isopropylidene-protected 1,2-diols at the primary site was achieved with either triethylsilane or trimethylallylsilane in the presence of $BF_3{\cdot}OEt_2$. Applied to 5,6-*O*-isopropylidenepentofuranosides, this reaction gave rise to the formation of the corresponding 1,3-diol precursors for the six-membered ring phosphates containing an *O*-isopropyl or *O*-1,1-dimethyl-3-butenyl functional group at C-6. The *O*-1,1-dimethyl-3-butenyl protecting group was efficiently removed after the phosphorylation with $BF_3{\cdot}OEt_2$, and the six-membered cyclic phosphates containing free hydroxyl groups were obtained. A cyclic phosphate with a free hydroxyl group oriented *cis* to the phosphoryl group shows a vicinal coupling constant $^3J_{HP}$ that is in accordance with the chair conformation. This is due to the formation of a seven-membered intramolecular hydrogen-bonded ring structure that stabilizes the chair conformation. Thus, the strong tendency of the phenoxy group to be in an axial position is diminished by the internal hydrogen bonding interaction. Computational studies provided strong support for the experimental observation.

Introduction

Conformational and configurational studies of 1,3,2-dioxaphosphorinanes (or neutral six-membered ring phosphates) are of interest principally due to the importance of the cyclic adenosine 3′,5′-monophosphate (cAMP) in enzymatic processes.[1] It has been demonstrated that the biological activity of analogous six-membered cyclic phosphates depends on the configuration at the phosphorus center.[2] Studies in both solution and the solid state have shown that the six-membered cyclic phosphates can exist

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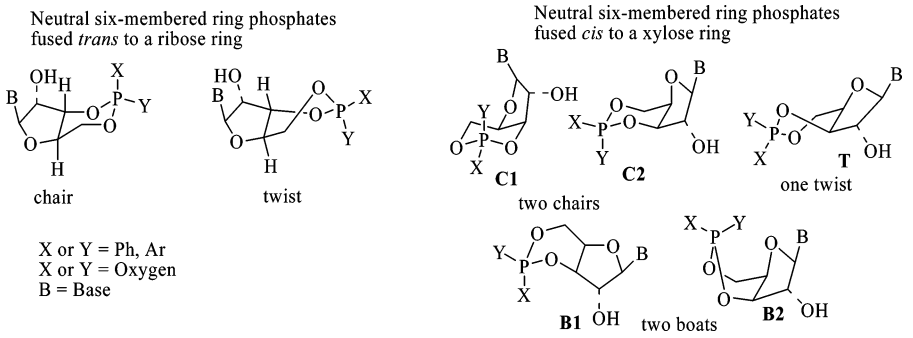

FIGURE 1. Conformational forms for neutral six-membered cyclic phosphates *cis*- and *trans*-fused to ribo- and xylofuranose rings.

in a spontaneous chair/twist equilibrium;[3] however, it has been suggested that there is a preferential population of the twist conformation in cellular media.[4] Apparently, the energy necessary to convert the chair form into the twist form can be gained from the interactions between enzymatic hydroxyl groups and the oxygen atoms of the cyclic phosphate.[4] This suggestion is based on conformational studies of neutral six-membered cyclic phosphates *trans*-fused to a ribose ring. Due to the strain imposed by the *trans*-fusion, only one twist and one chair form have been observed for these bicyclic compounds (Figure 1), although in phosphates *trans*-fused to cyclohexane derivatives,[5] a further boat-twist conformation should be considered.

On the other hand, six-membered cyclic phosphates *cis*-fused to a xylofuranose offer more conformational forms than the corresponding *trans*-fused phosphates.[3b,6] At least two chair forms[6] (**C1** and **C2**), one twist form T,[7] and two boat conformations are possible (**B1**[6] and **B2**[7]) (Figure 1). The two chair forms **C1** and **C2**, the twist form **T**, and the boat form **B1** were proposed on the basis of conformational studies of 3′,5′-*xylo*-cyclic adenosine monophosphates in solution and in the solid state,[6a] of six-membered cyclic phosphates *cis*-fused to cyclopentanes,[6a] and of 1,2-*O*-isopropylidene-*xylo*-furanose derivatives.[6c,7] We recently found for 5-substituted 1,2-*O*-isopropylidene-3,5-*O*-phenoxyphosphoryl-α-D-xylofuranose derivatives[7] that the boat conformation **B2** and the chair conformation **C2** exist in approximately equal amounts in solution and the solid state rather than in the **C1** ↔ **B1** equilibrium previously proposed.[6a] The existence of this conformational equilibrium was unambiguosuly demonstrated by NMR and X-ray crystallography. Notably, in the boat conformation the phenoxy group is placed in close proximity to H-1, causing a shielding effect.[7]

On this basis, a novel method for the determination of the absolute configuration at the phosphorus in this,[7] and other types,[8] of six-membered bicyclic phosphates was proposed. Additionally, VT-NMR studies of a compound, which crystallized in two conformations (chair and boat) within the same asymmetric unit, showed a marked temperature dependence of the chemical shift for H-1. On lowering the temperature, an upfield shift of H-1 was observed. The gradual displacement of H-1 from 5.60 ppm at 303 K to 5.31 ppm at 203 K indicates that the population of the boat conformation is increased because H-1 spends more time in proximity to the phenoxy group. In other words, the mole fraction of the boat conformer is increased at lower temperatures. Hermans and Buck previously arrived at a similar conclusion based on the H−P vicinal coupling constants ($^3J_{HP}$)[6a] for the 3′,5′-xylo-cAMP. This increased population of the boat conformation at lower temperatures is at odds with controversial arguments regarding the well-established $n_O \leftrightarrow \sigma^*_{P-OR}$ interactions, which indicate that in the ground state the phenoxy group should be axial.[5,9]

With the above in mind, we designed and synthesized a series of six-membered cyclic phosphates containing a strategically internal hydroxyl group with the expectation of stabilizing of the chair conformation by a seven-membered intramolecular hydrogen bond (Figure 2).

This study requires the phenoxy group to be located *cis* to H-1 in the boat conformation. Conversely, if the chair conformation is stabilized, then the phenoxy group should spend more time in an equatorial position (equilibrium A) and H-1 should be less affected by the phenoxy group than anticipated at higher populations of the boat conformer (equilibrium B). This can be monitored by the chemical shift of H-1, which should be in accordance with

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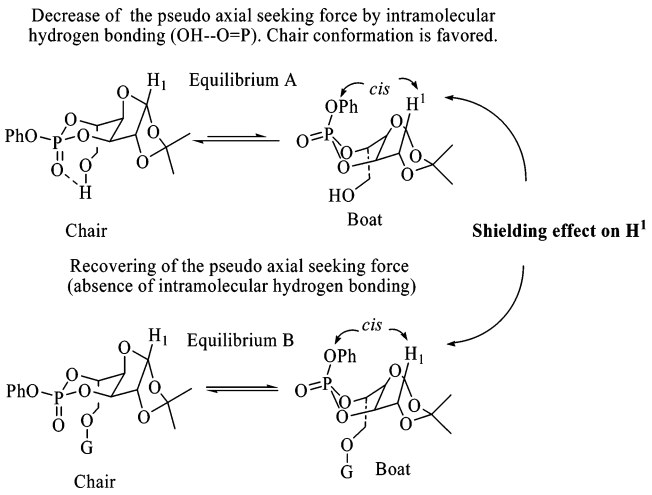


FIGURE 2. Hypothetic chair and boat conformations.

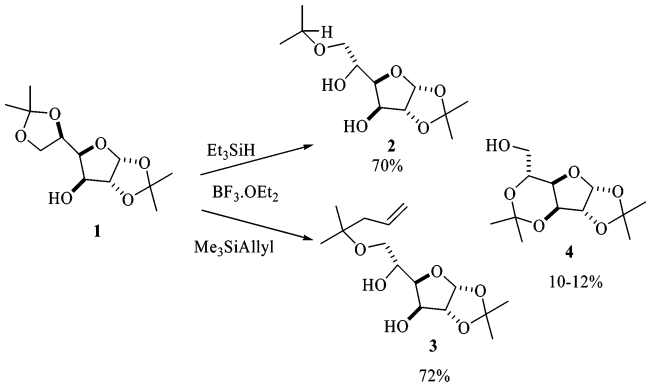
the vicinal H−P coupling constant ($^3J_{HP}$). On the other hand, if stabilization of the chair conformation is achieved by intramolecular hydrogen bonding, the nonchair conformation will be diminished by the same interaction that has been suggested to destabilize the chair and favor the nonchair conformation in cyclic adenosine 3′,5′-monophosphate derivatives.[4]

Results and Discussion

Computational Methods. The geometry of each stationary point was fully optimized with the Gaussian 98 software package[10] implementing the 6-31G(d,p) basis set using density functional theory (the Becke3LYP functional).[11] All points were characterized as minima by calculating the harmonic vibrational frequencies, using analytical second derivatives. The NMR shielding tensors were calculated and visualized with GaussView 3.0 at a higher level of theory (B3LYP/6 31+G(d,p)) using the same stationary points with the GIAO[12] (gauge-independent atomic orbital) method.

Synthesis of 1,3-Diol Precursors and Six-Membered Cyclic Phosphates. Synthesis of sterochemically defined model compounds began with 1,3-diol precursors **2** and **3** from 1:2,5:6-*O*-diisopropylidene-α-D-xylofuranose **1**. Instead of a two-step procedure involving two steps,[13] aqueous hydrolysis of the 5,6-*O*-isopropylidene group

SCHEME 1. Synthesis of 1,3-Diol Precursors 2 and 3 by Selective Opening of the 5,6-*O*-Isopropylidene Group of 1



followed by selective protection of the primary hydroxyl group, we explored a one-step nucleophilic opening of the terminal *O*-isopropylidene group of **1** by silanes and BF_3·OEt_2.[14] Thus, treatment of **1** with trimethylallylsilane or triethylsilane in the presence of BF_3·OEt_2 produced the 1,3-diol precursors **2** and **3** in yields of 70−72%, respectively (Scheme 1).

These reactions were highly regioselective, and the isomeric 1,4-diols (not shown) were not observed. However, a BF_3·OEt_2-catalyzed rearrangement of the isopropylidene group from *O*-5:6 to *O*-3:5 did take place in low yield (**4**, 10−12%).[15] Other Lewis acids were tested in order to increase the yields of **2** and **3**; however, the best results were obtained when 2 equiv of BF_3·OEt_2 and 4 equiv of silane were employed. Mechanistic studies of this selective nucleophilic ring opening are beyond the scope of this work; however, our observations indicate that the selectivity in the ring opening of the *O*-5,6 isopropylidene group depends on the orientation and position of the free hydroxyl group. This was confirmed when 1:2,5:6-*O*-diisopropylidene-α-D-ribofuranose **5** and solketal **6** were treated under the same conditions (BF_3·OEt_2/Et_3SiH). Compound **5**, with a different orientation of the free hydroxyl group, afforded the hydrolysis of both 5,6-*O*- and 1,2-*O*-isopropylidene groups (**7**). On the other hand, opening of solketal **6**, which contains the hydroxyl group at a different position, was not selective (**8** and **9** in a ratio of 1:1, see Scheme 2).

Diols **2** and **3** were converted to the cyclic phosphates **10**−**13** by treatment with phenyldichlorophosphate in the presence of triethylamine. Thee two pairs of diastereoisomeric six-membered cyclic phosphates were separated by chromatography over silica gel in good yields, and in a 1:1 ratio (Scheme 3).

We next proceeded to establish a protocol for the removal of the functional groups at C-6. Interestingly, we found that the 1,1-dimethyl-3-buetenyl group is quantitatively removed without hydrolysis of the 1,2-*O*-isopropylidene group using 5 equiv of BF_3·OEt_2 (Scheme 4). With this efficient cleavage of the 1,1-dimethyl-3-butenyl group, the six-membered cyclic phosphates **14**

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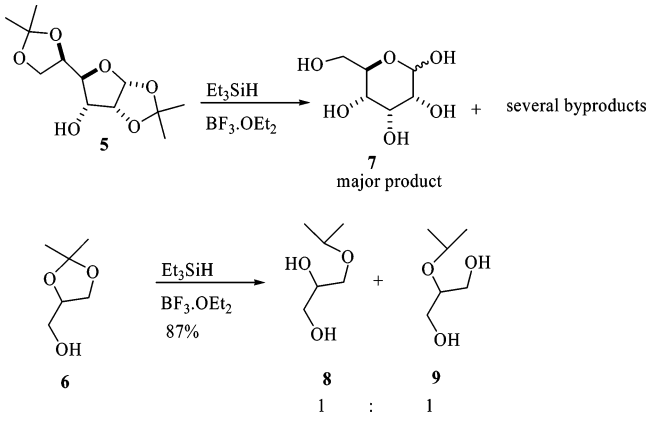
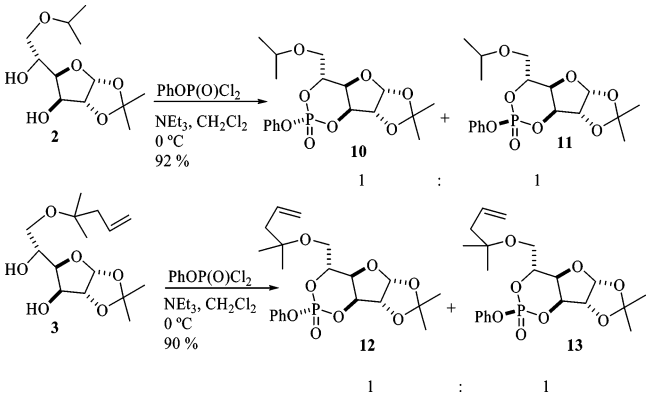
SCHEME 2. Influence of the Orientation and Position of the Hydroxyl Group upon the Ring Opening of the *O*-Isopropylidene Group



SCHEME 3. Synthesis of the Six-Membered Cyclic Phosphates 10−13



and **15** were synthesized in only three steps from the commercially available 1:2,5:6-*O*-diisopropylidene-α-D-xylofuranose **1.** Thus, with this selective nucleophilic opening of the terminal *O*-isopropylidene group followed by phosphorylation of the resulting 1,3-diol, and an efficient deprotecting method, a promising protocol for the selective transformation of acetonides has been introduced, which has efficiency comparable to that of the well-known cleavage of benzylidene acetals.[16]

Conformational and Configurational Analysis of the Six-Membered Ring Phosphates. Since the absolute stereochemistry of the carbohydrate framework present in these phosphates is known, only the conformation and configuration of the 1,3,2-dioxaphosphorinane ring remained to be determined. The relevant NMR data are depicted in Tables 1 and 2. To assign the absolute configuration at the phosphorus atom, we followed our recent criterion,[7,8] which is based on the shielding effect of the diamagnetic current induced by the aromatic ring of the phenoxy group on the chemical shift of H-1 when both are *cis* oriented. Accordingly, the six-membered cyclic phosphates **11**, **13**, and **15** (δ: 5.70, 5.73, and 5.52 ppm, respectively) are assigned the R_P configuration, and phosphates **10**, **12**, and **15** (all appear at δ: 6.05 ppm) have the S_P configuration.

X-ray crystallographic analysis of phosphate **10** confirmed the molecular structure and the absolute configuration at phosphorus.[17] From Figure 3 it can be seen that the 1,3,2-dioxaphosphorinane ring has a flattened chair conformation (to minimize steric repulsions), similar to that found in related structures.[18]

Although phosphate **10** adopted a chair conformation in the solid state, it did not exhibit the same behavior in solution. On the basis of the vicinal coupling constant $^3J_{H5-P}$ of 16.5 Hz, a chair/twist conformation is suggested

SCHEME 4. Protecting Group Cleavage in Phosphates 10−13

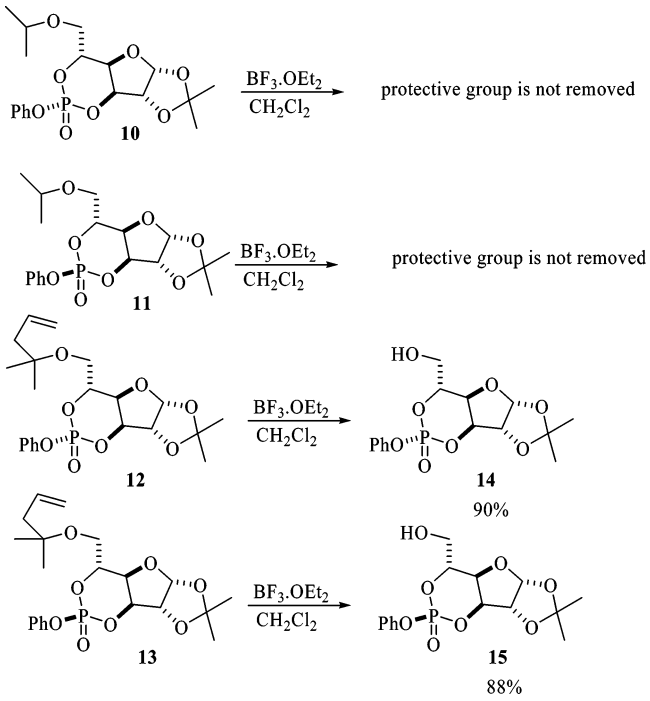
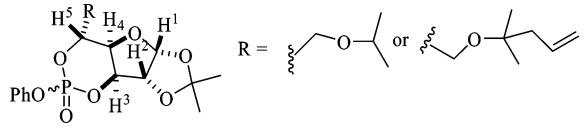


TABLE 1. Relevant ^{1}H and ^{31}P NMR Shifts for Phosphates 10−15[a,b]



phosphate	H^1	H^2	H^3	H^4	H^5	^{31}P
10	6.05	4.73	4.96	4.38	4.87	−16.6
11	5.70	4.64	5.06	4.38	4.73	−15.6
12	6.05	4.72	4.93	4.38	4.86	−16.4
13	5.73	4.65	5.08	4.39	4.75	−15.8
14	6.05	4.75	4.96	4.44	4.82	−15.4
15	5.52	4.57	5.21	4.32	4.75	−12.2

[a] All spectra were recorded at 400 and 161 MHz for ^{1}H and ^{31}P NMR, respectively. [b] Chemical shifts (δ) are given in ppm.

TABLE 2. Relevant Vicinal Coupling Constants (^3J) for 10−15[a,b]

phosphate	H^5-P	H^3-P	H^5-H^4	C^2-P
10	16.5	2.4	2.1	10.6
11	13.2	6.0	2.4	7.9
12	16.4	1.6	1.6	11.1
13	13.2	4.2	2.4	6.8
14	14.8	2.0	2.0	11.3
15	18.1	<1.0	<1.0	10.8

[a] All spectra were recorded at frequencies of 400 and 161 MHz for ^{1}H and ^{31}P NMR, respectively. [b] Coupling constants are given in Hz.

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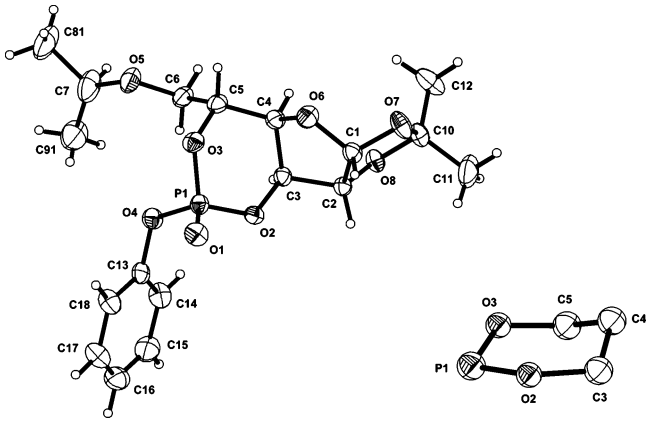


FIGURE 3. X-ray structure of phosphate **10** showing the flattened chair conformation of the 1,3,2-dioxaphosphorinane.

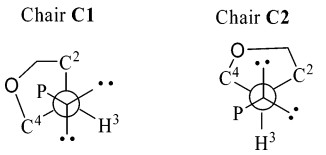


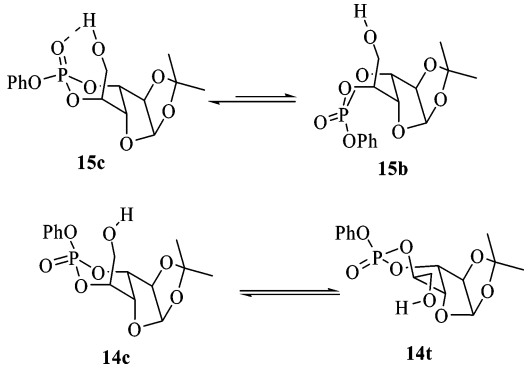
FIGURE 4. Newman projections showing the orientation between the phosphorus atom and carbon C-2 for each of the chair conformations.

instead of the chair/chair equilibrium (**C1** ↔ **C2** equilibrium depicted in Figure 1). The value of the vicinal coupling constant between carbon C-2 and the phosphorus atom ($^3J_{C2-P}$) is 10.6 Hz, suggesting an *anti* orientation. For the **C1** conformation, the gauche orientation between carbon C-2 and the phosphorus atom should lead to a smaller value of $^3J_{C2-P}$ (<5.0 Hz). Additionally, H-3 should be oriented equatorially and the value of $^3J_{H3-P}$ should be larger than 14 Hz (Figure 4).[19]

In the case of phosphate **11**, values of 13.2 and 7.9 Hz were found for $^3J_{H5-P}$ and $^3J_{C2-P}$, respectively, and an increment in the $^3J_{H3-P}$ (6.0 Hz) coupling constant occurred. This is in accordance with a chair/boat equilibrium (**C2/B2**, Figure 1), caused by the tendency of the phenoxy group to adopt the axial position, which is a consequence of the anomeric effect.

For the remaining pairs of diastereomeric phosphates (**12** and **13**; **14** and **15**), the conformational behavior was quite similar. However, the large value of the $^3J_{H5-P}$ (18.1 Hz) coupling constant for phosphate **15** is noteworthy.

SCHEME 5. Hydrogen Bonding Interaction Favoring the Chair Conformation



This is due to a high population of the chair conformation in solution, which obviously is caused by the presence of the free hydroxyl group. Comparing phosphate **15** to its analogues **11** and **13**, with the phenoxy group in equatorial or pseudoequatorial positions, a considerably higher population of the boat conformation for **11** and **13** is evident ($^3J_{H5-P}$ = 13.2 Hz for both phosphates **11** and **13**). Furthermore, if the $^3J_{H5-P}$ coupling constant of phosphate **15** is compared to the $^3J_{H5-P}$ coupling constant of its diastereoisomeric congener **14**, which also contains a free hydroxyl group in the same position, the small value of $^3J_{H5-P}$ (14.8 Hz) suggests a chair/nonchair equilibrium. It was recently demonstrated that in this case the nonchair conformation corresponds to a twist conformation.[7] So, according to the $^3J_{H5-P}$ coupling constant for phosphates **10** and **12**, a marked chair ↔ twist equilibrium is proposed (Scheme 5).

A reasonable explanation for the increase of the chair conformation in phosphate **15** postulates stabilization of the chair **15c** by internal hydrogen bonding (P═O--H−O) at the expense of the boat conformation **15b**. Absent the hydroxyl group, a high population of the boat conformation for phosphate **15** should be expected as this allows the phenoxy group to be axially located and take advantage of stabilizing hyperconjugation ($n_O \leftrightarrow \sigma^*_{P-OP}$) with the ring oxygens (Scheme 5).[5,7,8,9] In the hydrogen bond accepting solvent DMSO-d_6, the $^3J_{H5-P}$ had a smaller value (from 18.1 Hz in $CDCl_3$ to 13.6 Hz in DMSO-d_6), and the chemical shift for H-1 was downfield shifted (5.52 ppm in $CDCl_3$ to 5.80 ppm in DMSO-d_6), indicating restoration of the chair conformation with the $n_O \leftrightarrow \sigma^*_{P-OP}$ hyperconjugation, thereby providing further support for the hydrogen-bonding hypothesis.

To further demonstrate the existence of this unusual conformational behavior for **15**, in which the anomeric effect is opposed by an internal hydrogen bonding interaction (seven-membered intramolecular hydrogen bond structure), we performed DFT calculations (B3LYP/6-31G(d,p))[11] and found an intramolecular hydrogen bond (P═O- -HO) with a distance of 2.17 Å (Figure 5).

Having well established the geometry of the preferential conformer for phosphate **15**, we were surprised to find that the chemical shift of H-1 appears at higher field than in any of the analogous phosphates **13** and **11**, even though they possess the same configuration at the phosphorus atom (H-1 and PhO are oriented *cis*). This result is in apparent contradiction with the previous assumption that the benzene ring current should shield

(17) The X-ray crystallographic studies were done by using a Bruker P4 diffractometer ($\lambda_{MoK\alpha}$ = 0.71073 Å, monochromator: graphite, T = 296 K, ω-2θ scan). Direct methods (SHELXS-97) were used for structure solution, and a riding model software package (SHELXL-97) was used for refinement and data output. Hydrogen atoms were refined with isotropic U tied to their respective heavy atom. Crystallographic data for the structure reported in this paper has been deposited with the Cambridge Crystallographic Data Centre as supplementary. CCDC No. 266689. Copies of the material can be obtained, free of charge, on application to the Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, U.K. (fax: (+44)1223-336-033, e-mail: deposit@ccdc.cam.ac.uk, www: http://www.ccdc.cam.ac.uk).

(18) (a) Day, R. O.; Gorenstein, D. G.; Holmes, R. R. *Inorg. Chem.* **1983**, *22*, 2192−2195. (b) Magomedova, N. S.; Sobolev, A. N.; Koroteev, M. P.; Pugashova, N. M.; Bel'skii, V. K.; Nifant'ev, E. E. *Zh. Strukt. Khim.* **1991**, *32*, 67−73.

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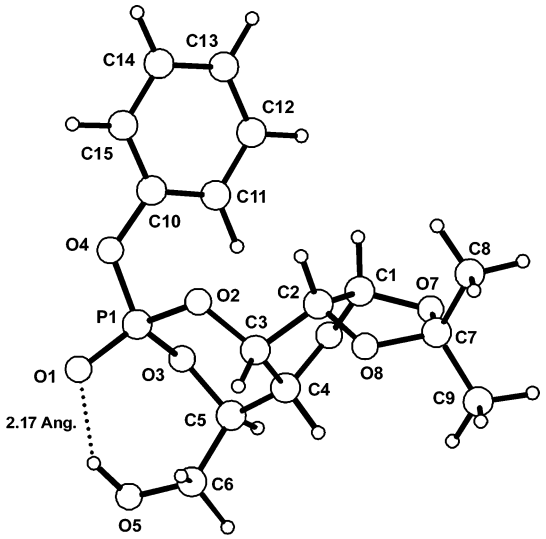

FIGURE 5. Optimized structure for **15** calculated at the B3LYP/6-31G(d,p) level.

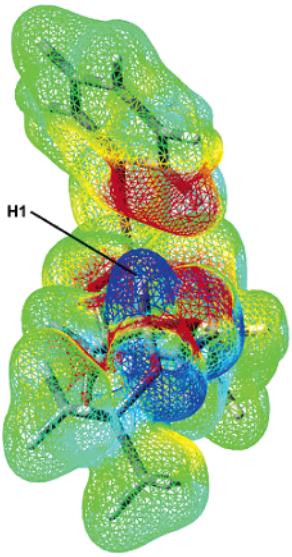

FIGURE 6. Shielding density for **15** in a chair conformation as seen by H-1 in the *ZZ* direction mapped between the values of −0.02 and 0.02 on the current density = *Z* (isosurface at a value of 0.00008).

the hydrogen atom H-1 more in the boat conformation than in the chair conformation. However, although the phenoxy group may be closer to H-1 in a boat than in a chair conformation, it is not necessary for H-1 to reside within the shielding region of the diamagnetic current induced by the aromatic ring. Two different orientations of the benzene ring with respect to H-1 are possible: one perpendicular (H-1 resides in the shielding region) and another one parallel (with H-1 away from the shielding region). NMR shielding tensors for phosphate **15** were calculated at the B3LYP/6-31+G(d,p) level using the same stationary point. The shielding density was mapped and is shown in Figure 6.

As seen from Figure 6, H-1 (blue color) is placed perpendicular to the shielding density (red color) when phosphate **15** is in the chair conformation. In support of this argument, we analyzed the chair and boat conformers of phosphate **16** that crystallized independently within the same asymmetric unit of the crystal lattice.[20] When the same computational treatment was applied to phosphate **16**, we found that both optimized structures, **16c** and **16b**, match in geometry to the molecules present in the solid state (Figure 7). It can be also seen that H-1 resides within the shielding region when the phosphate exists in the chair conformation (perpendicular) and out of it (parallel), in the boat conformation (Figure 7), enabling the previous discussion to be continued.[21] On the basis of the chemical shift of H-1[7] or the vicinal H−P coupling constants,[6a] it was assumed that the molar fraction of the boat conformer (or nonchair conformation) is increased upon lowering the temperature because H-1 was shifted upfield at lower temperatures (and the value of $^3J_{H-P}$ is increased). Now, it is clear that H-1 is more shielded by the diamagnetic current induced by the aromatic ring, when the phosphate ring has a chair conformation, not when it is in a boat conformation (Figure 7).

Empirical approximations to estimate the population and the $\Delta G°$ for the chair/nonchair equilibria in solution are known, but most are method dependent.[4,6a,22] Based on the very good matching between the X-ray structures and the calculated structures of phosphate **16**, we can establish the relative energies and free energies for conformer pairs **16c/16b** and **15c/15b** ($G = H - TS$, as the "sums of the electronic and thermal free energies", obtained at $T = 298.15$ K).[23] For the equilibrium **16c/16b**, $\Delta E°_{rel} = +0.78$ kcal/mol and the $G = +1.27$ kcal/mol, leading to an approximate population of 56% and 44% for the chair and boat conformations, respectively, and for the equilibrium **15c/15b**, $\Delta E°_{rel} = +1.21$ kcal/mol, $G = +0.69$ kcal/mol, 79% and 21% of **15c** and **15b**, respectively. Thus, it can be established that intramolecular hydrogen bonding stabilizes the chair conformation of cyclic phosphate **15** in the chair conformation with respect to those cyclic phosphates lacking the intramolecular hydrogen bond. To the best of our knowledge, this is the first example in which a chair conformation of a neutral six-membered cyclic phosphate is stabilized by an intramolecular hydrogen bonding interaction (P═O- - HO). For charged six-membered cyclic phosphates (analogous to cAMP), it has been suggested that in cellular media intermolecular interactions with the hydroxyl groups provide the driving force to change a chair conformation into a twist conformation. It is now apparent that such interactions can equally favor any conformation (chair, twist, or boat) and that the driving force that converts one form to another one comes from the natural $n_O \leftrightarrow \sigma^*_{P-OP}$ hyperconjugations, which are favored in highly polar environments (water). A previous theoretical work invoked intramolecular hydrogen bonding in cAMP and cGMP but suggested that these occurred

(20) Although,both molecules were reported in ref 7, no theoretic study was carried out, nor was there detailed observation on the orientation of the benzene ring over the *xylo*-furanose ring.

(21) Discussion regarding on the VT-NMR experiment.

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(23) The energies (electronic + thermal energies) and the free energies were corrected. All of these energies were extracted from the frequency calculations. We thank a reviewer for raising this point.

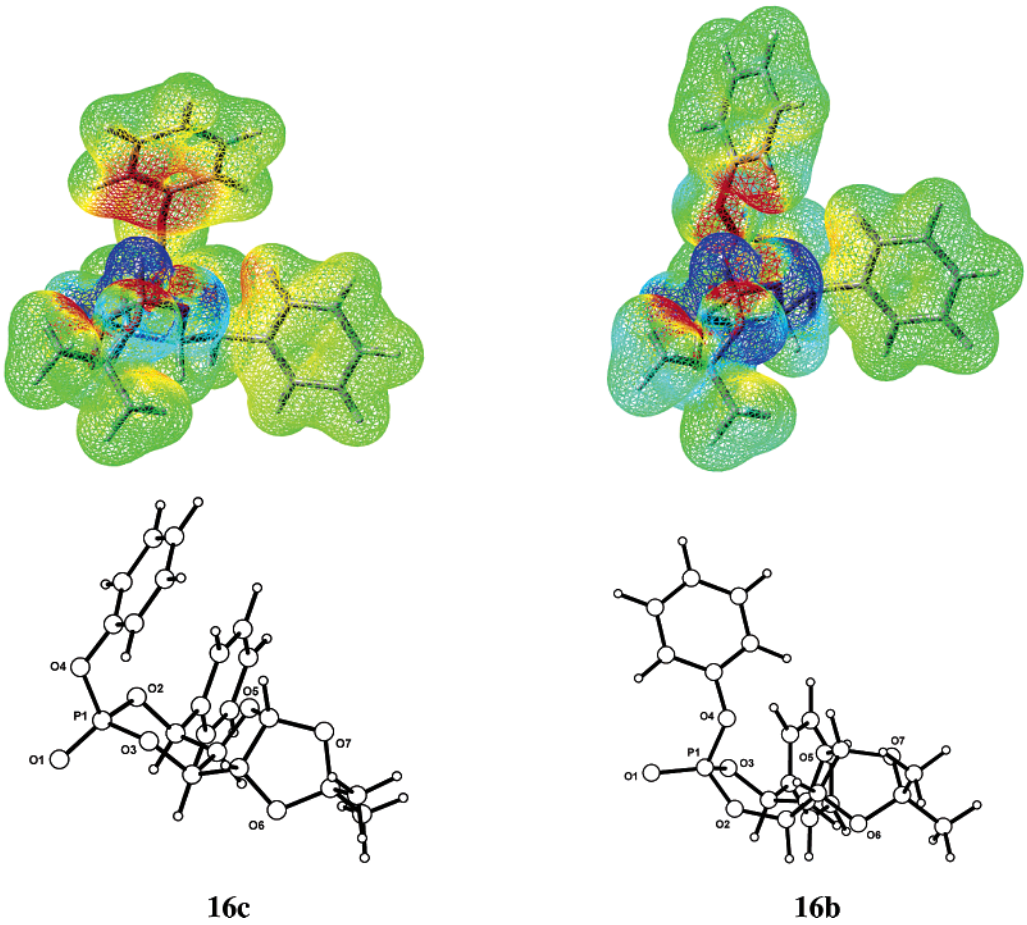

FIGURE 7. Shielding density (red color) for the chair and boat conformations of phosphate **16**.

between C2−OH and H4.[24] We note that the conformational study presented here has similar conclusions to one reported by Rebek,[25] although with different intramolecular interactions (C=O- -H−N), in which the conformational equilibria of cavitands that flutter between $C_{4v} \leftrightarrow C_{2v}$ symmetries, is determined by seven-membered intraannular hydrogen-bonded ring structures.

Conclusions

By NMR and computational methods, it has been demonstrated that intramolecular hydrogen bonds between the phosphoryl oxygen and a hydroxyl group stabilize the chair conformation of a neutral six-membered cyclic phosphate. Although intramolecular and intermolecular hydrogen-bonding interactions have different energies, our results demonstrate that intramolecular hydrogen-bonding interactions stabilize a conformation that is otherwise considered to be disfavored by stereoelectronic factors (mainly the anomeric effect). To synthesize the 1,3-diol precursors for the six-membered cyclic phosphates *cis*-fused to a glucofuranose derivative, a selective nucleophilic ring opening of 1,2-*O*-isopropylidene group by a silane was introduced. A method for the selective removal of a novel protecting hydroxyl group was also reported. This method is the subject of ongoing investigations and applications other synthetic procedures, to be reported in due course.

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Supporting Information Available: Experimental procedures and characterization data for all obtained compounds, copies of ^{1}H and ^{13}C NMR spectra for all new compounds, and Cartesian coordinates for conformers **15c**, **15b**, **16c**, and **16b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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