JOC Article

Six-Membered Ring Phosphates and Phosphonates As Model Compounds for Cyclic Phosphate Prodrugs: Is the Anomeric Effect Involved in the Selective and Spontaneous Cleavage of Cyclic Phosphate Prodrugs?

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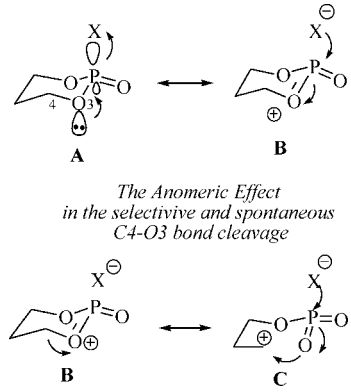

In recent years, several six-membered ring phosph(on)ates and phosphonamides have been reported as potent prodrugs against liver diseases such as hepatitis B and C and also as antitumor agents. Apparently, the success for their biological activity depends on the selective cleavage of the C4−O3 bond within the respective P-heterocyclic ring. Empirical observations have suggested that the group attached to the C4 position (aryl or pyridyl group) is responsible for the selective cleavage. In this regard, we show in the present work that the configuration at the P-atom, the conformation of the P-heterocyclic ring, and particularly, the anomeric effect are involved in the spontaneous and selective cleavage of the C4−O3 bond in cyclic phosph(on)ates. We arrived at this assumption based on the conformational and configurational study of simple model phosphates and phosphonates, where it was observed that the spontaneous conversion of unstable six-membered ring phosphates to their most stable six-membered ring phosphate (**4d**, **6d** and **7d** to **5d**), by a selective C4−O3 bond cleavage, depends on both: the stereochemistry of the aryl group at C4 and the electronic nature of the substituent attached to the P-atom. Thus, we postulated that the anomeric effect weakens the C4−O3 bond within the 1,3,2-dioxaphosphorinane ring, favoring thus their selective cleavage and spontaneous conversion, similarly to the proposed mechanistic mode of action of six-membered ring P-heterocyclic prodrugs.

Introduction

One of the topics in physical−organic chemistry is the conformational and configurational analysis of six-membered ring phosphates (2-oxo-1,3,2-dioxaphosphorinanes) and derivatives.[1−9] The information extracted from such studies stimulated the Bentrude group[10] to postulate an ingenious model of interaction between the active site of the enzyme and the dioxaphosphorinane ring of cyclic adenosine monophosphate (cAMP), also known as the second messenger for the cellular processes. On the basis of the empirical estimation of the $\Delta G°$ for the chair ⇌ twist equilibrium of neutral model

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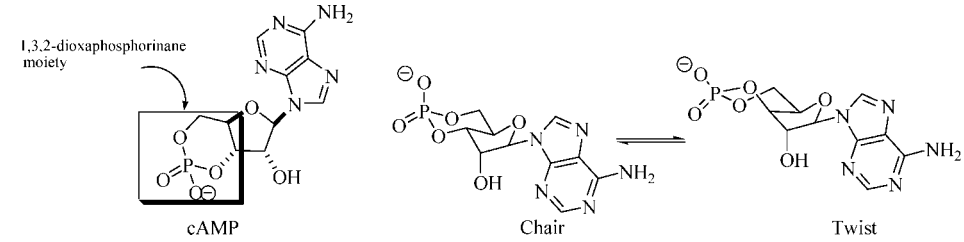


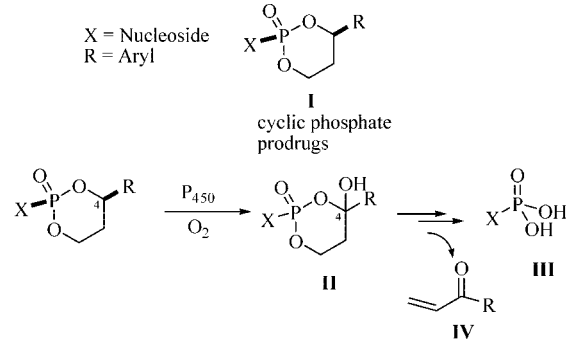
FIGURE 1. Chair−twist equilibrium of cyclic adenosine monophosphate (cAMP).

phosphates, they proposed that cAMP in a twisted conformation could be appropriate for such enzyme−cAMP interactions (Figure 1).[10]

On the other hand, more recently, Erion introduced a new class of six-membered ring phosphates and phosphonates for targeting phosph(on)ate-based drugs to the liver (HepDirect prodrugs).[12−15] Apparently, this new class of prodrugs combines properties of rapid liver cleavage with high plasma and tissue stability to achieve increased drug levels in the liver.[12] An additional feature of these new prodrugs is that the aryl group attached to the C4 position in a *cis* orientation, seems to be a crucial element for the biological activity.[12] Mechanistic studies suggested that prodrug **I** undergoes oxidation to the hydroxylated intermediate **II**, which subsequently eliminates unsaturated ketone **IV** and releases the biologically active nucleoside monophosphate **III** (Scheme 1).[12−15]

Similarly, cyclic aryl phosphoramides **V** represent another important class of prodrugs that have been used for drug delivery in tumor treatments.[16−18] Similar to Erion's prodrugs, this cyclic aryl-phosphoramides incorporate a *p*-nitrophenyl group at the C4 position that after bioreduction by nitroreductasa (NTR) affords hydroxylamine **VI** that facilitates the C4−O3 bond cleavage producing the anionic cytotoxic species **VII** (Scheme 2).[17,18]

SCHEME 1. Proposed Prodrug Cleavage Mechanism for Cyclic 4-Aryl-phosphorinanes



On this basis, it seems evident that the aryl group attached to the C4 position of the heterocyclic ring provides the driving force for the prodrug mechanism action; however, this is only a simple observation.[19] Therefore, we suppose that, as for cAMP, where the conformation of the 1,3,2-dioxaphosphorinane ring seems to be determinant for the mechanistic action in the cellular media,[10,11] the biological activity of these new cyclic prodrugs should depend on the conformation of the heterocyclic ring. In this sense, this article reports our results on the conformational and configurational study of conformationally restricted six-membered ring phosph(on)ates having an aryl group with different electronic demand at the C4 position and P-atom, which may provide mechanistic information on cyclic prodrug cleavage.

We have recently carried out the conformational and configurational study of a series of conformationally restricted 4-sustituted-1,3,2-dioxaphosphorinanes.[20−22] In this study we have found a new way for monitoring with high precision the conformational equilibria between two conformers. For those cyclic phosphates with R_P configuration that have a phenyl group equatorially oriented at C4 position, a chair−boat equilibrium (**C1⇌B1**) was proposed,[20−22] whereas a chair⇌twist equilibrium (**C1⇌T**) was suggested for their S_P-epimers (Scheme 3).

Conformers **C2** and **B2** (of which **B2** has been proposed in related cyclic phosphates[23−25]), were not considered in study, first because the equilibrium **C1⇌B1** was supported by trapping both conformers in the solid state within the same crystal

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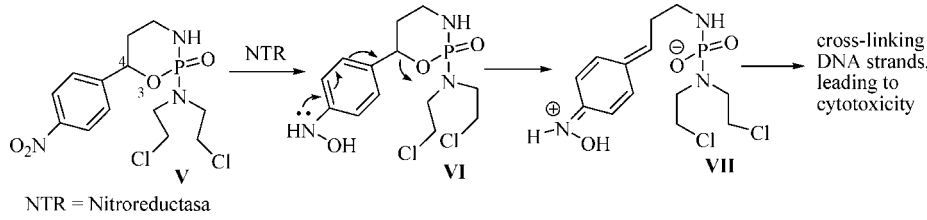
SCHEME 2. Proposed Prodrug Cleavage Mechanism for Cyclic 4-Nitro-aryl-phosphoramides



SCHEME 3. Conformations for Conformationally Restricted 4-Substituted-1,3,2-dioxaphosphorinanes

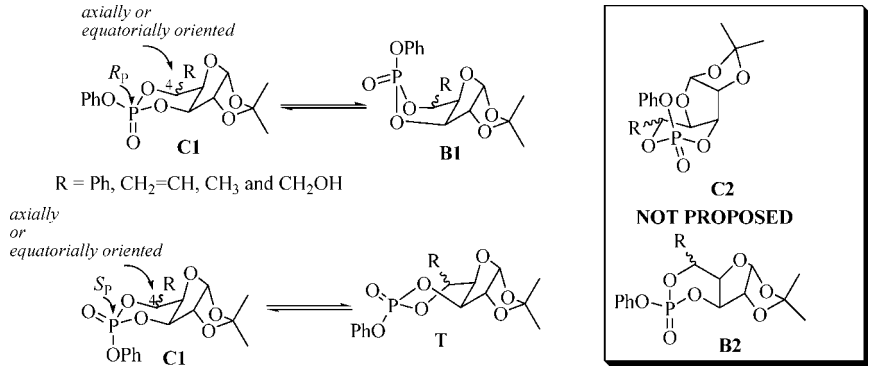
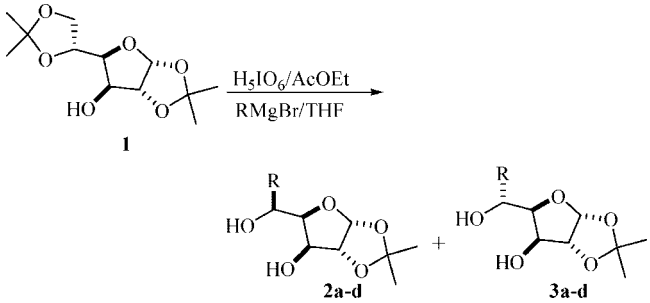


TABLE 1. Synthesis of the Diastereoisomeric 1,3-Diol Precursors 2 and 3



Entry	R	Yield (%)[a]	Products (Ratio)
1	H–	75	**2a** and **3a** (4/1)[b]
2	F–	86	**2b** and **3b** (2/1)
3	Cl–	82	**2c** and **3c** (4/1)
4	MeO–	85	**2d** and **3d** (1/2)

[a] Yields are for the mixture of diastereoisomers. [b] Information extracted from ref 22.

lattice[22] (for R = Ph equatorially oriented), and second, because the **C1⇌T** equilibrium could be established based on NMR data.

Interestingly, a reverse situation was observed for cyclic phosphate having R_P configuration and when R = Ph is axially oriented. In this case, the equilibrium observed was **C1⇌T** instead the expected **C1⇌B1** equilibrium. Apparently, the pseudoaxial force of the OPh group, which should induce that the heterocyclic ring acquires the **B1** conformation, was inhibited by steric interactions when the phenyl group is axially oriented.[26−31] It is important to note that the relative orientation between the phenoxy and the phenyl group was *cis*, and coincidently, Erion had found that better prodrugs were those with *cis* relative orientation.[12] Thus, the following questions are arising: (i) what is the role of the configuration and conformation of the 1,3,2-dioxaphosphorinane ring in the prodrug cleavage mechanism? (ii) Is the prodrug cleavage initiated by delocalization of the oxygen lone pair into the aromatic ring facilitating the C4−O3 bond cleavage? As previously proposed for cyclic phosphoramide prodrugs, or (iii) is the cleavage a combination of both contributions? To answer the above questions, we synthesized a series of conformationally restricted 4-aryl-1,3,2-dioxaphosphorinanes to analyze the effect that the aryl group placed at C4 position exerts on the conformation and configuration of the 1,3,2-dioxaphosphorinane ring.

Results and Discussions

The syntheses of the 4-aryl-1,3,2-dioxaphosphorinanes **4**−**7** were achieved in two steps starting from diacetone-D-glucose **1**. First, the diastereomeric 1,3-diol precursors **2** and **3** were prepared applying our one-pot procedure of sequential hydrolysis-oxidation-Grignard reagent addition to the commercially available diacetone-D-glucose (Table 1).[22] Phosphorylation of 1,3-diols with phenyldichlorophosphate and triethylamine in CH_2Cl_2 gave the corresponding diastereomeric 1,3,2-dioxaphosphorinane pairs in good yields (Scheme 4).

The diastereoisomeric mixtures were separated by column chromatography (except for **4d**, **6d**, and **7d**) allowing to record and assign completely the ^1H, ^{13}C and ^{31}P NMR data for each

(26) The phenyl group placed at the C4 position has been used to lock the spontaneous chair-chair equilibrium of 1,3,2-dioxaphosphorinane rings into a chair conformation that orients the phenyl group equatorially. See refs 27−31.

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(32) It is important to mention that in this work, the C4 position of the 1,3,2-dioxaphosphorinane nomenclature corresponds to the C5′ position of xylofuranose nomenclature.

SCHEME 4. Synthesis of the 4-Aryl-1,3,2-dioxaphosphorinanes 4−7

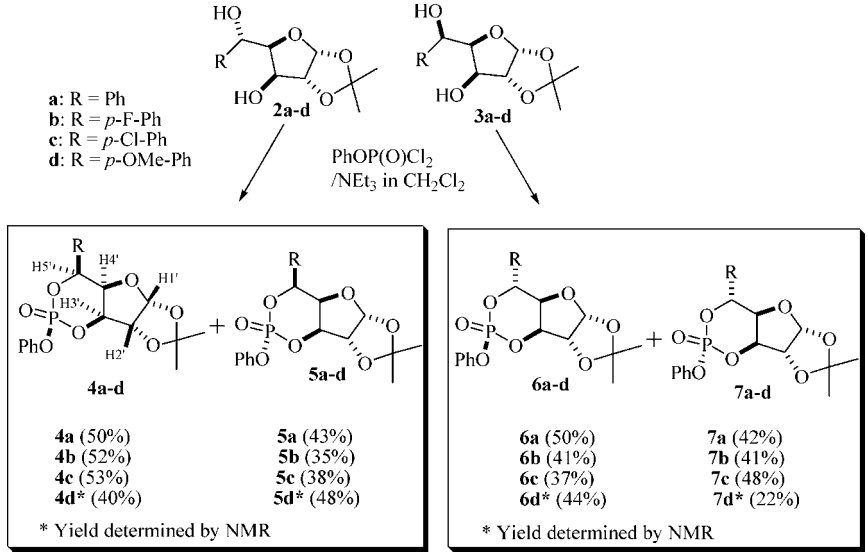

TABLE 2. Representative ^{1}H and ^{31}P NMR Chemical Shifts for Cyclic Phosphates[a,b]

phosphate	H1′	H2′	H3′	H4′	H5′	^{31}P
4a	5.60	4.61	5.12	4.42	5.84	−12.9
5a	6.02	4.73	5.01	4.40	5.75	−15.2
6a	6.01	4.78	4.95	4.53	5.63	−13.8
7a	6.15	4.83	4.92	4.63	5.68	−13.0
4b	5.63	4.62	5.12	4.38	5.83	−12.6
5b	6.03	4.73	5.00	4.37	5.73	−14.9
6b	6.02	4.79	4.96	4.51	5.57	−12.9
7b	6.15	4.84	4.93	4.61	5.64	−12.1
4c	5.63	4.62	5.12	4.38	5.82	−12.6
5c	6.02	4.73	5.00	4.37	5.73	−15.0
6c	6.02	4.79	4.94	4.49	5.55	−12.9
7c	6.16	4.84	4.91	4.59	5.63	−12.0
4d[c]	5.63	4.61	5.09	4.39	5.78	−12.4
5d	6.06	4.73	4.98	4.36	5.69	−14.8
6d[c]	5.99	4.77	4.96	4.52	5.57	−13.4
7d[c]	6.14	4.83	4.98	4.63	5.66	−12.9

[a] Spectra recorded at 400 and 161.8 MHz in $CDCl_3$ for ^{1}H and ^{31}P, respectively. [b] Chemical shifts (δ) given in ppm. [c] NMR data measured from the crude reaction mixture.

TABLE 3. Representative Coupling Constants for Cyclic Phosphates[a,b]

phosphate	H5′−P	H3′−P	H5′−H4′	H4′−H3′
4a	<1	4.8	2.3	3.0
5a	<1	<1	1.6	2.0
6a	10.2	7.2	3.6	3.2
7a	11.4	3.6	4.0	3.2
4b	<1	4.8	1.6a	2.8
5b	<1	<1	<1	2.0
6b	9.6	7.2	4.0	3.6
7b	10.8	3.2	4.4	3.2
4c	<1	4.8	<1	2.4
5c	<1	<1	<1	2
6c	9.9	6.8	4.4	3.6
7c	10	3.6	4.4	3.6
4d[c]	<1	4.5	<1	2.1
5d	<1	<1	<1	2.1
6d[c]	10.0	−	3.6	3.6
7d[c]	9.3	−	3.6	3.2

[a] Spectra recorded at 400 and 161.8 MHz in $CDCl_3$ for ^{1}H and ^{31}P, respectively. [b] Coupling constants (J) given in Hz. [c] NMR data measured from the crude reaction mixture.

cyclic phosphate, in order to establish the absolute configuration at the phosphorus atom, and the C4 carbon (or C5′),[32] as well as to determine the conformational equilibrium for the 1,3,2-dioxaphosphorinane rings (see Tables 2 and 3).

For phosphates **4a** and **5a**, the absolute configuration at the phosphorus atom has been determined previously, taking into account an analysis of the chemical shifts of the anomeric hydrogen atoms (H1′).[22] The remaining phosphates **4b**−**d** and **5b**−**d** were assigned by analogy. Thus, when the OPh group is oriented *cis* to H1′, the signal of this anomeric hydrogen atom is shifted to upper field (compared with its P-epimer) and the absolute configuration at the phosphorus atom is R_P. For this reason, phosphates **4a**, **4b**, **4c**, and **4d** possess R_P configuration, and phosphates **5a**, **5b**, **5c**, and **5d** S_P configuration (see Figure 2).

The value of the vicinal H−P coupling constants for **4a**−**d** and **5a**−**d** ($^3J_{H5'\text{-}P} < 1$ Hz) suggests that the aryl group is located in equatorial or pseudoequatorial position. Therefore, the absolute configuration at C4 (or C5′) have to be *R*. As mentioned above, for phosphate **4a**, a **C1⇌B1** equilibrium was proposed previously,[21,22] based on NMR, X-ray diffraction[22] and theoretical calculations.[20] Due to the structural relationship and similar NMR data for **4b**, **4c**, and **4d**, the same **C1⇌B1** can be proposed. For their P-epimers **5a**−**d**, in which the phenoxy groups are axially and the aryl groups are equatorially oriented, it can be proposed that the **C1** conformer is highly populated. The X-ray crystallographic study for phosphate **5d** confirmed that the assignments of their conformation and configuration are correct (Figure 3).[33]

On the other hand, the determination of the configuration at the phosphorus atoms for the cyclic phosphates **6** and **7** turned out to be more complicated. It is important to mention that based on Gorenstein's criteria (which establish that upfield shifted ^{31}P NMR signals can be attributed to phosphorinanes having their phenoxy group axially oriented[34−36]), the absolute configuration at the P-atom for **6a** and **7a** has been previously assigned.[22]

(33) Crystallographic data were deposited in Cambridge Crystallographic Data Base (CCDC-660542).

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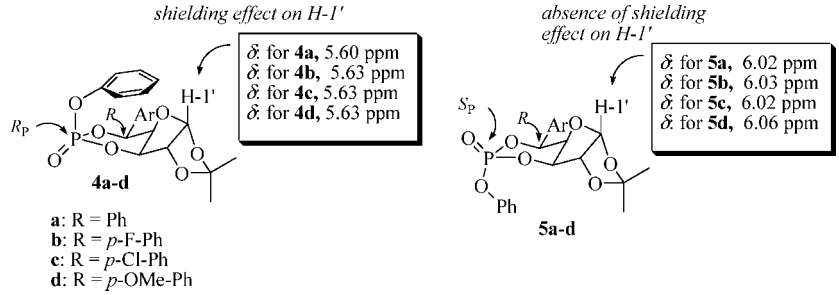


FIGURE 2. Assignment of the absolute configuration at the phosphorus atom in phosphates **4** and **5**.

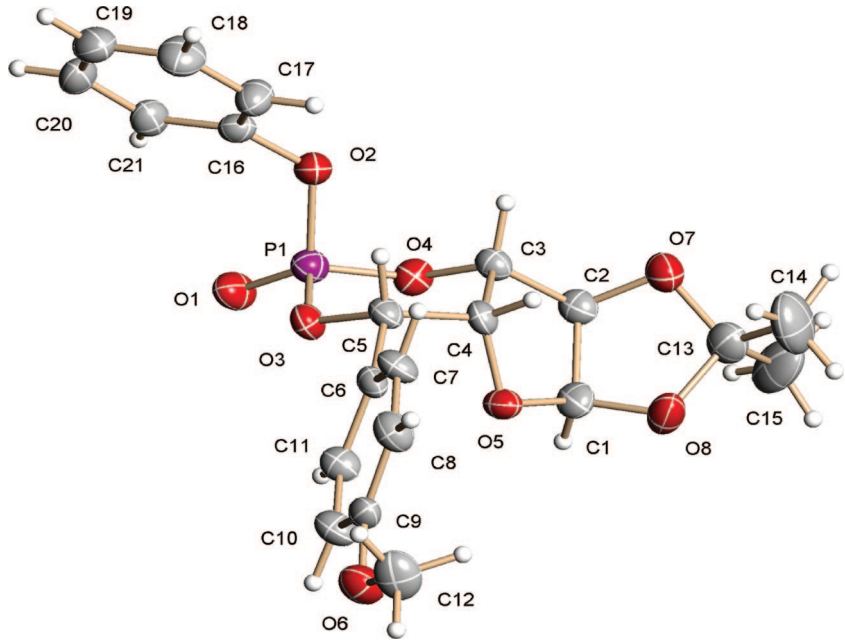


FIGURE 3. Perspective view of the molecular structure of **5d** showing that it possesses **C1** conformation.

However, we now believe that this criteria could give misleading assignments of the P-atom configuration for phosphorinanes that are unable to permanently orient the phenoxy group in an axial position. Unfortunately, our own criteria for the assignment of the configuration at P-atom can not be applied because both: the proposed chair **C1** (with the phenoxy group axially oriented) and the twist conformation **T** orient the phenoxy groups away from H1′. However, according to the $^3J_{H5'\text{-}P}$ coupling constants for phosphates **6** and **7** ($^3J_{H5'\text{-}P}$ = 9.0−11.5 Hz, see Table 3) a **C1**⇌**T** equilibrium that is strongly directed to **T** could be suggested. This was corroborated by X-ray crystallographic study of phosphate **6c**,[37] showing an almost perfect **T** conformation (Figure 4).

In the perspective view given in Figure 4, we can see that the aryl group at C4 is located in an apparent pseudoequatorial position, so that the phosphorinane ring acquires the **T** conformation. We can also observe that the phenoxy group is directed away from H1′, and the presence of any shielding effect on H1′ becomes evident. The X-ray crystallographic study of phosphate **6c** allowed determining the absolute configuration at the P-atom for the diastereomeric phosphate mixture (**6c**/**7c**). Therefore, with the aid of their ^{31}P NMR chemical shifts we could assign the absolute configuration at the P-atom for the rest of the cyclic phosphates. Thus, cyclic phosphates shifted to higher field like **6a**, **6b**, and **6d** (−13.8, −12.9 and −13.4 ppm, respectively) were assigned as R_P, and their respective diastereoisomeric cyclic phosphates **7a**, **7b**, and **7d** (−13.0, −12.1 and −12.9 ppm, respectively) were assigned as S_P (Table 2). Thus, with the aid of the crystallographic study for **6c**, we realized that the absolute configurations at the P-atom for cyclic phosphates **6a** and **7a** were previously misassigned (cyclic phosphates **4b** and **4b′** in reference [22]).

Apparently, the conformational and configurational behavior of all new 4-aryl-1,3,2-dioxaphosphorinanes resulted as expected, according to the conformational equilibria proposed in Scheme 3. Furthermore, a very interesting result was observed when we tried to phosphorylate the 1,3-diol **2d** under standard conditions (see Scheme 4). Analyzing the crude mixture reaction, an equimolar amount of cyclic phosphates **4d** and **5d** was observed; however, when we tried to separate them by column chromatography, we obtained a fraction that contained only **5d** in high yield (65%) plus a fraction which was a mixture of **4d** and **5d** in a ratio of 2:1 (15%). An even more interesting observation was made for 1,3-diol **3d**. Under the same reaction conditions for the phosphorylation, diol **3d** was not converted to the expected cyclic phosphates **6d** and **7d**, instead **5d** was obtained exclusively[38] (Scheme 5). This suggests that under this reaction conditions, the cyclic phosphates **6d** and **7d** are rapidly and spontaneously converted to the apparently more stable cyclic

(37) Crystallographic data were deposited in Cambridge Crystallographic Data Base (CCDC-660543).

(38) Observed by ^{1}H and ^{31}P-NMR after purification by column chromatography.

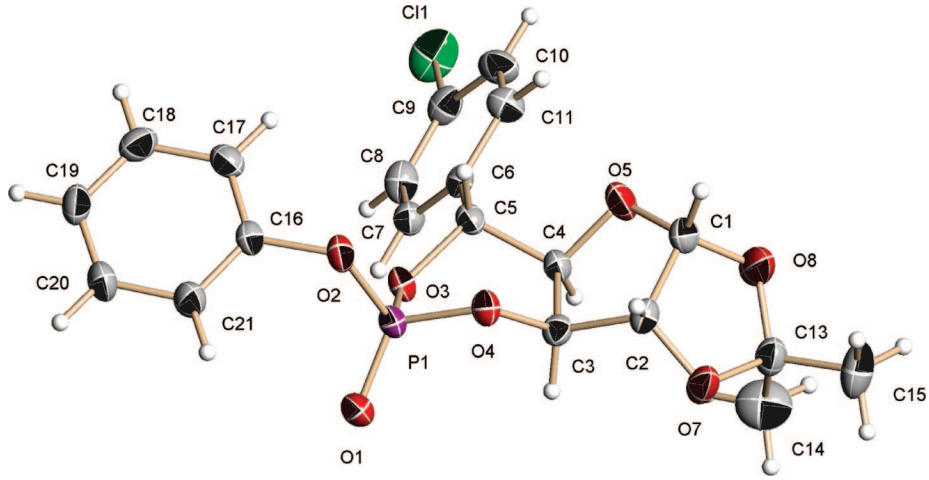
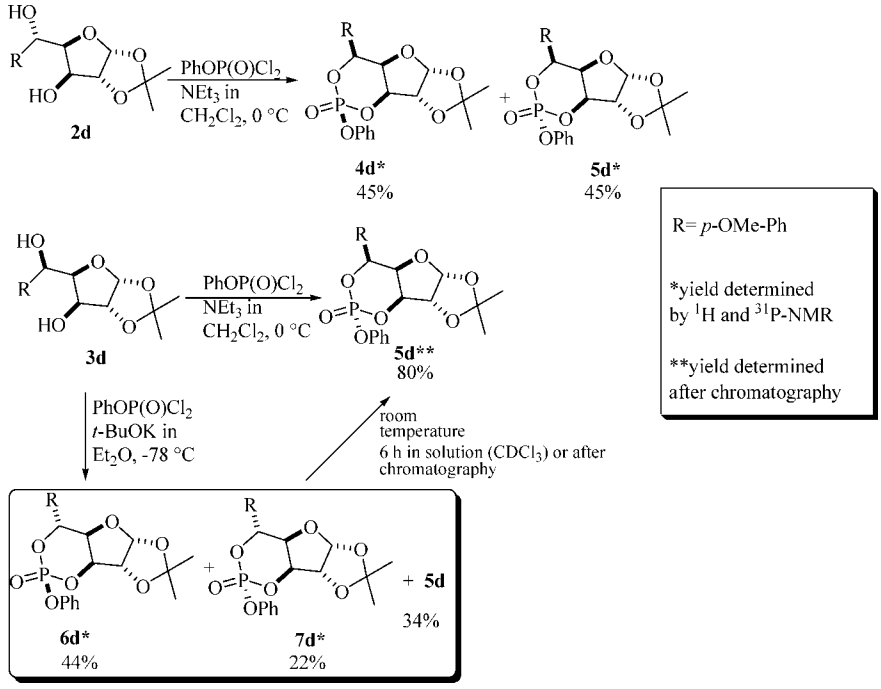


FIGURE 4. Perspective view of the molecular structure of **6c** showing that it possesses **T** conformation.

SCHEME 5. Unexpected Phosphorylation of 1,3-Diols, 2d and 3d



phosphate **5d**. To prove this, diol **3d** was treated with a stronger base (*t*-BuOK) at −78 °C and indeed, initially an almost equimolar amount of **6d** and **7d** was observed by ^{1}H and ^{31}P NMR, which within a period of 8 h at room temperature in $CDCl_3$, were spontaneously converted to **5d** (Scheme 5).

Apparently, the cyclic phosphates **4d**, **6d**, and **7d** prefer to spontaneously convert to **5d** rather than hydrolyze the 1,3,2-dioxaphosphorinane ring.[39] By monitoring the phosphorylation reactions of diols **2d** and **3d**, we could determine the time required for the spontaneous conversions of **4d**, **6d**, and **7d** to **5d**. The cyclic phosphates **6d** and **7d** are converted to **5d** in approximately 10 h in $CDCl_3$, meanwhile phosphate **4d** required more than 50 h in $CDCl_3$ to convert into **5d** (Scheme 6).

It is important to mention that the conversions of **4d**, **6d**, and **7d** into **5d** follow a linear behavior until 85% of conversion, therefore we found that t_{85} (time to convert 85% of **6d** and **7d** to **5d**) was >45 h for **4d**, 7.5 h for **7d** and 6.5 h for **6d** (Figure 6 and Table 4). The observation of a linear behavior in the spontaneous conversion suggests nonequilibration processes of **4d**, **6d**, and **7d** during the conversion to **5d**, so that a common intermediary **F** it might be proposed, which is followed by a very fast recombination. This mechanism would be similar to the prodrug cleavage mechanism proposed for cyclic aryl-phosphoramides.[17]

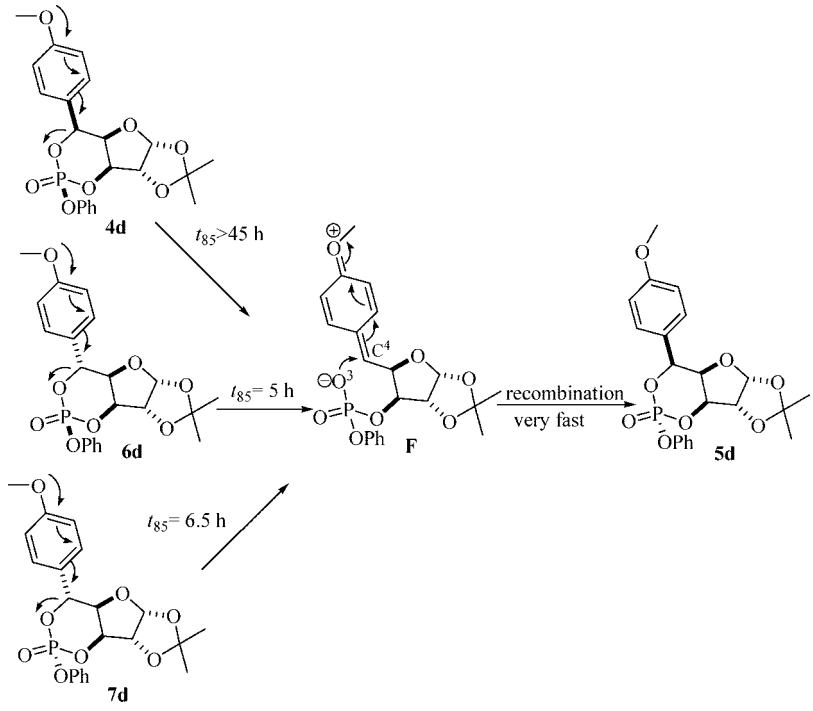
These results indicate that phosphate **5d** is the most stable cyclic phosphate among the four possible diastereoisomers (**4d**, **5d**, **6d**, and **7d,** see Scheme 7). This is because, first of all, the axial orientation of the phenoxy group at the phosphorus atom provides stability to **5d** by the anomeric effect,[40,41] and additionally, the equatorial orientation of the aryl group at the

(39) It is well documented that cyclic phosphates undergo hydrolysis in protic media or basic conditions (see refs 7 and 34), however, the cyclic phosphates **4d**, **6d**, and **7d** showed to be resistant to hydrolysis in methanol.

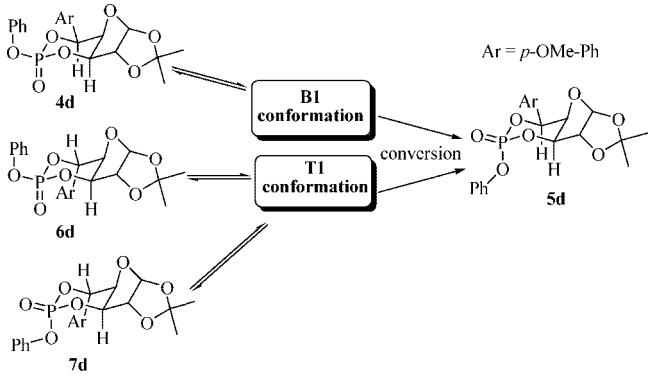
(40) Juaristi, E.; Cuevas, G. *The Anomeric Effect*; CRC Press, Inc.: Boca Raton, FL, 1995.

(41) Juaristi, E.; Cuevas, G. *Tetrahedron* **1992**, *48*, 5019.

SCHEME 6. Proposed Mechanism for the C4−O3 Bond Cleavage of Phosphates 4d, 6d, and 7d and Proposed Putative Intermediate F



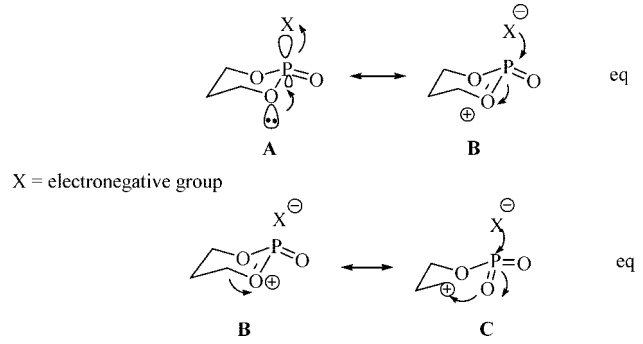
SCHEME 7. Proposed Route for the Conversion of 4d, 6d, and 7d to 5d



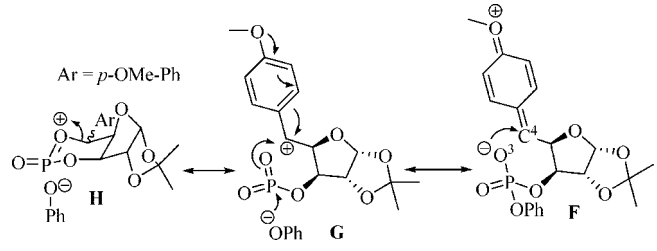
C4 position reduces steric interactions considerably (see X-ray structure **5d** in Figure 3). In the case of **4d**, the nonaxial orientation of the phenoxy group does not provide stabilization by the anomeric effect; meanwhile strong steric repulsions are present in **7d** due to the axial orientation of the aryl group at C4. The absence of an anomeric effect (nonaxially orientation of phenoxy group), and strong steric repulsions (axial orientation of the aryl group at C4), make phosphate **6d** the most unstable cyclic phosphate and, therefore, it converts more rapidly into the most stable phosphate **5d** (see Scheme 7).

Now, it is evident that the spontaneous conversion of **4d**, **6d** and **7d** to **5d** is not exclusively caused by the delocalization of the oxygen lone pair through the aromatic ring, as previously considered[17,18] (based on the analogy with phosphoramides prodrugs, see Schemes 2 and 6), but that the configuration and the conformation of the 1,3,2-dioxaphosphorinane rings are also determinant, and therefore, we postulate that: in the spontaneous conversion of **4d**, **6d** and **7d** to **5d**, the anomeric effect plays a major role in the above-mentioned, prodrug cleavage mechanism.

SCHEME 8. Anomeric Effect in 1,3,2-Dioxaphosphorinanes (eq 1) That Might Weaken the C4−O3 Bonds (eq 2)

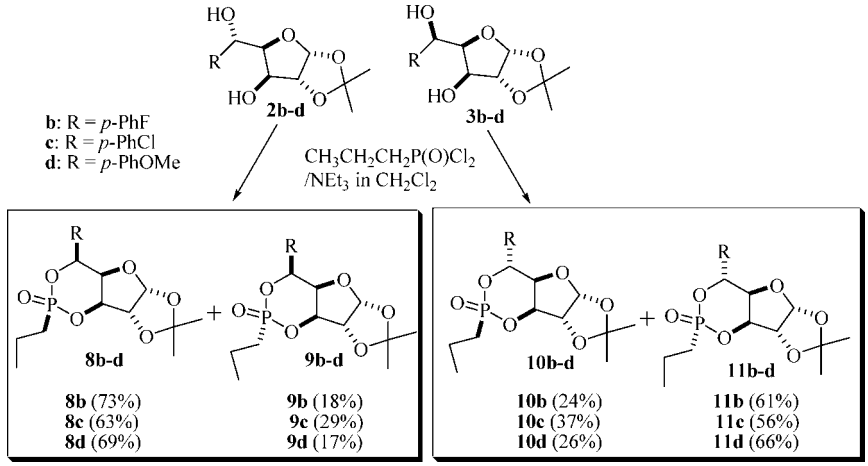


SCHEME 9. Postulated Mesomers H, G, and F Involved in the Conversion of 4d, 6d, and 7d to 5d

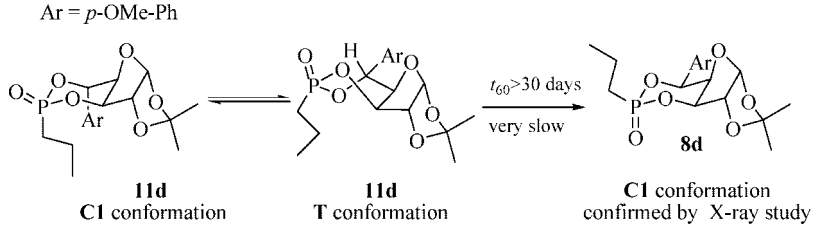


A question that still has to be addressed is: how does the anomeric effect affect the spontaneous cleavage of the C4−O3 bond? Thus, if it is assumed that the anomeric effect consists in the interaction of two orbitals in the ground state ($n_O \leftrightarrow \sigma^*_{P\text{-}OR}$),[7,40,41] giving thus a double-bond-no-bond resonance structure **B** (Scheme 8, eq 1), then a congruent explanation for the C4−O3 bond cleavage is that the contribution of mesomer **B** weaken the C4−O3 bond strength, thus favoring the formation of mesomer **C** (Scheme 8, eq 2).

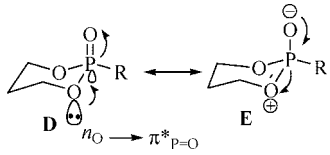
SCHEME 10. Synthesis of 4-Alkyl-1,3,2-dioxaphosphonates 8−11



SCHEME 11. Route Proposed for the Conversion of 11d to the More Stable Cyclic Phosphonate 8d



SCHEME 12. Orbital Interactions ($n_O \leftrightarrow \pi^*_{P=O}$) in 1,3,2-Dioxaphosphonates (Anomeric Effect)



Therefore, the previous assumption that: "the cleavage of the C4−O3 bond is caused by a simple delocalization of the oxygen lone pair through the aromatic ring affording intermediate **F**" (see Scheme 6) seems to be insufficient to explain our results. Therefore, mesomers **G** and **H** should be proposed as additional electronic structures involved in the spontaneous cleavage of the C4−O3 bond in 1,3,2-dioxaphosphorinanes (Scheme 9).

With this new assumption related to the intervention of the anomeric effect in the spontaneous cleavage of the C4−O3 bond, we should expect a strong manifestation of above mesomers when an efficient electron-donating group is attached to C4 and when the antibonding $\sigma^*_{P\text{-}X}$ orbital is a good electron acceptor (e. g., P−OPh).[42,43] In this context, it is reasonable to expect a lower spontaneous conversion of cyclic phosphates, if the phenoxy group is replaced by a less electronegative group, such as an alkyl group. In order to prove this statement, we proceeded to synthesize and examine a series of 4-alkyl-1,3,2-dioxaphosphonates, which have been prepared from 1,3-diols (**2b−d** and **3b−d**) through phosphorylation reactions using propyl dichlorophosphonate (Scheme 10).

As we anticipated, the cyclic 4-aryl-phosphonates **8d**, **9d**, **10d**, and **11d** have been shown to be very stable in solution and are stable to chromatography.[44] However, it is important to mention

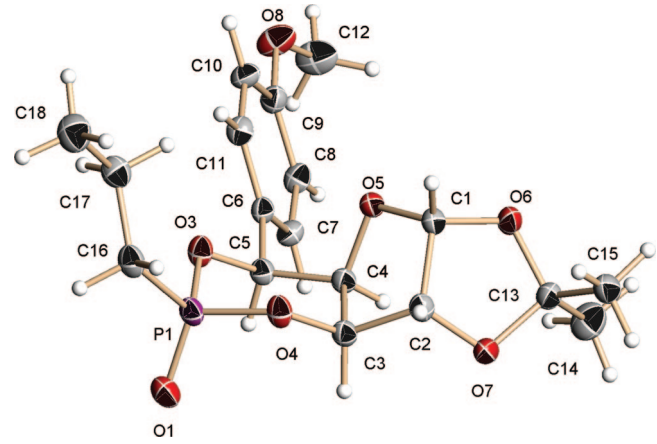


FIGURE 5. Perspective view of the molecular structure of **8d** showing that it possesses **C1** conformation.

that phosphonate **11d** was the only phosphonate that converted to the more stable cyclic phosphonate **8d** in 60% yield by NMR over 30 days (Scheme 11).

Now, phosphonate **8d** is the most stable cyclic phosphonate, because the aryl group is oriented equatorially and the phosphoryl group is oriented axially. The latter provides stabilization by the anomeric effect, although in this case through different orbital interactions ($n_O \leftrightarrow \pi^*_{P=O}$) (Scheme 12).[45,46]

The molecular structure and conformation (in solid state) of phosphonate **8d** has been confirmed by X-ray diffraction (Figure 5).[47]

(42) Deslongchamps, P. Kinetic Anomeric Effect. In *Stereoelectronic effects in Organic Chemistry*; Pergamon: Oxford, 1983.
(43) Kirby, A. J. *The Anomeric and Related Stereoelectronic Effects at Oxygen*; Springer: Berlin, 1983.
(44) Fully spectroscopic characterization is provided in the Supporting Information.
(45) Hernández, J.; Ramos, R.; Sastre, N.; Meza, R.; Hommer, H.; Salas, M.; Gordillo, B. *Tetrahedron* **2004**, *60*, 10927.
(46) Verkade, J. G. *Phosphorus Sulfur* **1976**, *2*, 251.
(47) Crystallographic data were deposited in Cambridge Crystallographic Data Base (CCDC-687297).

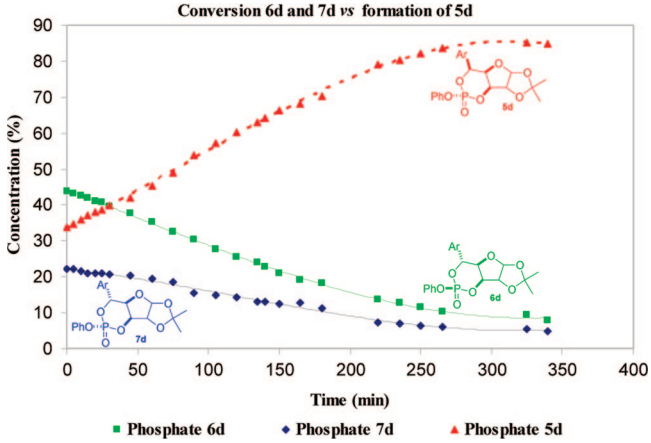


FIGURE 6. Conversion of **6b** and **7b** versus formation of **5d**.

TABLE 4. Conversion of 6d and 7d versus Formation of 5d Monitored by ^{31}P NMR

time (min)	phoshate **7d** (%)	phosphate **6d** (%)	phosphate **5d** (%)
0	22.3	43.8	33.9
5	22.2	43.3	34.5
10	21.7	42.5	35.8
15	21.0	42.0	37.0
20	21.0	41.1	37.9
25	20.9	40.6	38.5
30	20.8	39.4	39.8
45	20.3	37.7	42.0
60	19.5	35.3	45.2
75	18.4	32.7	48.9
90	15.6	30.5	53.9
105	15.0	27.8	57.3
120	14.4	25.6	60.1
135	13.2	24.0	62.8
140	13.1	22.7	64.2
150	12.5	21.1	66.4
165	12.6	19.2	68.1
180	11.4	18.3	70.3
220	7.3	13.7	79.0
235	6.9	12.7	80.4
250	6.3	11.6	82.0
265	6.0	10.4	83.6
325	5.6	9.3	85.1
340	5.0	8.0	85.0

These results demonstrate that aryls group having an electron-donating group placed at C4 position are not sufficient to promote the C4−O3 bond cleavage in 1,3,2-dioxaphosphorinane compounds, but that stereoelectronic interactions are even more important and determinant factors.

It is noteworthy to mention that, in this work have been presented experimental evidence that suggest that both cyclic prodrug cleavage mechanism (for the cyclic phosph(on)ate and phosphoramide prodrugs) might function similarly. However, it is also important to understand that the results presented here do not attempt to show a close relationship between instability and biologically activity of the cyclic prodrugs, however, we do try to expose, by affecting the reactivity or stability of the cyclic phosphates, that stereoelectronic interactions like the anomeric effect are involved in the cyclic prodrugs cleavage. Additionally, although the presented study was carried out with cyclic phosph(on)ates, we anticipated similar behavior with other heterocyclic systems and will function analogously albeit on different time scales. In this regard, related experimental efforts and theoretical calculations are in progress and will be published in due course.

Conclusions

We can summarize the following findings: the 1,2-*O*-isopropylidene-xylofuranose moiety functions efficiently as conformationally restricted template for the conformational and configurational study of cyclic phosph(on)ates, providing thus a convenient way for monitoring conformational equilibria and assigning the relative configuration at the P-atom. Experimental evidence that support that the anomeric effect can weaken the C4−O3 bond in six-membered ring phosph(on)ates, causing a spontaneous conversion of conformationally unstable cyclic phosph(on)ates to their corresponding cyclic more stable phosph(on)ates has been presented. Finally, this spontaneous conversion of phosphates **6d** and **7d** to **5d** represents a novel two step way for the inversion of the configuration at the C5-atom in some 5-aryl-*xylo*furanose derivatives (e.g., **3d** → **2d**).[48]

Experimental Section

General. The reagents were obtained from commercial sources and used without purification. The solvents were used as technical grade, and freshly distilled prior use. NMR studies were carried out with 400 and 300 MHz spectrometers. Internal reference (TMS) for ^{1}H and ^{13}C. Chemical shifts are stated in parts per million. COSY, HSQC, and NOESY experiments have been carried out in order to assign the ^{1}H and ^{13}C spectra completely. High resolution Mass spectra (FAB^{+} ion mode).

Protocol for the Synthesis of Unstable Cyclic Phosphates 6d and 7d and Determination of t_{85}. To a solution of diol **3d** (0.2 g, 0.67 mmol) and potassium *t*-butoxide (1.69 mL, 1.7 mmol) in dry Et_2O (30 mL) at −78 °C, was added dropwise phenyl dichlorophosphate dissolved in 2 mL of dry Et_2O (0.12 mL, 0.8 mmol). The reaction mixture was allowed to stir for 10 min before to add 1 mL of H_2O at −30 °C. The organic phase was separated from the aqueous phase and dried with Na_2SO_4. The organic phase was evaporated under reduced pressure at −20 °C. NMR data for unstable phosphates **6d** and **7d** were obtained from the crude reaction mixture (Table 4).

Acknowledgment. We gratefully acknowledge the financial support from CONACyT (grant number: 62203). We dedicate this work to Professor Dr. Hermann Roth for the unconditional support to this research group.

Supporting Information Available: Experimental section including spectroscopic, crystallographic data, and Cif files for compounds **5d**, **6c**, and **8d**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO8017473

(48) First, phosphorylation, then spontaneous conversion (*in situ*), and finally removal of the phosphate group with lithium aluminium hydride (LAH):