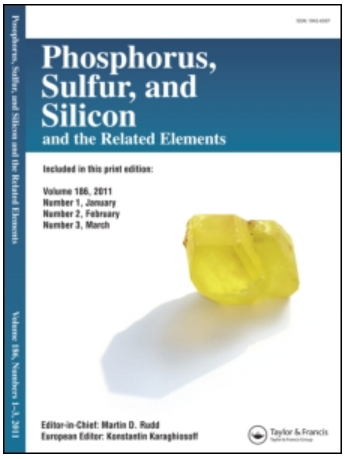

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STEREOCHEMISTRY OF 1,2-OXAPHOSPHOLANES. IX. CONFORMATIONAL BEHAVIOR OF SUBSTITUTED 2-METHOXY-2-OXO-1,2-OXAPHOSPHOLAN-3-OLS AND RELATED COMPOUNDS

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STEREOCHEMISTRY OF 1,2-OXAPHOSPHOLANES. IX. CONFORMATIONAL BEHAVIOR OF SUBSTITUTED 2-METHOXY-2-OXO-1,2-OXAPHOSPHOLAN-3-OLS AND RELATED COMPOUNDS

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Conformational behavior of the 1,2-oxaphospholane ring is discussed in terms of pseudorotation using the Altona-Sundaralingam approach. From the known angular dependences of vicinal H—C—C—H, H—C—C—P, H—C—O—P, C—C—C—P and C—C—O—P coupling constants, "the best" Karplus-like relationships are selected and they are employed in establishing vicinal coupling constant *vs.* angle of pseudorotation relationships for use in the conformational analysis of the 1,2-oxaphospholane ring. Based on the available vicinal coupling constants, conformational preferences for 33 compounds are discussed. Some of them exist in well-defined single conformations, others as equilibrating mixtures of different forms. In a few instances, however, the spectroscopic data could not be interpreted unequivocally. Pseudoequatorial orientation of C-substituents (alkyl, aryl) attached to carbon atoms is a primary factor governing conformations of the 1,2-oxaphospholanes studied. It is not clear whether the orientation of substituents at phosphorus (anomeric effect) has a significant influence on the conformation of the ring in diastereoisomeric pairs. Gauche effects are found to operate in some cases.

Key words: 1,2-Oxaphospholanes: conformational analysis; pseudorotation; ^{1}H NMR; ^{13}C NMR; vicinal coupling constants.

INTRODUCTION

Conformational analysis of the 1,2-oxaphospholane ring has focused on 3-and 4-hydroxy derivatives.[1-9] In these studies, initial ^{1}H and later ^{13}C NMR spectroscopy was employed to obtain values of various vicinal H—P and C—P coupling constants which were interpreted in terms of corresponding dihedral angles allowing conclusions to be drawn about the conformation of particular compounds. The general strategy was to establish the preferred conformation in solution, i.e. to gather spectroscopic evidence that *only one* of 20 conformations from the pseudorotational cycle of the five-membered ring dominates over the others.

A meaningful step in our understanding of conformational preferences of 1,2-oxaphospholane derivatives was made by Russian workers[2] who suggested that particular compounds can exist either as single conformers or in equilibria between several conformations within a fairly well-defined range of conformations.

In recent years we have investigated the synthesis and stereochemistry of 2-methoxy-2-oxo-1,2-oxaphospholan-3-ols[10] and related compounds.[11] During these studies, a significant number of derivatives has been prepared and for most of them first-order ^{1}H NMR spectra have been obtained. This unique set of C—substituted P—epimeric 1,2-oxaphospholan-3-ols has been selected to study the influence of

substituents on C atoms on conformational behavior of the 1,2-oxaphospholane ring and this is the major objective of this report.

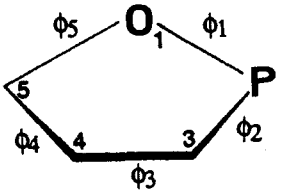
PSEUDOROTATION ANALYSIS OF THE 1,2-OXAPHOSPHOLANE RING

It has been firmly established that conformation of five-membered rings can be unequivocally analyzed using the concept of pseudorotation,[12,13] and many examples of the application of this approach to conformational analysis especially of natural products can be found in the literature.[14,15] Thus far, no one has applied the concept of pseudorotation to the conformational analysis of the 1,2-oxaphospholane ring.

By analogy to related systems, pseudorotation of the 1,2-oxaphospholane ring is best described by a set of pseudorotation equations of general formula:

$$\phi_j = a_j \cdot \phi_m \cdot \cos(\mathrm{P} + \varepsilon_j + \delta \cdot j) \tag{1}$$

where ϕ_j denotes endocyclic torsion angles, ϕ_m is the puckering amplitude, P is the phase angle of pseudorotation, while a_j and ε_j are refinement parameters.[16] Throughout this paper we define the five torsion angles in the following way: ϕ_1-about the O1—P2 bond, ϕ_2-about P2—C3 bond, ϕ_3-about C3—C4 and so on in a clockwise manner.



The puckering amplitude ϕ_m and parameters a_j and ε_j are best derived from X-ray structural data for the particular class of compounds,[16] as was done earlier for the furanose ring of ribonucleosides.[14] Unfortunately, X-ray analyses of compounds containing the 1,2-oxaphospholane ring were performed for only a few examples[3,6,9] and the data available are not sufficient to derive pseudorotation parameters a_j and ε_j for this ring precisely. For this reason we focused our attention on a closely related 1,2-oxathiolane (sultine) system (Table I), because pseudorotation of this ring has been described in detail.[16] After comparison of bond distances of the 1,2-oxathiolane and 1,2-oxaphospholane rings, we decided to employ values of the a_j and ε_j parameters obtained for the 1,2-oxathiolane ring in our *approximation* of pseudorotation of 1,2-oxaphospholanes (Table II).

When the ${}^{1}_{2}T$ conformation was arbitrarily chosen as a "standard" one for P = O, pseudorotation equation 2 is obtained for the 1,2-oxaphospholane ring. Although the pseudorotational description of the 1,2-oxaphospholane system

$$\phi_j = a_j \cdot \phi_m \cdot \cos\left(\mathrm{P} + \varepsilon_j - \frac{4}{5}\pi j\right) \tag{2}$$

by equation 2 is only an approximation, we believe that values of the torsion angles ϕ_j obtained by this method are more accurate than those calculated for the original equation.[14]

TABLE I

Selected bond distances (in Å) of the 1,2-oxathiolane and 1,2-oxaphospholane rings

Bond	O1-X2	X2-C3	C3-C4	C4-C5	C5-O1
1,2-oxathiolane[16]	1.61	1.80	1.53	1.53	1.45
1,2-oxaphospholane[3,6,9]	1.57-1.61	1.79-1.82	1.52-1.53	1.49-1.54	1.48-1.49

TABLE II

Empirical a_j and ε_j parameters for the 1,2-oxathiolane ring for use with Equation 2 (taken from Reference 16)

j	1	2	3	4	5
a_j	0.974	0.934	1.021	1.004	1.072
ε_j	0.53	1.76	-3.28	-2.47	+3.43

The major problem which arises is the range of puckering amplitudes ϕ_m accessible to substituted 2-methoxy-2-oxo-1,2-oxaphospholan-3-ols. The puckering amplitude for the 1,2-oxathiolane ring[16] was found to reach 42.9°, for a representative series of ribonucleosides ϕ_m of the furanose ring[14] ranges from 31° to 45°, while for the γ-butyrolacetone ring, ϕ_m of 30.7° was calculated theoretically.[17] Using equation 2, available X-ray structural data for 1,2-oxaphospholanes allow us to calculate averaged puckering amplitudes of 37.4° and 37.2° for *cis*-2-methoxy- and *trans*-2-diethylamino-2-oxo-3,5,5-trimethyl-1,2-oxaphospholan-3-ols,[3,6] respectively, and 43.1° for *cis*-2-diethylamino-2-oxo-3,5,5-trimethyl-1,2-oxaphospholan-3-ol.[3] Taking into account puckering amplitudes already calculated for 1,2-oxaphospholane-3-ols and those found in the literature for structurally similar systems, two ϕ_m values (42.9° and 37.4°) are chosen as representative for other substituted 1,2-oxaphospholan-3-ols.

For these two puckering amplitudes, endocyclic torsion angles ϕ_1 to ϕ_5 were calculated according to Equation 2 over the pseudorotation cycle ($0° < P < 360°$) and they are collected in Table III.

In order to calculate approximate values of exocyclic dihedral angles of interest in our conformational studies of the 1,2-oxaphospholane ring, Newman projections shown on Figure 1 were analyzed. As a result, twelve exocyclic dihedral angles were correlated with three (ϕ_3, ϕ_4, ϕ_5) endocyclic angles (Figure 1). The limited accuracy of these relationships should be kept in mind, because deviations from trigonal symmetry (120°) were not taken into account. Based on values of the ϕ_3, ϕ_4, and ϕ_5 angles collected in Table III and using angular dependences shown in Figure 1, values of exocyclic dihedral angles can be easily calculated for each conformation in the pseudorotation cycle. The relationships between twelve exocyclic dihedral angles and the angle of pseudorotation P are graphically represented in Figure 2 as nine double (for two ϕ_m values) cosine functions.

TABLE III

Approximated endocyclic torsion angles ϕ_1 to ϕ_5 for the pseudorotation itinerary of the 1,2-oxaphospholane ring†

	P	ϕ_1		ϕ_2		ϕ_3		ϕ_4		ϕ_5	
		a	b	a	b	a	b	a	b	a	b
$^{1}_{5}T$	0	-33.6	-29.2	11.2	9.8	11.1	9.7	-33.7	-29.4	45.9	40.0
$_{5}T$	18	-24.2	-21.1	-1.2	-1.1	23.7	20.6	-40.4	-35.2	42.8	37.3
$^{4}_{5}T$	36	-12.5	-10.9	-13.5	-11.8	33.9	29.5	-43.0	-37.5	35.5	31.0
^{4}T	54	0.4	0.3	-24.5	-21.4	40.8	35.5	-41.5	-36.2	24.8	21.6
$^{4}_{3}T$	72	13.3	11.6	-33.1	-28.9	43.7	38.1	-35.9	-31.3	11.6	10.1
$_{3}E$	90	24.9	21.7	-38.5	-33.5	42.4	36.9	-26.8	-23.3	-2.8	-2.4
$^{2}_{3}T$	108	34.0	29.7	-40.0	-34.9	36.9	32.1	-15.1	-13.1	-16.8	-14.6
^{2}E	126	39.9	34.7	-37.7	-32.9	27.7	24.2	-1.9	-1.6	-29.2	-25.5
$^{2}_{1}T$	144	41.8	36.4	-31.7	-27.6	15.9	13.8	11.5	10.0	-38.8	-33.8
$_{1}E$	162	39.6	34.5	-22.5	-19.6	2.5	2.2	23.8	20.7	-44.5	-38.8
$^{5}_{1}T$	180	33.6	29.2	-11.2	-9.8	-11.1	-9.7	33.7	29.4	-45.9	-40.0
^{5}T	198	24.2	21.1	1.2	1.1	-23.7	-20.6	40.4	35.2	-42.8	-37.3
$^{5}_{4}T$	216	12.5	10.9	13.5	11.8	-33.9	-29.5	43.0	37.5	-35.5	-31.0
$_{5}E$	234	-0.4	-0.3	24.5	21.4	-40.8	-35.5	41.5	36.2	-24.8	-21.6
$^{3}_{4}T$	252	-13.3	-11.6	33.1	28.9	-43.7	-38.1	35.9	31.3	-11.6	-10.1
^{3}E	270	-24.9	-21.7	38.5	33.5	-42.4	-36.9	26.8	23.3	2.8	2.4
$^{3}_{2}T$	288	-34.0	-29.7	40.0	34.9	-36.9	-32.1	15.1	13.1	16.8	14.6
^{2}E	306	-39.9	-34.7	37.7	32.9	-27.7	-24.2	1.9	1.6	29.2	25.5
$^{1}_{2}T$	324	-41.8	-36.4	31.7	27.6	-15.9	-13.8	-11.5	-10.0	38.8	33.8
^{1}E	342	-39.6	-34.5	22.5	19.6	-2.5	-2.2	-23.8	-20.7	44.5	38.8
$^{1}_{5}T$	360	-33.6	-29.2	11.2	9.8	11.1	9.7	-33.7	-29.4	45.9	40.0

† Throughout this paper the *E/T* nomenclature used in Reference 14 is employed.
[a] $\phi_m = 42.9°$.
[b] $\phi_m = 37.4°$.

SELECTION OF KARPLUS EQUATIONS

Analyses shown on Figure 1 lead us to the conclusion that several angular dependences of vicinal coupling constants should be considered. They include $^{3}J(HH)$, $^{3}J(HP)$[18] and $^{3}J(CP)$,[19] the latter two over different coupling pathways, namely, H—C—C—P and H—C—O—P and C—C—C—P and C—C—O—P, respectively.

The H—C—C—P Coupling

According to Figure 2 for the 1,2-oxaphospholane ring, two H4—C4—C3—P dihedral angles φ range from 77.6° to 163.7°. Comparison of $^{3}J(HCCP)$ couplings

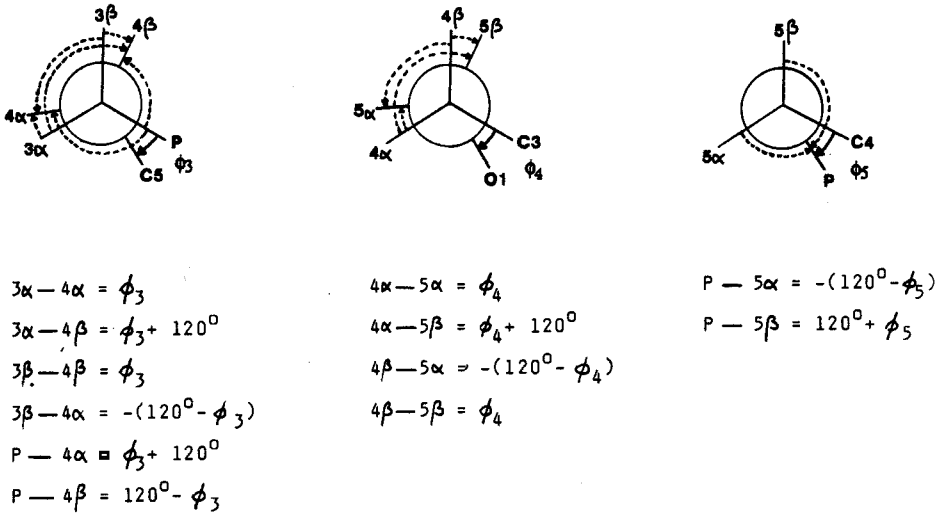


FIGURE 1 Newman projections of the 1,2-oxaphospholane ring along the C3—C4, C4—C5 and C5—O1 bonds and correlation between exocyclic and endocyclic dihedral angles.

calculated from angular relationships given by Benezra[20] (Equation 3) and Tronchet[21] indicates that significant differences occur for angles φ larger than 140° and smaller than 90°. In our conformational considerations, equations

$$^3J(HCCP) = 18 \cos^2 \varphi \qquad 0° < \varphi < 90°$$
$$^3J(HCCP) = 41 \cos^2 \varphi \qquad 0° < \varphi < 180° \tag{3}$$

developed by Benezra will be employed because of their general applicability, although they do not reflect the presence of electronegative (e.g. oxygen) substituents on the coupling path which causes a decrease in the ^3J values. The extent to which this occurs has not yet been precisely established.

The H—C—O—P Coupling

A significant number of $^3J(HP)$ *vs.* HCOP dihedral angle ("Karplus-like") relationships has been proposed in the literature because of their crucial importance in conformational studies of nucleoside phosphates.[22] Equation 4 introduced by Lee and Sarma[23] was selected for our studies, because of its extensive use in the conformational analysis of six-membered ring phosphates.[24] Our H5—C5—O—P dihedral angles fall into a 74.1° to 165.9° range (Figure 2). When graphic representations of Equation 4 and related ones were compared, it appeared that moderate differences between curves could only be found in the upper limits of dihedral angles range of interest. We will be using this relationship with confidence because only the configuration of the substituents on the P atom is being changed in the series of compounds studied in this paper.[25]

$$^3J(HCOP) = 18.1 \cos^2 \varphi - 4.8 \cos \varphi \tag{4}$$

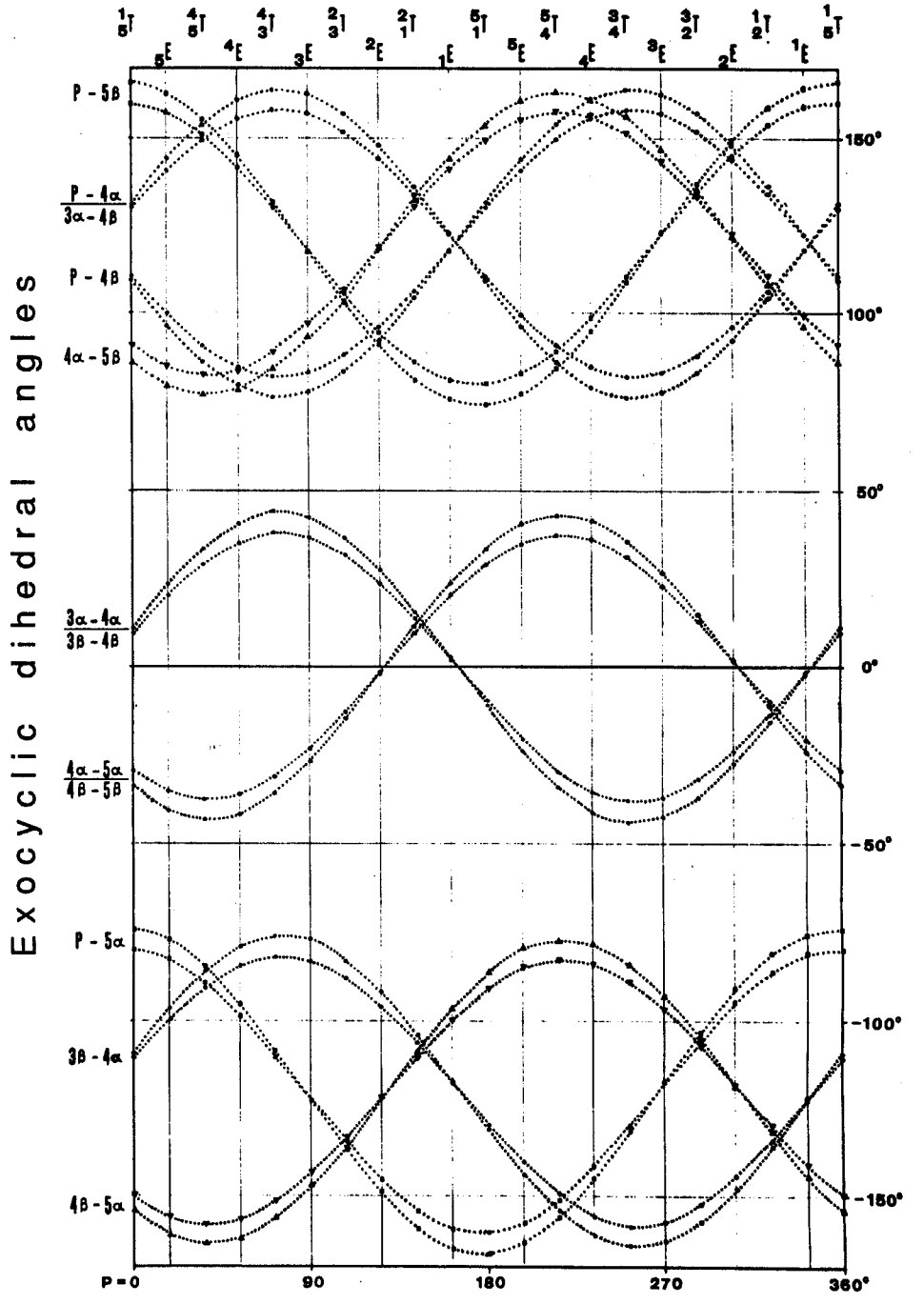


FIGURE 2 Selected exocyclic dihedral angles *vs.* the angle of pseudorotation P relationships for the 1,2-oxaphospholane ring.

The C—C—C—P Coupling

Several reports in the literature have shown that the presence of electronegative substituents (such as hydroxy or alkoxy groups) on the coupling path decreases the magnitude of ^3J(CCCP) up to 5 Hz, in comparison to unsubstituted derivatives.[26] In the CH_3—C4 substituted 1,2-oxaphospholanes whose conformations are studied in this paper, one hydroxy group is attached to the C3 atom on the coupling path. For this reason, ^3J(CP) *vs.* φ(CCCP) relationships which originate from the analysis of compounds containing PC(OH)CC or PCC(OH)C subunits, namely, those introduced by Thiem[27] and by Tronchet[21] (Equation 5), are taken into consideration. However, only the latter treatment accommodates Buchanan's recent reference data[28] of ^3J(*trans*) = 11.6–12.7 Hz and ^3J(*cis*) = 1.0 Hz found for conformationally biased cyclohexyl-α-hydroxyphosphonates and for this reason Equation 5 will be used herein.

$$^3J(CCCP) = 10.3 \cos^2 \varphi - 3.0 \cos \varphi \quad (5)$$

The C—C—O—P Coupling

Several "Karplus-like" ^3J(CP) *vs.* CCOP dihedral angle relationships have been described so far[29–33] but it is not recognized to what extent they include the influence of important factors such as a ring strain, orientation of electronegative substituents, and possible distortions of bond angles.[34,35] Under such circumstances these relationships should be considered as semiquantitative and in order to obtain estimates of ^3J(CCOP) for the pseudorotational cycle of the 1,2-oxaphospholane ring, Equation 6[29] was arbitrarily selected.

$$^3J(CCOP) = 8 \cos^2 \varphi - 2 \cos \varphi \quad (6)$$

The H—C—C—H Coupling

The original ^3J(HH) *vs.* H—C—C—H dihedral angle relationship introduced by Karplus many years ago[36] has since been intensively modified to include electronegativity and orientation effects of substituents attached to both carbon atoms on the coupling path.[37,38] Two very recent reports[39,40] have offered very complex equations. In order to obtain a preliminary insight into the magnitudes of ^3J(HCCH) couplings, a simple equation frequently used for a ribofuranose system[41] will be employed in this study (Equation 7).

$$^3J(HCCH) = 10.5 \cos^2 \varphi - 1.2 \cos \varphi \quad (7)$$

RELATIONSHIPS OF VICINAL COUPLING CONSTANTS AND ANGLE OF PSEUDOROTATION

Taking into account Equations 3–7, approximated magnitudes of vicinal coupling constants ^3J(HCCP), ^3J(HCOP), ^3J(CCCP), ^3J(CCOP) and ^3J(HCCH) were calculated for the respective dihedral angles characteristic of a particular conformation (see Figure 2), and they are shown in Figure 3. For these exocyclic dihedral angles,

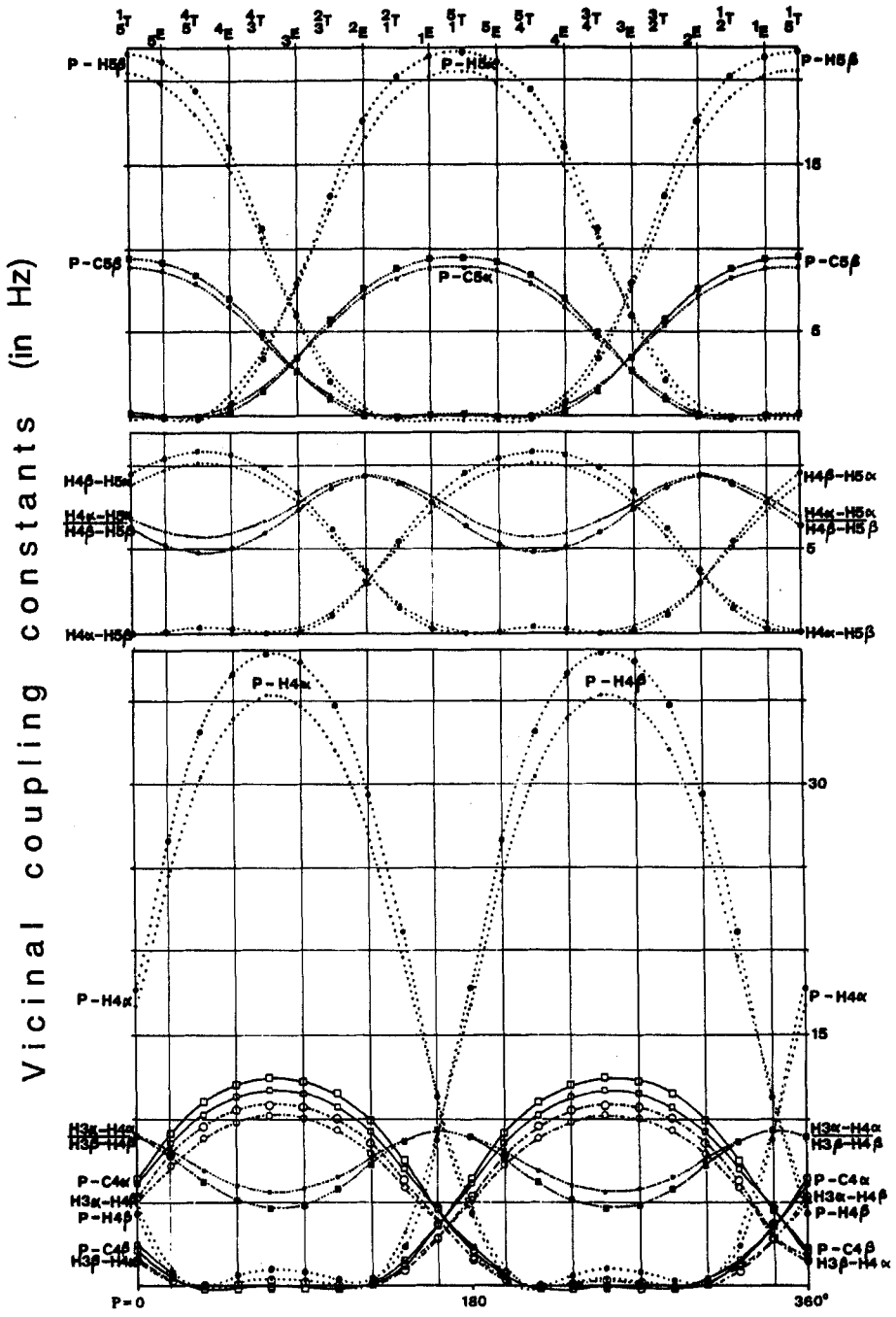


FIGURE 3 Selected vicinal coupling constants *vs.* the angle of pseudorotation P relationships for the 1,2-oxaphospholane ring (large characters—points, circle, squares—are for ϕ_m = 42.9°, small ones for ϕ_m = 37.4°).

which are equal to endocyclic angles ϕ_3 or ϕ_4, the H3β—H4β and H3α—H4α, as well as, H4α—H5α and H4β—H5β vicinal coupling constants are described by simple cosine functions having a maximum value of 9.3 Hz which is independent of the puckering amplitude ϕ_m and two minimum values of 5.3 and 4.6 Hz for smaller and larger puckering amplitudes, respectively. These exocyclic dihedral angles, which are 120°-phase-shifted in relation to the endocyclic angles ϕ_3, ϕ_4 and ϕ_5, give characteristic vicinal coupling *vs.* pseudorotation angle (P) curves always having a region of ^{3}J values close to zero (< 1 Hz) for seven consecutive conformations, while for the residual 13 conformations, broad symmetrical curves are formed. Thus, for the ${}_5E$ to ${}^2E$ conformations, the H3β—H4α, P—C4β and P—H4β couplings are expected to disappear and the same applies to the H3α—H4β, P—C4α and P—H4α couplings in the ${}^5E$ to ${}_2E$ conformational range. In a similar fashion, the H4α—H5β and H4β—H5α couplings are close to zero for the ${}^1E$ to ${}_3E$ and ${}_1E$ to ${}^3E$ conformers, respectively. On the other hand, for the ${}^2E$ to ${}_4E$ and ${}_2E$ to ${}^4E$ conformational regions, the zero-valued vicinal P—H5β and P—C5β, and P—H5α and P—C5α coupling constants, respectively, are predicted. The maximum values of the vicinal couplings shown on Figure 3 depend on the coupled nuclei, their coupling path and other factors already mentioned above. A similar approach to the conformational analysis of other five-membered rings has been recently elaborated.[42]

COMPOUNDS

The structures of compounds subjected to conformational analysis in this paper are collected in Table IV. All of them, except two, have been previously synthesized and their ^{1}H NMR characteristics published.[5,10–11,43–46]

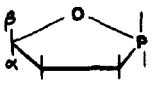
RESULTS

3,5,5-Trisubstituted Derivatives

Proton and ^{13}C NMR data for compounds **1** to **7** relevant to the conformational analysis are collected in Table V. For most compounds in the **a** series, i.e. **1a**, **2a**, **4a**, **6a**, **7a**, but also for **4b**, characteristic pairs of large (24.5 to 29.1 Hz) and small (0 to 1.2 Hz) vicinal H4—P coupling constants are observed. For these compounds, values of both ^{3}J(C—C5—O—P) are comparable and they do not exceed 4.4 Hz,[47] generally forming approximately a 2.7 and 3.4 Hz pair (e.g. **7b**). According to our analysis shown in Figure 3, ${}_3E({}^3E)$ and/or ${}^4_3T$ (${}^3_4T$) conformations could be assigned to these compounds in a chloroform solution. However, based on the influence of benzene on the chemical shifts of **1a** in comparison with a chloroform solution,[5] results of conformational studies by Mukhametov *et al.*,[2] as well as the conformation of **1a** found in the solid state,[6] we propose for **1a**, **2a**, **4a**, **6a**, **7a** and **4b** the ${}_3E$ and ${}^4_3T$ conformations as the most favorable. In these conformations, the CH_3—C3 (in compounds **1a** and **2a**) and the C_6H_5—C3 groups (in compounds **4a**, **4b**, **6a** and **7b**) occupy the pseudoequatorial position, while the HO—C3 or $(CH_3)_2$N—NH—C3 groups are pseudoaxial.

TABLE IV

Structures of 1,2-oxaphospholanes



	5β	5α	4β	4α	3β	3α	2β	2α	refs.
1a	CH_3	CH_3	H	H	CH_3	OH	OCH_3	O	5
1b	CH_3	CH_3	H	H	CH_3	OH	O	OCH_3	5
2a	CH_3	CH_3	H	H	CH_3	OCH_3	OCH_3	O	5
2b	CH_3	CH_3	H	H	CH_3	OCH_3	O	OCH_3	5
3a	CH_3	CH_3	H	H	CH_3	OR	OCH_3	O	5
3b	CH_3	CH_3	H	H	CH_3	OR	O	OCH_3	5
4a	CH_3	CH_3	H	H	C_6H_5	OH	OCH_3	O	43
4b	CH_3	CH_3	H	H	C_6H_5	OH	O	OCH_3	43
5a	CH_3	CH_3	H	H	CH_3	$NHN(CH_3)_2$	OCH_3	O	11
5b	CH_3	CH_3	H	H	CH_3	$NHN(CH_3)_2$	O	OCH_3	11
6a	CH_3	CH_3	H	H	C_6H_5	$NHN(CH_3)_2$	OCH_3	O	11
6b	CH_3	CH_3	H	H	C_6H_5	$NHN(CH_3)_2$	O	OCH_3	11
7a	C_6H_5	C_6H_5	H	H	C_6H_5	$NHN(CH_3)_2$	OCH_3	O	11
7b	C_6H_5	C_6H_5	H	H	C_6H_5	$NHN(CH_3)_2$	O	OCH_3	11
8a	H	H	H	CH_3	CH_3	OH	OCH_3	O	44
8b	H	H	H	CH_3	CH_3	OH	O	OCH_3	44
9b	H	H	CH_3	H	CH_3	OH	O	OCH_3	44
10a	H	H	CH_3	CH_3	H	OH	OCH_3	O	43
10b	H	H	CH_3	CH_3	H	OH	O	OCH_3	43
11a	CH_3	H	H	H	H	OH	OCH_3	O	10
11b	CH_3	H	H	H	H	OH	O	OCH_3	10
12a	H	CH_3	H	H	H	OH	OCH_3	O	10
12b	H	CH_3	H	H	H	OH	O	OCH_3	10
13a	H	CH_3	H	H	H	OR	OCH_3	O	10
13b	H	CH_3	H	H	H	OR	O	OCH_3	10
14	H	H	H	O–	OH	$CH_2OC(CH_3)_2$–	O	OCH_3	45, 46
15	H	H	H	OH	OH	CH_2OH	O	OCH_3	46
16	H	H	H	OAc	OH	CH_2OAc	O	OCH_3	this paper
17	H	H	H	OAc	OAc	CH_2OAc	O	OCH_3	this paper
18a	H	H	H	OR	O–	$CH_2OC(CH_3)_2$–	O	OCH_3	46
18b	H	H	H	OR	O–	$CH_2OC(CH_3)_2$–	OCH_3	O	46
19	H	H	H	O–	CH_2OH	$OC(CH_3)_2$–	OCH_3	O	46
20	H	H	H	O–	CH_2OR	$OC(CH_3)_2$–	OCH_3	O	46

R = $OC(O)C_6H_4$—NO_2—*p*. *Ac* = $OC(O)CH_3$.

Another group of 3,5,5-trisubstituted derivatives consists of compounds **1b**, **3a**, **5a**, **5b**, **6b** and **7b** which displayed a pair of large (19.3 to 23.2 Hz) and medium (6.3 to 8.0 Hz) vicinal H4—P couplings together with, again, comparable values of both C—C5—O—P couplings (2.9 to 3.3 Hz). However, a pair of H4—C—C—P coupling constants of 21.3 Hz and 6.3 Hz (**1b**) cannot represent a single conformer according to Figure 3. For this reason we interpret these observations as a ${}_3E({}^4_3T) \rightleftarrows {}^3E({}^3_4T)$ conformational equilibrium containing ca. 80%[48] of the ${}_3E({}^4_3T)$ forms

TABLE V

Selected ^1H and ^{13}C NMR data for compounds **1** to **7**

Cpd.	^2J(H4a,H4b)	^3J(H4a,P)	^3J(4Hb,P)	^3J(C5a,P)	^3J(C5b,P)	δ(H4a)	δ(H4b)	Remarks
1a	14.1	25.7	1.2	~0	~0	2.22	1.99	a
1b	14.1	21.3	6.3	~0	~2.9	2.24	2.15	a
2a	14.1	24.5	1.1	3.3	2.2	2.22	1.98	a
2b	14.1	17.2	10.3	~0	0.7	2.34	2.06	a
3a	14.1	19.3	8.0	2.9	~0	2.89	2.38	a
3b	14.5	13.4	12.4	2.0	4.9	2.72	2.48	a
4a	14.2	27.2	1.2	2.9	2.9	2.50	2.62	b
4b	14.4	27.8	1.2	2.7	3.4	2.49	2.58	b
5a	13.7	20.1	7.7	3.3	3.3	2.36	1.83	c
5b	13.7	20.3	7.5			2.00	2.09	c
6a	13.5	28.2	0.5	2.9	4.4	2.98	2.48	c
6b	13.5	21.6	7.8			2.78	2.61	c
7a	13.2	29.1	0	2.9	4.4	4.04	3.46	c
7b	13.8	23.3	7.8	2.9	2.9	3.87	3.54	c

[a] Taken from Reference 5.
[b] ^1H NMR spectrum taken at 300 MHz.
[c] See Reference 11.

for **1b**. This conclusion makes our previous conformational assignments[5] for **1b** and **3a** more precise.

A similar approach is applied to conformational behavior of **2b** and **3b**, for which we again postulate the same equilibria consisting of *ca.* 65%[49] and 52% of ${}_3E({}^4_3T)$ conformers, respectively, contrary to our previous assignment[5] of the ${}_1E$ conformation for **3b**. For the ${}_1E({}^1E)$ conformations, not only similar values of vicinal H4—C—C—P couplings are necessary but also two different (*ca.* 9 Hz and 0 Hz) vicinal C—C5—O—P couplings should be observed which is not the case for **3b**.

3,4- and 4,4-Dimethyl Derivatives

Spectroscopic data of interest in the conformational analysis of dimethyl derivatives are shown in Table VI. P-epimeric compounds **8a** and **8b** exist in a chloroform solution in the same almost pure ${}^4E$ conformations. Observed vicinal H4β—P (0 Hz), C4α—C4—C—P (10.3 Hz), H5α—P and H5β—P coupling constants are in good agreement with those expected from our analysis shown in Figure 3 for this conformation. Furthermore, approximate values[41] of H4β—H5α (10.6–9.9 Hz) and H4β—H5β (5.9–5.0 Hz) couplings (Figure 3) show no significant differences from the experimental ones of 11.0 and 7.0–6.6 Hz, respectively. Conformational homogeneity of **8a** and **8b** results from the equatorial and pseudoequatorial orientations of the CH_3—C4 and CH_3—C3 groups, respectively, while the HO—C3 group resides in a pseudoaxial position.

Based on magnitudes of six vicinal couplings (Table VI) found for **9b** and the relationships shown in Figure 3, it is obvious that this compound does not exist in

TABLE VI

Selected ^1H and ^{13}C NMR data for compounds **8** to **13**

Cpds. / Couplings	8a	8b	9b	10a	10b	11a	11b	12a	12b	13a	13b
^3J(H3,H4a)						1.8	3.1	6.9	10.0	8.8	6.8
^3J(H3,H4b)						4.8	5.1	7.3	7.8	8.4	7.5
^2J(H4a,H4b)						14.1	14.2	13.6	13.2	13.4	13.9
^3J(H4a,H5a)			6.9			4.8	5.1				
^3J(H4a,H5b)			9.2					6.9	10.0	9.2	6.8
^3J(H4b,H5a)	11.0	11.0				10.3	8.9				
^3J(H4b,H5b)	7.0	6.6						6.0	5.1	5.1	6.2
^2J(H5a,H5b)	8.3	8.5	9.2	9.1	9.0						
^2J(H3,P)				4.4	0	7.5	4.0	1.6	0	3.7	3.3
^3J(H4a,P)			5.7			26.4	22.1	12.5	6.6	5.9	11.9
^3J(H4b,P)	0	0				2.5	7.5	19.3	29.0	25.1	18.0
^3J(H5a,P)	3.4	2.6	10.1	14.1	11.3	4.3	3.5				
^3J(H5b,P)	15.5	16.9	6.7	9.8	10.4			4.5	3.0	2.9	6.6
^4J(H5^1,P)						0.7	0.9	1.6	1.0	1.3	0.9
^3J(C4a,P)	10.3	10.3		7.3	6.3						
^3J(C4b,P)			8.8	5.4	5.9						
^3J(C5b,P)						3.9	5.4	5.4	4.4		
δ(H3)						4.18	4.35	4.26	4.46	5.24	5.38
δ(H4a)			2.59			2.36	2.32	2.05	1.97	2.31	2.16
δ(H4b)	2.24	2.36				1.92	2.10	2.59	2.60	2.82	2.94
δ(H5a)	3.94	3.82	4.23	3.71	3.43	4.78	4.64				
δ(H5b)	4.09	4.18	3.64	4.00	3.59			4.34	4.46	4.42	4.67
Remarks	a,b	a,b	a	c	c,d	e	e	e	e	e	e

[a] See Reference 44.
[b] ^1H NMR spectrum taken at 360 MHz.
[c] ^1H NMR spectrum taken at 300 MHz.
[d] Benzene-d_6 solution.
[e] See Reference 10.

chloroform solution as a single conformer, but is involved in a conformational equilibrium. We suggest that the $_4E$ conformation having the CH_3—C4 and HO—C3 groups in the equatorial and pseudoequatorial positions, respectively, and the CH_3—C3 group pseudoaxially oriented predominates in the equilibrium with its ^4E counterpart. However, the existence of other components of this equilibrium, such as ^3_4T and ^4_3T, cannot be ruled out.

Compounds **10a** and **10b** are not conformationally homogeneous in chloroform

and benzene solutions, respectively. Pairs of H5—C—O—P and C4—P coupling constants observed for these compounds (Table VI) allow us to propose a complex equilibrium involving at least several possibilities from the range of conformations ${}^{2}E$, ${}^{2}_{1}T$, ${}_{2}E$, ${}^{1}_{2}T$.

5-Methyl Derivatives

None of six compounds under consideration (**11–13**) is conformationally homogeneous in a chloroform solution. Eight vicinal coupling constants (Table VI) available for **11a** may be interpreted as results of its existence in a complex equilibrium consisting of ${}^{4}_{5}T$, ${}^{4}E$, ${}^{4}_{3}T$ conformations containing small amounts (*ca.* 10–20%) of their ${}^{5}_{4}T$, ${}_{4}E$, ${}^{3}_{4}T$ counterparts. A pair of H4—C—C—P couplings (26.4 and 2.5 Hz) observed for **11a** cannot be found in a single conformer according to the analysis shown in Figure 3. Taking into account the H4β—H5α coupling constant (10.3 Hz), we find the ${}^{4}_{5}T$ to ${}^{4}_{3}T$ region fulfils the requirement of having large H4α—C—C—P and near-zero H4β—C—C—P coupling constants. The presence of conformations from the ${}^{5}_{4}T$ to ${}^{3}_{4}T$ range will decrease the magnitudes of predicted H4α—P and H4β—H5α coupling constants, while the H4β—P coupling is expected to increase its value. For the same reason, the observed H5α—C—O—P and C5β—C—O—P couplings can be considered as averaged values for the proposed conformational equilibrium. The H3β—H4β and H4α—H5α coupling constants (both of 4.8 Hz) have the same predicted magnitudes in both conformational regions: 6.2 to 4.6 Hz and 4.7 to 5.9 Hz, respectively, for a smaller puckering amplitude when Equation 7 is applied.

Similar to **11a**, compound **11b** also exists in a conformational equilibrium in which ${}^{4}_{5}T$, ${}^{4}E$, ${}^{4}_{3}T$ conformations dominate ${}^{5}_{4}T$, ${}_{4}E$ and ${}^{3}_{4}T$ but to a larger extent (*ca.* 75:25) than was found for **11a**. This conclusion is based on a comparison of ^{3}J(H4a—P) and ^{3}J(H4b—H5a) as well as of ^{3}J(H4b—P) and ^{3}J(H3b, H4a) in both P-epimers **11a** and **11b**. The former pair of couplings decreased while the latter increased in **11b** when compared with magnitudes of these coupling constants in **11a**. Similar behavior of P-epimers was noticed previously for **1a** and **1b**. In the ${}^{4}_{5}T$, ${}^{4}E$, ${}^{4}_{3}T$ conformations of **11a** and **11b**, the CH_3—C5 group occupies the pseudoequatorial position and the HO—C3 group is pseudoaxially oriented.

The conformation of **12b** is unequivocally described by the presence of large H4β—P and small H4α—P vicinal coupling constants together with the values of ^{3}J(H3β—H4α) and ^{3}J(H4α—H5β) (each 10.0 Hz). Based on these couplings only, one may conclude that for **12b**, ${}^{5}_{4}T$, ${}_{4}E$, ${}^{3}_{4}T$ conformations dominate in chloroform solution. Additionally taking into account values of ^{3}J(H5β—P) and ^{3}J(C5α—P), the ${}^{3}_{4}T$ conformation better fits the magnitudes of the observed coupling constants. In this conformation, the CH_3—C5 and HO—C3 groups are located in pseudoequatorial positions. The results of our analysis shown in Figure 3, however, clearly show that **12b** is involved in an equilibration process, possibly with the ${}^{4}_{3}T$ conformer, because ^{3}J(H4α—P) is larger than 1 Hz and the magnitude of ^{3}J(H4α, H5β) is expected to reach 11.0 Hz, as was found for a pair of *trans*-oriented hydrogen atoms in conformationally homogeneous **8a** and **8b**.

In a similar way we suggest that compound **13a** in a chloroform solution is engaged in a ${}^{3}_{4}T \rightleftarrows {}^{4}_{3}T$ conformational equilibrium, although it is likely that the percentage

of the ${}^{4}_{3}T$ form is even higher than that ascribed to **12a** because the $^3J(H3\beta—H4\alpha)$ and $^3J(H4\alpha—H5\beta)$ values found for **13a** are smaller than the analogous couplings observed for **12b**.

Numerous attempts to establish the conformational behavior of compounds **12a** and **13b** based on two sets of eight vicinal coupling constants of similar values (Table VI) were not successful because the unequivocal assignment of α and β orientations to H4a and H4b was not possible. However, it is reasonable to envisage energetically favored pseudoequatorial orientations for both the CH_3—C5 and HO—C3 substituents (e.g. conformations ${}^{5}_{4}T$, ${}_{4}E$, ${}^{3}_{4}T$) existing in an unspecified equilibrium (possibly 50:50) with conformers having these substituents in pseudoaxial orientations.

(4R)-4-Hydroxy-3-hydroxymethyl Derivatives

Proton and ^{13}C NMR parameters relevant to the conformational analysis of compounds **14–20** are shown in Table VII. Configurational as well as conformational studies of (2*R*, 3*R*, 4*R*)-3[1], 4-*O*-isopropylidene-3-(hydroxymethyl)-2-methoxy-2-oxo-1,2-oxaphospholane-3,4-diol (**14**) previously,[45] led us to the conclusion that the 1,2-oxaphospholane ring of this compound adopts the ${}_{4}E$ conformation. This is in good agreement with values predicted from Figure 3 for $^3J(H4\beta—P)$, $^3J(H5\alpha, P)$, $^3J(H5\beta—P)$, $^3J(H4\beta, H5\alpha)$ and $^3J(H4\beta, H5\beta)$ when compared with magnitudes of the experimental couplings. However, the ${}^{3}_{4}T$, ${}^{5}_{4}T$ and even ${}^{5}E$ conformations are also acceptable for the vicinal coupling constants observed for **14**. It is highly likely that the 1,2-oxaphospholane ring in bicyclic compound **14** experiences limited pseudorotation between the ${}^{3}_{4}T$ and ${}^{5}E$ conformations because the 1,3-dioxane ring is in a rigid chair conformation.[45] In these four possible conformations, the $—OCH_2—$C3 substituent occupies pseudoequatorial positions while —O—C4 and HO—C3 moieties are always pseudoaxially oriented.

The $^3J(H4\beta, P)$, $^3J(H5\alpha, P)$, $^3J(H5\beta, P)$, $^3J(H4\beta, H5\alpha)$ and $^3J(H4\beta, H5\beta)$ coupling constants found for **15** in methanol solution and for **16** in chloroform solution are very close in magnitude to those observed for **14** and for this reason we conclude that the conformational behavior of compounds **15** and **16** is similar to that of **14**. In **15** and **16** the —O—C4 and HO—C3 oxygen atoms are pseudoaxially oriented and the $—OCH_2—$C3 group is in a pseudoequatorial position. A non-zero value of $^3J(H4\beta, H5\alpha)$ for monocyclic compounds **15** and **16** can result from the minor presence of conformations from the ${}^{4}_{3}T$ to ${}_{5}E$ region of the pseudorotation cycle.

It was tempting to interpret the vicinal coupling constants observed for triacetate **17** in terms of a biased ${}_{3}E$ conformation,[50] in which two acetate groups (at C4 and C3) and the CH_3O—P group occupy pseudoequatorial positions while the acetoxymethyl group at C—3 is pseudoaxial. Employing the results of the analysis shown in Figure 3, we may accept for this conformation two pairs of equal coupling constants [$^3J(H4\beta, H5\alpha) = {}^3J(H4\beta, H5\beta)$ and $^3J(H5\alpha, P) = {}^3J(H5\beta, P)$] but the magnitude of the observed $^3J(H4\beta, P)$ coupling is far larger than expected. We postulate the ${}_{3}E \rightleftarrows {}^{3}E$ conformational equilbrium containing approximately 10% of the ${}^{3}E$ form to explain this discrepancy. For this equilibrium, pairs of $^3J(H4\beta, H5)$ and $^3J(H5, P)$ coupling constants remain equal while $^3J(H4\beta, P)$ is expected to attain its maximum value in the ${}^{3}E$ conformation.

TABLE VII
Selected ^1H and ^{13}C NMR data for compounds **14–20**

Compds / Couplings	**14**	**15**	**16**	**17**	**18a**	**18b**	**19**	**20**
$^2J(H3^1a,H3^1b)$	13.5	11.6	12.1	11.6	9.8	9.9	0	12.1
$^3J(H4b,H5a)$	0	1.2	0.9	7.6	1.8	4.0	0	0
$^3J(H4b,H5b)$	3.2	3.7	3.5	7.6	3.8	4.7	2.9	3.1
$^2J(H5a,H5b)$	10.3	9.8	11.0	9.4	11.2	10.8	11.3	11.4
$^3J(H3^1a,P)$	23.7	22.9	4.0	15.8	15.3	11.5	9.7	4.0
$^3J(H3^1b,P)$	12.9	3.7	18.0	8.1	8.2	11.5		15.5
$^3J(H4b,P)$	24.5	23.5	23.3	2.6	20.7	14.5	21.4	19.1
$^3J(H5a,P)$	18.2	17.4	18.9	10.4	15.2	14.1	23.7	25.3
$^3J(H5b,P)$	3.2	3.7	3.3	10.8	5.0	6.0	1.5	1.8
$^3J(COCP)$	0	-	-	-		5.9	6.6	
$\delta(H3^1a)$	4.00	3.84	4.38	4.45	4.31	4.41	3.88	4.65
$\delta(H3^1b)$	4.14	3.97	4.42	4.85	4.32	4.53	3.88	4.75
$\delta(H4b)$	4.25	4.08	5.23	5.75	5.41	5.50	4.70	4.75
$\delta(H5a)$	4.08	4.01	4.13	3.88	4.23	4.22	4.30	4.34
$\delta(H5b)$	4.55	4.46	4.61	4.55	4.65	4.57	4.00	4.06
Remarks	a	b,c	d	e	b	b	b	b

[a] Taken from Reference 45.
[b] See Reference 46.
[c] Taken at 350 MHz for methanol-d_4 solution.
[d] δ 2.118 and 2.125 (2*s*, 6H, CH_3COO), 3.89 (*d*, J_{HP} = 11.0 Hz, 3H, CH_3OP).
[e] δ 2.09, 2.12, 2.16 (3*s*, 9H, CH_3COO), 3.97 (*d*, J_{HP} = 11.9 Hz, 3H, CH_3OP).

Esters **18a** and **18b** are not conformationally stable as judged (Figure 3) from the appearance of a pair of ^3J(H5—P) couplings of 15.2 and 14.1 Hz to the H5α and 5.0 and 6.0 Hz to the β-oriented H5. Based on a quantitative comparison of magnitudes of vicinal H4β—H5α, H4β—H5β, H4β—P, H5α—P, H5β—P coupling constants, we suggest that compounds **18a** and **18b** undergo complex conformational equilibration similar to that established for **14** in which ^5E to ^3_4T conformers dominate. However, those from the $_5E$ to ^4_3T region of the pseudorotation cycle are also present although in an unspecified amount. In the favored conformational range, i.e. ^5E to ^3_4T, the —OCH_2—C3 moiety is pseudoequatorially oriented and the —O—C3 and RO—C4 groups are in pseudoaxial positions.

On the other hand, the 1,2-oxaphospholane rings of compound **19** and its *p*-nitrobenzoate **20** are biased in the ^5E conformation. The experimental vicinal coupling constants: H4β—H5α, H4β—H5β, H4β—P, H5α—P, and H5β—P fit well to the values expected for these couplings according to the analysis shown in

Figure 3. In this conformation, the hydroxymethyl and *p*-nitrobenzoyloxymethyl groups of **19** and **20**, respectively, occupy pseudoaxial positions, while the oxygen atoms attached to C4 and C3 are oriented pseudoaxially and pseudoequatorially, respectively. Furthermore, the substituents at P and C3 atoms are in a synperiplanar conformation.

DISCUSSION

Several approximations introduced during this study allows us to discuss specific intramolecular interactions governing the conformational behavior of the 1,2-oxaphospholane ring qualitatively. Usually steric (1,2- and 1,3-interactions) and stereoelectronic (anomeric,[51] gauche[52]) effects are considered to account for stabilization of a particular conformer.

The so-called gauche effect[52] describes preference for the gauche over anti conformation in X—C—C—Y units in which X and Y are electronegative substituents. The most significant gauche stabilization is noted for the most electronegative groups, i.e. oxygen and fluorine.[53a] Among substituted 1,2-oxaphospholanes studied in this report, the gauche effect might be considered in compounds **14** to **20** for the O3—C3—C4—O4α and O4α—C4—C5—O1 fragments, and *eventually* in all derivatives for the O—P—C3—O moieties. Assuming that the gauche effect is operative for torsion angles range 30° to 90°[54] we find from Table III according to the relationship (120°-ϕ_4) that in compounds **14** to **20**, O4α—C4—C5—O1 interactions should stabilize ${}^5E$, ${}^5_4T$, ${}_4E$, ${}^3_4T$ conformations while additional stabilization through gauche effects can only be expected within the O3α—C3—C4—O4α fragment for almost all conformations. However, in compounds **14** to **18**, antiperiplanar orientation of O3β—C3—C4—O4α unit competes with stabilization introduced by the gauche arrangement of the O4α—C4—C5—O1 fragment.

In a similar way, the dihedral angles of O—P—C3—O3 fragments are considered and conformational regions of *possible* operation of gauche effects are collected in Table VIII. It should be noted, however, that in conformations in which the gauche effect within the O—P—C3—O fragment could be responsible for greater conformational stabilization, two gauche and one anti arrangement are always present.

The anomeric effect in 5-membered rings containing oxygen (e.g. furanose derivatives) is demonstrated by strong preference for a pseudoaxial orientation of OR groups attached to the anomeric center.[42b] For 5- and especially 6-membered phosphates, it is fairly well established that alkoxy (aryloxy) substituents at phosphorus favor axial positions, leaving the phosphoryl oxygen equatorially oriented.[53b] Among the 1,2-oxaphospholanes studied here, conformational stabilization by the anomeric effect could be suggested for conformers having pseudoaxial CH_3O—P groups (i.e. for ${}_3E$, ${}^2_3T$, ${}^2E$, ${}^2_1T$, ${}_1E$ and ${}^3E$, ${}^3_2T$, ${}_2E$, ${}^1_2T$, ${}^1E$ conformations) in isomers containing the CH_3O—P groups in the β and α positions, respectively.

In compound **1a**, the ${}_3E$-${}^4_3T$ conformations can be stabilized by two HO—C3—P—O1(O2α) gauche effects, pseudoaxial orientation of the methoxy group and lack of 1,3-repulsive interactions between $CH_3(\beta)$—C5 and CH_3—C3 groups. Destabilizing factors include one anti HO—C3—P—O2β arrangement and near 1,3-dipseudoaxial disposition of the $CH_3(\alpha)$—C5 and HO—C3 substituents.

TABLE VIII
Gauche effects within the O—P—C3—O3 moiety

Angle	Relationship to ϕ_2	Gauche effect possible for conformations:
O1-P-C3-O3α	$120^\circ + \phi_2$	$({}^4_3T)$, ${}_3E$, ${}^2_3T$, ${}^2E$, $({}^2_1T)$
O1-P-C3-O3β	$120^\circ - \phi_2$	$({}^3_4T)$, ${}^3E$, ${}^3_2T$, ${}_2E$, $({}^1_2T)$
O2α-P-C3-O3α	ϕ_2	${}_3E$, ${}^2_3T$, ${}^2E$; ${}^3E$, ${}^3_2T$, ${}_2E$
O2α-P-C3-O3β	$120^\circ + \phi_2$	$({}^4_3T)$, ${}_3E$, ${}^2_3T$, ${}^2E$, $({}^2_1T)$
O2β-P-C3-O3α	$-(120^\circ - \phi_2)$	$({}^3_4T)$, ${}^3E$, ${}^3_2T$, ${}_2E$, $({}^1_2T)$
O2β-P-C3-O3β	ϕ_2	${}_3E$, ${}^2_3T$, ${}^2E$; ${}^3E$, ${}^3_2T$, ${}_2E$

Its P-epimer **1b**, however, contains some ${}^3E$-${}^3_4T$ conformers in addition to ${}_3E$-${}^4_3T$ forms. One could propose that existence of the former conformations results from a tendency of the MeO—P group to become pseudoaxial, but 1,3-dipseudoaxial repulsions of the $CH_3(\beta)$—C5 and CH_3—C3 groups oppose this tendency.

Introduction of the methoxy group into the 3α position of the 1,2-oxaphospholane ring (compound **2a**) does not change its conformation relative to that of **1a**. Although the methoxy group is bulkier than the hydroxy group, other factors stabilizing ${}_3E$-${}^4_3T$ conformations override increasing 1,3-interactions of the CH_3O—C3 and $CH_3(\alpha)$—C5 substituents. We suggest that these increasing repulsions are responsible for the higher fraction of ${}^3E$-${}^3_4T$ conformers in isomer **2b** compared to those for **1b**.

Conformational equilibria observed for P-epimers **3a** and **3b** result from competition of several steric and stereoelectronic factors. In **3a**, ${}_3E$-${}^4_3T$ conformers are favored because of pseudoaxial disposition of the CH_3O—P group, and 1,3-repulsions of α- and β-positioned substituents at C3 and C5 account for the contribution of ${}^3E$-${}^3_4T$ forms. The latter conformations probably reflect increasing bulkiness of the *p*-nitrobenzoyloxy group which in ${}^3E$-${}^3_4T$ conformations occupies a pseudoequatorial position. This conclusion receives some support in the further increase of the ratio of ${}^3E$-${}^3_4T$ conformations for **3b** in which the CH_3O—P group is pseudoaxial. Gauche effects in competing conformers of **3a** and **3b** are equal.

Conformations of **4a** and **4b** are independent of the configuration at the P atom. In both isomers, the phenyl groups are pseudoequatorially oriented, and the ${}^3E$-${}^3_4T$ conformers of **4b** having pseudoaxial CH_3O—P and C_6H_5—C3 groups are not detected because of possible significant 1,3-repulsions of the C_6H_5—C3 and $CH_3(\beta)$—C5 groups.

Replacement of the HO—C3 group by a β,β-dimethylhydrazino group has significant influence on the conformation of the P-epimeric compounds **5**, **6** and **7**

when compared to that of their analogues **1** and **4**. The existence of both P-epimeric compounds **5a** and **5b** as the same mixture of ${}_3E\text{-}{}^4_3T$ and ${}^3E\text{-}{}^3_4T$ conformers could be explained by strong domination of 1,3-interactions of substituents at C3 and C5 over stereoelectronic pseudoaxial preferences for the CH_3O—P group. Conformational homogeneity of **6a** and **7a** can result from pseudoequatorial disposition of the C_6H_5—C3 groups and also the pseudoaxial orientation of CH_3O—P groups. However, it appears that their epimers **6b** and **7b** exist in a conformational equilibrium similar to that found for **1b**, **3a**, **5a** and **5b**, although in minor ${}^3E\text{-}{}^3_4T$ conformers serious 1,3-dipseudoaxial repulsions of the C_6H_5—C3 and $CH_3(C_6H_5)$—C5 groups can arise. One may conclude that steric requirements of the β,β-dimethylhydrazino group are higher than those of the hydroxy group and that 1,3-repulsive interactions of α-positioned $C_6H_5(CH_3)$—C5 and $(CH_3)_2N$—NH groups are balanced by the respective interactions of β-oriented substituents at C3 and C5. Pseudoaxial disposition of the CH_3O—P group in minor conformers may add extra stabilization.

Conformational ${}^4E$ stability of P-epimeric compounds **8a** and **8b** is exclusively governed by steric factors, i.e. orientation of both methyl groups attached to C3 and C4 in pseudoequatorial positions. Steric effects also dominate conformational preferences for compound **9b** in which CH_3—C3 and CH_3—C4 groups have a *cis* configuration. The ${}_4E\text{-}{}^3_4T$ conformers containing the CH_3-C4 and HO—C3 groups in pseudoequatorial positions are favored over those with a pseudoequatorial CH_3—C3 group and when CH_3—C4 and HO—C3 groups are pseudoaxially oriented.

In the ${}_2E\text{-}{}^1_2T$ and ${}^2E\text{-}{}^2_1T$ conformations suggested for **10a** and **10b**, possible 1,2-repulsive interactions of the HO—C3 and both CH_3—C4 groups are almost minimized, and gauche effects may additionally stabilize the conformers.

Conformational isomers having pseudoequatorial CH_3—C5 and pseudoaxial HO—C3 groups predominate in epimers **11a** and **11b** over those in which the CH_3—C5 group is pseudoaxially and the HO—C3 substituent is pseudoequatorially oriented. On the other hand in **12b** and **13a**, conformers with CH_3—C5 and HO—C3 groups in pseudoequatorial positions are favored. In all the 5-methyl derivatives discussed in this paper, steric preferences for the CH_3—C5 group to reside in the least crowded environment are of primary importance.

In the rigid bicyclic system of compound **14**, conformations of the 1,2-oxaphospholane ring result first of all from its *cis*-junction with the 1,3-dioxane ring. However, two stabilizing effects can be pointed out. They include pseudoequatorial disposition of the —OCH_2—C3 moiety and gauche orientation of oxygen atoms in the O—C4—C5—O1 fragment. Although in related monocyclic (**15** and **16**) and spiro (**18a** and **18b**) compounds conformational freedom of the 1,2-oxaphospholane ring is assured, conformers having pseudoequatorial —OCH_2—C3 and pseudoaxial —O—C4 groups are favored. It is difficult to estimate to what extent the gauche effect within the O—C4—C5—O1 unit (stereoelectronic) is responsible for the conformational stability of compounds **15**, **16**, **18a** and **18b** because simultaneously, pseudoequatorial orientation of the —OCH_2—C3 substituent brings stabilization to these conformers on steric grounds. These two stabilizing factors dominate over a destabilizing antiperiplanar arrangement of oxygen atoms in the —O—C3—C4—O— fragment.

On the other hand in the triacetate **17**, the steric preference observed for the

—OCH_2—C3 substituent to occupy a pseudoequatorial position is overridden by other steric effects (i.e. pseudoequatorial orientations of the AcO—C3 and AcO—C4 groups) possibly combined with the gauche effect within —O—C3—C4—O— unit. Besides pseudoaxial orientation of the —OCH_2—C3 group, antiperiplanar disposition of oxygen atoms within the —O—C4—C5—O1 unit destabilizes the $_3E$ conformation of **17** while both these effects are considered as stabilizing in the minor ^3E conformer.

cis-Junction (3α, 4α) of a 1,2-oxaphospholane and 1,3-dioxolane ring does not influence the conformational freedom of the former significantly. So, it is surprising that compounds **19** and **20** exist exclusively as ^5E conformers, because synperiplanar arrangement of substituents at P and C3 could produce repulsive 1,2-interactions. We expect them to be smaller than those in respective carbon compounds because the C—P bond is longer than the C—C bond. The unfavorable 1,2-interactions are overcome by two gauche effects within the O3α—C3—C4—O4α and O4α—C4—C5—O1 moieties. In the ^5E conformation, the gauche effect in the latter moiety attains its highest value.

Based on the structures studied in this report, the conformation of the 1,2-oxaphospholane ring is dominated by steric preferences of alkyl and aryl substituents at carbon atoms to occupy pseudoequatorial positions. The influence of the configuration at phosphorus on the conformation of the ring in diastereoisomeric pairs, and thus the existence of the anomeric effect, is not well defined. On the other hand, orientation of oxygen-bearing substituents in O—C—C—O fragments significantly influences the conformation of those derivatives in which two gauche arrangements are possible.

EXPERIMENTAL

Proton NMR spectra were taken for solutions in deuteriochloroform (5–10 mg in 0.5 ml of the solvent) unless stated otherwise. The following spectrometers were used: Bruker HX-90 (90 MHz), Nicolet NT 300 (300 MHz) for compounds **4a**, **4b**, **10a** and **10b**, Bruker HX-360 (360 MHz) for compounds **8a** and **8b**, and Cameca 350 (350 MHz) for compound **15**. All spectra were obtained in FT mode and they were analyzed as described earlier.[5]

Carbon-13 NMR spectra were obtained on a Bruker HX-90 spectrometer at 22.63 MHz.

Acetylation of (2R, 3R, 4R)-3-(hydroxymethyl)-2-methoxy-2-oxo-1,2-oxaphospholane-3,4-diol (**15**). A mixture of compound **15** (29 mg, 0.15 mmol), acetic anhydride (0.5 mL) and pyridine (0.5 mL) was left at room temperature for 20 hrs. The solution was concentrated *in vacuo* and coevaporated with toluene (20 mL) three times. The residue was subjected to column chromatography on 3 g of silica gel (Merck 60, 0.063–0.200 mm) and the column was developed with chloroform to give the triacetate **17** and the diacetate **16** as colorless oils. Compound **17**: yield 14.2 mg (29.2%), R_F (Silica Gel 60 F254-Merck, chloroform/methanol, 50:1, v/v) 0.37, $[\alpha]_D^{25}$-31.4 (*c* 0.71, chloroform). IR (neat) 1735 (vs) and 1270 (vs) cm^{-1}. ^1H NMR in Table VII. Compound **16**: yield 11.0 mg (26.0%), R_F 0.20, $[\alpha]_D^{25}$-29.2 (*c* 0.25 chloroform). IR (neat) 3500–3000 (*s*), 1735 (*vs*) and 1240 (*vs*) cm^{-1}. ^1H NMR in Table VII.

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