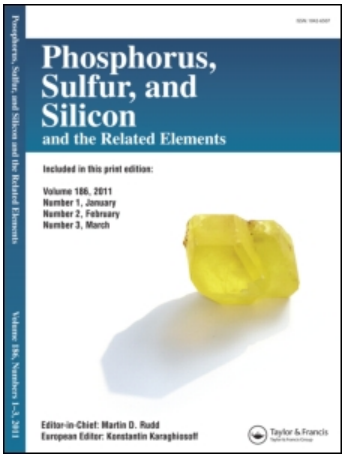

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Kinetic Studies of the Thermal *cis*-to-*trans* Isomerization of Dioxaphospholanes

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*By following a previously reported method,[1] the synthesis of r-2-alkoxy-cis-4-cis-5-dimethyl-1,3,2-λ^3-dioxaphospholanes ligands (**1** and **3**) was carried out. The purpose of this work is the kinetic study of the inversion barrier at phosphorus for **1** and **3** and the comparison with the already informed dioxaphospholane **2**. The kinetic measurements of the thermal isomerization cis-to-trans were performed by ^{31}P NMR spectroscopy, observing a first order kinetics for both compounds. The energy of activation (E_a) for the epimerization of compounds cis-**1** and cis-**3** was calculated to be 16.0 ± 0.6 and 11.8 ± 0.8 kcal/mol, respectively. The values of the thermodynamic parameters of the transition state ($\Delta H^{\neq}$, $\Delta S^{\neq}$, $\Delta G^{\neq}$) suggest that the inversion at phosphorus not only depends on the spatial requirements of the alkoxy substituent but also on entropic effects. The thermodynamic parameters ΔH^0, ΔS^0, and ΔG^0 were also evaluated and they show that the cis isomers are preferred from enthalpic point of view, but entropic effects dominate the equilibrium trans $\rightleftharpoons$ cis leading to the entropically favored trans isomers. Furthermore, the results are supported by density functional theory calculations of **1–4** at the B3LYP/6-31G** level.*

Keywords Inversion barrier at phosphorus; kinetic studies; thermodynamic parameters of the transition state; 1,3,2-dioxaphosholanes

INTRODUCTION

Organophosphorus ligands are important in inorganic and organic compounds, therefore their synthesis have become fundamental.[2] Some

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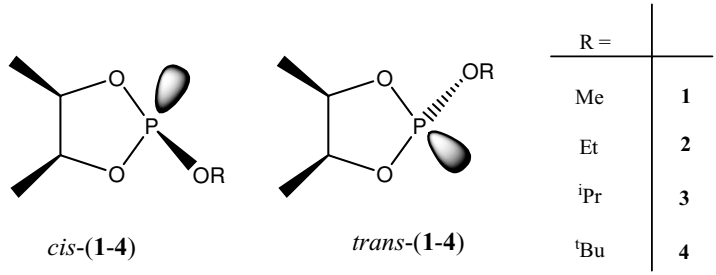
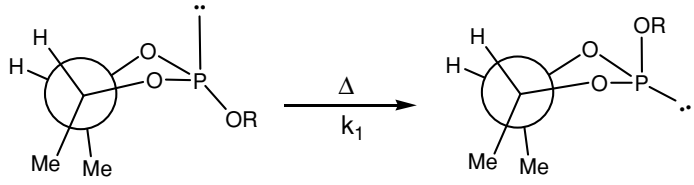


cis-(**1-4**) *trans*-(**1-4**)

FIGURE 1 Cyclic Phosphites **1–4** in their *cis* and *trans* configurations.

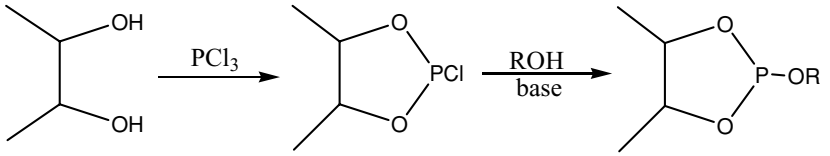
well-known reactions involve trivalent phosphorus intermediates, for example the conversion of alcohols to alkyl iodides via o-phenylen phosphorochloridites,[3a,b] or the conversion of 1,2-diols to *syn* olefins by the so–called Corey-Winter olefination.[3c,d] With regard to their applications, ready access to phosphotriester compounds has facilitated the automated synthesis of oligonucleotides with diverse and novel biological properties.[4] By the same token, chiral tripod ligands bearing cyclic phosphite donors are reagents in enantioselective catalysis.[5]

Studies related to the reactivity and physical properties of trivalent cyclic five- and six-membered ring phosphites focus on the conformational analysis of the heterocycle.[6,7] A cyclic five-membered ring phosphite (phospholane) is configurationally stable[8]; however, when the substituents at phosphorus are good leaving groups like Cl, OR, or NR_2, phospholanes are usually configurationally unstable.[9] Therefore, the synthesis of anancomeric phospholanes as those reported here (**1–4** in Figure 1) under normal conditions, frequently lead to mixtures of *cis* and *trans* isomers, where the *trans* isomer predominates. In addition, it has been reported that attempts to prepare the *cis* isomer, by methods that have been successful for six-membered phosphites, have failed for phospholanes since any approach essentially yield the same ratio of *cis/trans* isomers,[10] driven by thermodynamic control.



cis *trans*

SCHEME 1



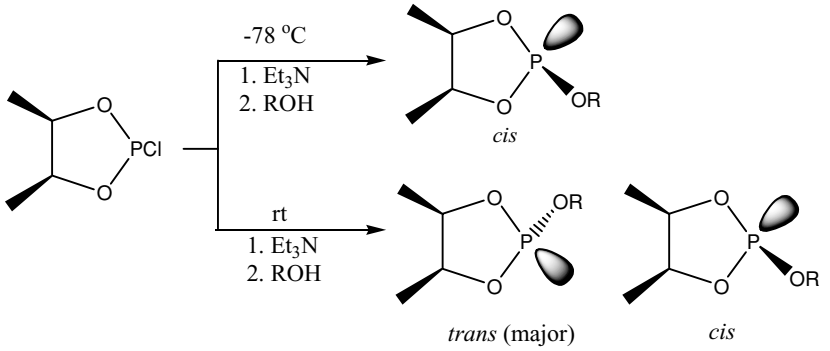
SCHEME 2

In this paper, we report the preparation of exclusive r-2-alkoxy-*c*4-*c*5-dimethyl-1,3,2-λ^3-dioxaphospholanes **1** and **3**, hereafter referred to as *cis*. The *cis*-to-*trans* isomerization was followed by kinetic measurements using ^{31}P NMR. The phosphorus inversion barrier ($\Delta G^{\neq}$) was calculated and compared with the barrier reported for *cis*-**2** Scheme 1.[1] The thermodynamic *cis*/*trans* ratios were also evaluated by ^{31}P NMR and rationalized by ab initio calculations.

RESULTS AND DISCUSSION

2-Alkyl substituted phosphites (**1**–**4**) were prepared from *meso*-2,3-butanediol and phosphorus trichloride, followed by the addition of the corresponding alkoxy group in a modification to the method described by Lucas et al[11] (Scheme 2).

By the addition of triethylamine to a solution of 2-chloro-4,5-dimethyl-1,3,2-λ^3-dioxaphospholane in toluene at –78°C, followed by a very sluggish and dropwise addition of the corresponding alcohol (MeOH or ^{i}PrOH), we were able to obtain the *cis* isomers in a yield better than 98% in relation to the *trans* isomers. On the other hand, rapid addition of the alcohol at room temperature leads to a mixture of the *cis* and *trans* isomers, where the *trans* isomer is the major product



SCHEME 3

(Scheme 3). As stated somewhere else for similar reactions,[6] the excess of alkoxide during the experiment can preclude isolation of *cis*-phosphites because of a highly favored second attack of the alkoxide ion on the in-situ formed *cis*-phosphites;, therefore, it might be due to the low solubility of ^{t}BuOH in toluene at –78°C that the *cis*-phosphite **4** was obtained in a maximum of 60% in the mixture of isomers. Therefore, a kinetic study of the epimerization of *cis*-**4** was not carried out.

Spectral Analysis

The assignment of the formula and stereochemistry of **1–4** was performed by a combination of ^{31}P, ^{1}H, and ^{13}C NMR spectroscopy as it has been reported by analog compounds.[12] Nevertheless, the *cis* isomers were epimerized to the thermodynamically stable *trans* isomers during isolation, therefore *cis* **1–4** isomers were only characterized by ^{31}P NMR. The ^{31}P NMR signal of the *cis* isomers is shifted downfield relative to the *trans* isomers (Table I) as it is observed for analog dioxaphospholanes.[10,12–16]

It is interesting to note from the data in Table I, that the ^{31}P NMR signal of phospholanes is upfield shifted on going from methoxy to *tert*-butoxy. The most significant shift difference is observed by changing the *iso*-propoxy group for the *tert*-butoxy group ($\Delta\delta^{31}P = 3.2$ ppm) while the shift differences OMe - OEt or OEt - O^{i}Pr are only of about 1 ppm. On the other hand, the ^{31}P NMR shifts for *trans* isomers only differ in about 1 ppm with no trend among them.[17]

Proton and C-13 NMR Analysis

The complete assignment and the backbone coupling constants of proton and carbon-13 signals of *trans* **1–4** are shown in Tables II and III, respectively. The chemical shift of H4,5 is around 4.5 ppm with vicinal $^{3}J_{HP}$ coupling constants of *ca.* 2 Hz for all the compounds, suggesting that the heterocycle adopts a twist-envelope conformation as

TABLE I ^{31}P NMR Chemical Shifts (in ppm) for Compounds 1–4 (in ppm) for Compounds 1–4

cpd	OR	*cis*	*trans*
1	OMe	149.7	137.0
2[a]	OEt	148.7	136.6
3	O^{i}Pr	147.6	137.1
4	O^{t}Bu	144.4	136.0

[a]Ref. 1.

TABLE II ^{1}H NMR Chemical Shifts (δ, in ppm) and Coupling Constants (J, in Hz) for Compounds *trans* 1–4

δ(J)	**1**	**2**	**3**	**4**
H4,5	4.43 ($J_{HH} = 6.3$) ($J_{HP} = 2.2$)	4.49 ($J_{HH} = 5.9$) ($J_{HP} = 2.6$)	4.54 ($J_{HH} = 5.1$) ($J_{HP} = 1.8$)	4.55 ($J_{HH} = 5.9$) ($J_{HP} = 2.0$)
Me	1.10 ($J_{HH} = 6.3$)	1.10 ($J_{HH} = 5.9$)	1.10 ($J_{HH} = 5.1$)	1.10 ($J_{HH} = 5.9$)
OCH_3	3.40 ($J_{HP} = 10.9$)	—	—	—
OCH_2CH_3	—	1.16 ($J_{HH} = 6.9$) 3.81 ($J_{HH} = 6.9$) ($J_{HP} = 8.6$)	—	—
$OCH(CH_3)_2$	—	—	1.22 ($J_{HH} = 6.2$) 4.35 ($J_{HH} = 6.2$) ($J_{HP} = 8.8$)	—
$OC(CH_3)_3$	—	—	—	1.39

TABLE III ^{13}C NMR Chemical Shifts (δ, in ppm) and Coupling Constants (J, in Hz) for Compounds *trans* 1–4

δ(J)	**1**	**2**	**3**	**4**
C4,5	75.0 ($J_{CP} = 7.9$)	74.2 ($J_{CP} = 7.7$)	73.8 ($J_{CP} = 6.6$)	73.4 ($J_{CP} = 7.7$)
Me	16.1 ($J_{CP} = 3.9$)	15.8 ($J_{CP} = 4.4$)	15.8 ($J_{CP} = 3.3$)	15.8 ($J_{CP} = 3.3$)
OCH_3	49.3 ($J_{CP} = 10.5$)	—	—	—
OCH_2CH_3	—	17.0 ($J_{CP} = 4.4$) 58.5 ($J_{CP} = 5.4$)	—	—
$OCH(CH_3)_2$	—	—	24.6 ($J_{CP} = 4.4$) 66.4 ($J_{CP} = 18.8$)	—
$OC(CH_3)_3$	—	—	—	31.1 ($J_{CP} = 8.8$) 75.5 ($J_{CP} = 8.8$)

observed in analog phosphites.[12,13] The methyl groups attached to C4,5 are characterized by possessing a small long-range coupling constant $^4J_{HP} < 1$ Hz. The methyl group in the exocyclic OR substituents are differentiated from those of the ring, by means of the chemical shift (for example in compound **1**) or multiplicity (for example in **2–4**). The $^3J_{HP}$ coupling constants of the R groups are of around 9–11 Hz; these values are substantially higher than $^3J_{HP}$ of C4,5. In ^{13}C NMR (Table III), the $^3J_{CP}$ coupling constants of the methyl groups at C4,5 are in the range 3.3–4.4 Hz supporting the suggested twist-envelope conformation. The chemical shift of the carbon directly bonded to the oxygen in the OR groups varies from around 50 to 75 ppm depending on the degree of substitution, the $^2J_{CP}$ coupling constant also varies however this variation is a result of the rotameric conformation of the R group.[13]

Kinetic Analysis

The preparation of nearly exclusive *cis* phosphites allowed us to study the thermal *cis*-to-*trans* isomerization shown in Scheme 1.

Attempts to isolate the *cis*-phosphites were unsuccessful; therefore, they were prepared in toluene that allows the kinetic study to be performed directly. The *cis/trans* ratio of each *cis*-2-alkoxy-1,3,2-dioxaphospholane derivatives **1** and **3** were quantified at different times by ^{31}P NMR from 50 to 80°C. Regression values ($R > 0.98$) of the straight lines observed for the plots ln c(*cis*) vs. time (about 10–18 data points), indicate that the epimerization process follows a first order kinetics, as observed for P-pyramidal inversion. The rate constants (k_1) of the processes were obtained from the slopes of the curves (Table IV).

The energy of activation (E_a) was calculated from Arrhenius plots (values of linear regression $R = 0.99$) and the frequency factor A from

TABLE IV Rate Constants and Half-Life Times for the Epimerization *cis*-to-*trans* of Compounds 1 and 3

Compound	Temp. (°C)	k_1 (s^{-1})10^4	$t_{1/2}$ (h)
1	60	1.48 ± 0.02	1.30
	65	2.29 ± 0.04	0.84
	70	3.12 ± 0.06	0.62
	80	6.0 ± 0.3	0.32
3	50	2.6 ± 0.1	0.74
	55	3.7 ± 0.1	0.52
	60	4.5 ± 0.1	0.43
	65	6.1 ± 0.3	0.32

TABLE V Activation Parameters for the Epimerization *cis*-to-*trans* of compounds 1–3; e.u. = 1 cal mol^{-1} K^{-1}

Compound	**1**	**2**[a]	**3**
ln A	15.5	19.8	10.2
E_a (kcal mol^{-1})	16.0 ± 0.6	19.1 ± 1.2	11.8 ± 0.8
$\Delta H^{\neq}$(kcal mol^{-1})	16.7 ± 0.3	19.5 ± 0.8	12.5 ± 0.5
$-\Delta S^{\neq}$(e.u.)[b]	30.0 ± 0.7	22.0 ± 2.2	40.5 ± 1.2
$\Delta G^{\neq}$(kcal mol^{-1})[b]	27.0 ± 0.4	26.9 ± 1.0	26.0 ± 0.6

[a]Ref. 1; and [b]at 60°C.

Equation (1) (Table V). The thermodynamic parameters of the transition state ($\Delta H^{\neq}$, $\Delta S^{\neq}$, $\Delta G^{\neq}$) were evaluated with Equations (2–4)[18] (see Table V).

$$k_1 = A\exp(-E_a/RT) \quad \text{or} \quad \ln k_1 = \ln A - (E_a/RT) \tag{1}$$

$$E_a = \Delta H^{\neq} - RT \tag{2}$$

$$\Delta S^{\neq} = 4.576 \log k_1 - 10.753 - \log T + E_a/(4.576\,T) \tag{3}$$

$$\Delta G^{\neq} = \Delta H^{\neq} - T\Delta S^{\neq} \tag{4}$$

It is interesting to compare our results with those obtained by Goldwhite,[8b] who found that analogous phosphochloridites undergo a rapid inversion of configuration at phosphorus through a bimolecular exchange mechanism (Figure 2). Nevertheless, later studies showed that the exchange was catalyzed by impurities (presumably free amine).[19]

The fact that an unknown substance can catalyze the epimerization process prompted us to perform some additional kinetic experiments for phosphites **1** and **3** in the presence of a pure sample of $Et_3HN^+Cl^-$, or triethylamine, or the corresponding alcohol. We observed that neither the ammonium chloride nor the free amine altered the epimerization rate, while adding a small amount of alcohol led to complete

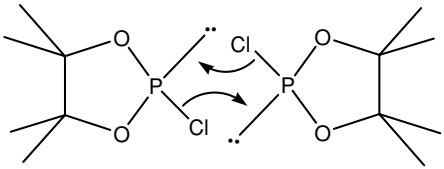


FIGURE 2 Bimolecular exchange mechanism at phosphorus in phosphochloridites.

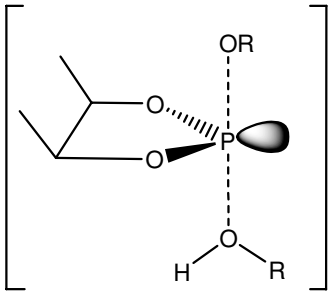


FIGURE 3 Proposed transition state for the catalyzed *cis*-to-*trans* epimerization.

isomerization of any of the *cis*-phosphites within less than 3 min. It is clear from these experiments that the kinetic data presented in Tables IV and V do not correspond to a catalyzed process.[20] However, a mechanism compatible with the alcohol catalyzed reaction is presented in Figure 3. The transition state resembles the one proposed for the epimerization of anancomeric six-membered *cis* phosphites.[6b,21]

Inasmuch as the pyramidal inversion obeys a first order kinetics, and since all of the examined phosphites have the same behavior, it was assumed that the epimerization process follows a unimolecular mechanism. The factors that mainly affect the magnitude of the inversion barrier are (a) steric effects, (b) conjugative and hyperconjugative effects, (c) angular constraint, and (d) the heteroatomic substitution adjacent to the inverting center.[22] In the studied series, we can exclude aspects of conjugative or hyperconjugative effects or consider them equal. All compounds have three oxygen atoms connected to phosphorus; thus, there is no reason to consider angular constraints significantly different among the compounds. Therefore, it is considered that the inversion barrier depends mainly on steric effects. Indeed as expected, derivative **3** with a branched substituent, has the smallest activation barrier of all (Table IV); however, somewhat at odds, the activation barrier of compound **1** is smaller than that of compound **2** for about 3 kcal/mol.[23] The $\Delta G^{\neq}$ values (Table V) differ only slightly (26–27 kcal/mol) for **1**–**3**, even though changes in $\Delta H^{\neq}$ are substantial and follow the same trend than E_a. It is clear from the data that modifications of the reaction rate are reflected in the energy term E_a. The enthalpy $\Delta H^{\neq}$ is compensated by a large and unfavorable negative entropy of activation ($\Delta S^{\neq}$) whose absolute values are in the range of about 20 to 40 entropy units. This means that on going from the ground to the transition state, an extensive restriction in the degrees of freedom

TABLE VI Free Energy (ΔG_0) kcal mol^{-1} for the Configurational Equilibria *trans* ⇌ *cis* in Phosphites 1–3

T (°C)	cpd **1**	cpd **2**	cpd **3**
40	—	—	0.97 ± 0.03
45	—	—	1.08 ± 0.04
50	—	1.11 ± 0.11	1.13 ± 0.02
55	0.99 ± 0.03	1.15 ± 0.02	1.29 ± 0.04
60	1.04 ± 0.01	1.21 ± 0.01	1.36 ± 0.10
65	1.19 ± 0.07	1.21 ± 0.02	1.49 ± 0.04
70	1.32 ± 0.02	1.29 ± 0.03	—
75	1.32 ± 0.02	1.34 ± 0.01	—
80	1.38 ± 0.01	—	—

must be considered; alternatively, an ionic transition state might be invoked.[24]

It is also important to note that all $\Delta G^{\neq}$ values are smaller than those determined for the inversion process of *cis*–to-*trans*-4-*tert*-butyl-1-phenylphosphorinane (53.7 kcal/mol at temperatures between 145-180°C),[25] and similar to the epimerization barrier of the chlorodioxaphospholane of Figure 2, which was calculated to be of 19.4 kcal/mol at 100°C,[26] following a bimolecular exchange mechanism.[8b] On the other hand, in several chiral acyclic phosphines the pyramidal inversion at phosphorus follows a first order kinetics, with barriers ($\Delta G^{\neq}$)at 130°C in the range of 29–36 kcal/mol.[27]

Thermodynamic Analysis

In order to obtain additional information about the energetic profile observed for *cis*-to-*trans* epimerization of **1–3**, the thermodynamic parameters (ΔG^0, ΔH^0, ΔS^0) were evaluated and are shown in Tables VI and VII. The ΔG^0 values were calculated from samples at equilibrium conditions by using Gibbs equation $\Delta G^0 = -RT \ln K_{eq}$ for the equilibrium *trans*⇌ *cis*. The van't Hoff curves obtained by plotting $\ln K_{eq}$ vs. T^{-1} (temperature) show straight lines with the slope being $-\Delta H^0/R$ and the intercept $\Delta S^0/R$ (regression values $R > 0.97$). The values of ΔG^0 for compounds **1–3** are positive indicating that the *trans* isomers are favored in all cases. The trend in ΔG^0 indicates that the thermodynamic of the epimerization process is driven by the steric demand of the substituents at phosphorus atom (i.e., at 60°C, ΔG^0 for **1–3** are 1.04, 1.21, and 1.36 kcal/mol correspondingly).[28] The ΔH^0 values (Table V) show

TABLE VII Enthalpy ΔH^0 kcal mol^{-1} and Entropy ΔS^0e.u. for the Configurational Equilibria *trans* ⇌ *cis* in Phosphites 1–3

Compound	$-\Delta H^0$(kcal mol^{-1})	$-\Delta S^0$(e.u.)
1	4.38 ± 0.51	16.4 ± 1.7
2	2.38 ± 0.22	10.7 ± 0.8
3	5.49 ± 0.40	20.6 ± 1.4

that the *cis*-phosphites are more favored than the *trans* isomers by enthalpy, this result was not expected, considering that stereoelectronic effects favor the *trans* isomers.[29,30] Thus, the isomerization *cis*-to-*trans* is determined by an entropic effect ($-\Delta S^0$) that favors the *trans* isomer in the equilibrium. These results would be explained by a restraint of the rotation of the P-O (alkoxy substituent) bond in the *cis*-form, as suggested by ab initio calculations (*vide infra*).

Computational Results

Geometries were optimized with density functional Becke3LYP theory and 6-31G** basis set using the GAUSSIAN 92 program.[31] The energies obtained from the optimization of at least two rotamers of compounds

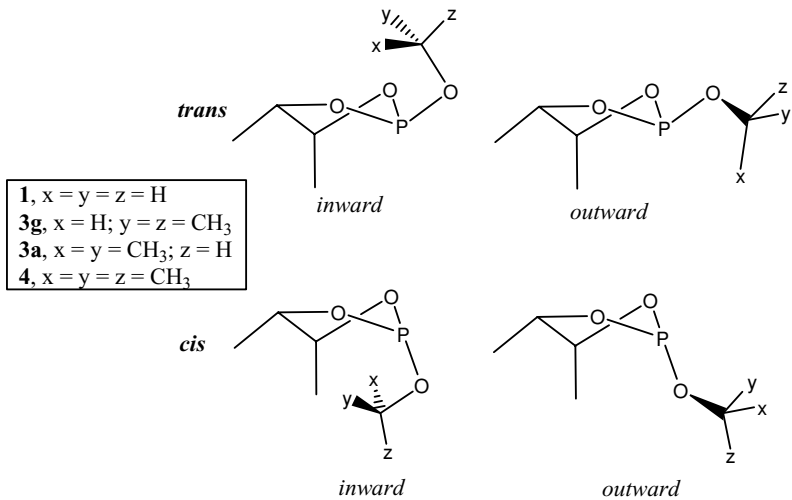


FIGURE 4 Optimized geometries of phosphites 1, 3, and 4 from B-3LYP/6-31G** calculations.

TABLE VIII Calculated B-3LYP/6-31 G Energies, in Hartrees,[a,b] of Phosphites 1, 3, and 4 in Several Conformations**

cpd	Inward	Outward
1-*trans*	–764.23420 (–2.09)	–764.23363 (–1.73)
1-cis	–764.23087 (0)	–764.23239 (–0.95)
3g-*trans*	–842.87755 (–7.52)	–842.87814 (–7.92)
3a-*trans*	–842.87067 (–3.23)	–842.87449 (–5.63)
3g-*cis*	–842.87386 (–5.23)	–842.87682 (–7.09)
3a-*cis*	–842.86552 (0)	–842.87174 (–3.90)
4-*trans*	–882.19067 (–3.17)	–882.19506 (–5.92)
4-*cis*	–882.18562 (0)	–882.19220 (–4.13)

[a]In parentheses ΔE in kcal/mol (ΔE = Ecpd – Ecpd underlined, for each series); and [b]1 hartree = 627.51 kcal/mol.

1 and **4**, and 4 rotamers for **3** in their *cis* and *trans* configurations (Figure 4), are given in Table VIII.

Calculations of *inward* and *outward* conformations were performed to estimate the steric and stereoelectronic effects, as well as to account for the entropy contribution to the stabilization of the *trans*-phosphites.

Data on Table VIII show that the *cis-inward* conformation has the highest energy suggesting that this conformation is not stable for any phosphite. Analysis of the non-bonded interactions allowed us to conclude that in this conformation the substituent has severe steric interactions with the atoms of the ring, especially in the case of **4** as it would be expected. In order to calculate the entropy contribution for **1** and **4**, nine rotameric conformations were considered for the *trans*-isomers (three *inward* and six isoenergetic *outward* conformations) and only six for the *cis*-isomers. The *trans* $\rightleftharpoons$ *cis* equilibria for **1** and **4** is shifted to the *trans* isomer for at least 0.27 kcal/mol [RTln(9/6) at 60°C as a result of the entropy contribution. On the other hand, phosphite **3** has two **3g** and one **3a** rotamers for each *inward* and *outward* conformations (Figure 6). Since only the **3a-***cis* rotamer is unfavorable by steric interactions, a lower contribution of entropy than that for **1** and **4** is expected for the thermodynamic equilibrium of **3** [RTln (9/8) = 0.08 kcal/mol at 60°C.

CONCLUSION

The exclusive synthesis of the thermodynamically unstable *r*-2-alkoxy-*c*4-*c*5-dimethyl-1,3,2λ^3-dioxaphospholanes *cis*-**1** and *cis*-**3** was achieved. The *cis* compounds were thermally equilibrated to the more

stable *trans* isomers. The spectral characteristics of the *trans* compounds are discussed in detail for to validate the proposed formulas. The kinetic studies of the *cis*-to-*trans* epimerization were followed by ^{31}P NMR. The inversion processes follows a first order kinetics. The E_a of the inversion barrier at phosphorus for compounds **1**–**3** is in the range of 11–19 kcal/mol. The inversion barrier depends mainly on steric effects, thus derivative **3** substituted with O^iPr group has the lowest activation barrier (E_a = 11.8 kcal mol^{-1}). The $\Delta G^{\neq}$ values for **1**–**3** are similar among them (26–27 kcal mol^{-1}). The enthalpy $\Delta H^{\neq}$ is compensated by a large and negative entropy of activation ($\Delta S^{\neq}$) with values in the range of about 20 to 40 entropy units, meaning that on going from the ground to the transition state, there is a considerable lost of degrees of freedom. Furthermore, ΔG^0 values for *trans* $\rightleftharpoons$ *cis* equilibrium of **1**–**3** indicate that the *trans* isomers are favored. The equilibrium is driven by the steric demand of the substituents at phosphorus (i.e., at 60°C, ΔG^0 for **1**–**3** are 1.04, 1.21, and 1.36 kcal/mol correspondingly). The ΔH^0 and ΔS^0 were calculated from van't Hoff curves; *cis* isomers are favored by enthalpy, however entropy favors *trans* isomers. Ab initio calculations also indicate that the *cis*-to-*trans* epimerization of phospholanes **1**–**3** is driven mainly by entropy.

EXPERIMENTAL

Spectral Analyses

^1H and ^{13}C NMR were measured in $CDCl_3$ at 270 and 67.5 MHz, respectively, and are referenced to internal TMS. The ^{31}P NMR spectra were recorded in toluene at 109.25 MHz and are reported in ppm downfield from external 85% H_3PO_4.

Kinetic and Thermodynamic Measurements

First-order rate constants for the *cis*-to-*trans* epimerization of **1**–**3** were determined by the change in the ratio of the isomers quantified by integration of their corresponding ^{31}P NMR signals. The acquisition parameters were as follows: PD = 0.1 s, PW1 = 6.0 s, Acq. time = 396 ms, SW = 41.3 kHz, data points = 200–250. A pulse delay of 0.1 s was considered to be a good compromise between the recording time and reliability on integration. A test experiment with a pulse delay of 0.6 s gave no change in integration. The kinetic data were recorded in the time interval of around 3 min at 80°C and around 10 min at 60°C for compound **1**. The time intervals were from 7 to 10 min for **3**. In the treatment of the data, the errors were calculated using a

linear regression program. The equilibrium constants were obtained from the unchanged ratio of the isomers at the end of the kinetic experiments.

Synthesis

All experiments were carried out under anhydrous conditions by using dry argon. Solvents and alcohols were dried by standard procedures, distilled and stored under argon. *meso*-2,3-Butanodiol (97%) was purchased from Aldrich and used without further purification. Phosphites *cis*-(**1** and **3**) were epimerized in crude form since attempts to isolation failed because they are sensitive to humidity. These samples contained no starting material, however, decomposition products 2-hydro-2-oxo-1,3,2λ^5-dioxaphospholanes[20] and phosphoric acid were observed as byproducts in percentages up to 10%. The ^{1}H and ^{13}C NMR data for the *trans* phosphites **3** and **4** were taken after distillation of the crude products. The NMR data for phosphites **1** and **2** are in accordance to that reported in the literature.[1,13]

r-2-Chloro-t4-t5-dimethyl-1,3,2-λ^3-dioxaphospholane (5)[10]

To a solution of 2.54 g (28.18 mmol) of *meso*-2,3-butanediol in 15 mL of CH_2Cl_2, set in an ice-bath, was added 3.87 g (28.18 mmol) of PCl_3. When the addition was complete the solution was stirred for additional 20 min while reaching ambient temperature. After removing the solvent, a short-path distillation at 32°C/2 mm Hg or 52°C/8 mm Hg, (66°C/15 mm Hg) gave 3.52 g (81%) of the product as a colorless, fuming liquid. ^{31}P NMR δ 168.2 ppm; ^{1}H NMR δ 1.26 (d, 6H, Me, $J_{HH} = 6.1$ Hz), 4.79 (m, 2H, OC<u>H</u>); ^{13}C NMR δ 15.6 (s, Me), 76.5 (d, CH, $J_{CP} = 8.3$ Hz).

*r-2-Methoxy-c4-c5-dimethyl-1,3,2-λ^3-dioxaphospholane (***cis-*1)

To a solution of 0.26 g (1.68 mmol) of **5** in 30 mL of toluene at –78°C under argon was added 0.23 mL (1.68 mmol) of Et_3N. Methanol 0.07 mL (1.68 mmol) was then added dropwise with a syringe over 20 min. After the mixture reached ambient temp., the triethylammonium chloride was filtered off and 0.70 mL of the solution were passed into nmr-tubes and sealed with a cap and parafilm. ^{31}P NMR δ 149.7 ppm (cis).

*r-2-Methoxy-t4-t5-dimethyl-1,3,2-λ^3-dioxaphospholane (***trans-*1)[13]

^{31}P NMR δ 137 ppm (this work), δ 132.5 ppm[13]; ^{1}H NMR δ 1.10 (d, 6H, Me, $J_{HH} = 6.3$ Hz, $J_{HP} = 0.5$ Hz), 3.4 (d, 3H, OC<u>H</u>$_3$ $J_{HP} = 10.9$ Hz), 4.43 (dq, 2H, CH, $J_{HH} = 6.3$ Hz, $J_{HP} = 2.2$ Hz); ^{13}C NMR δ 16.1 (d, Me,

J_{CP} = 3.9 Hz), 49.3 (d, O<u>C</u>H$_3$, J_{CP} = 10.5 Hz), 75.0 (d, CH, J_{CP} = 7.9 Hz).

*r2-Ethoxy-c4-c5-dimethyl-1,3,2-dioxaphospholane (***cis***-2)*[1]

^{31}P NMR δ 148.7 ppm.

*r2-Ethoxy-t4-t5-dimethyl-1,3,2-dioxaphospholane (***trans***-2)*[1]

^{31}P NMR δ 136.6 ppm; ^{1}H NMR δ 1.11 (d, 6H, Me, J_{HH} = 5.9 Hz, J_{HP} < 0.7 Hz), 1.16 (t, 3H, OCH$_2$C<u>H</u>$_3$, J_{HH} = 6.9 Hz, J_{HP} < 0.7 Hz), 3.81 (dq, 2H, OC<u>H</u>$_2$CH$_3$, J_{HH} = 6.9 Hz, J_{HP} = 8.6 Hz), 4.49 (m, 2H, CH, J_{HH} = 5.9 Hz, J_{HP} = 2.6 Hz); ^{13}C NMR δ 15.8 (d, Me, J_{PC} = 4.4 Hz), 17.0 (d, OCH$_2$<u>C</u>H$_3$, J_{PC} = 4.4 Hz), 58.5 (d, O<u>C</u>H$_2$CH$_3$, J_{CP} = 5.4 Hz), 74.2 (d, CH, J_{PC} = 7.7 Hz).

r-2-iso-Propoxy-c4-c5-dimethyl-1,3,2-λ^3*-dioxaphospholane (***cis***-3)*

To a solution of 0.28 g (1.81 mmol) of **5** in 20 mL of toluene at –78°C under argon was added 0.31 mL (1.81 mmol) of Et$_3$N. *iso*-Propanol 0.14 mL (1.81 mmol) was then added dropwise with a syringe over 20 min. After the mixture reached ambient temp., the triethylammonium chloride was filtered off and 0.70 mL of the solution were passed into NMR-tubes and sealed with a cap and parafilm. ^{31}P NMR δ 147.6 ppm.

r-2-iso-Propoxy-t4-t5-dimethyl-1,3,2-λ^3*-dioxaphospholane (***trans***-3)*

A sample of *cis*-**3** was distilled under vacuum (38°C/1 Torr) to give a pure sample of *trans*-**3** isomer. ^{31}P NMR δ 137.1 ppm; ^{1}H NMR δ 1.18 (d, 6H, Me, J_{HH} = 5.1 Hz, J_{HP} < 0.4 Hz), 1.22 (d, 6H, OCH(C<u>H</u>$_3$)$_2$ J_{HH} = 6.2 Hz, J_{HP} < 0.4 Hz), 4.35 (m, 1H, OC<u>H</u>(CH$_3$)$_2$, J_{HH} = 6.2 Hz, J_{HP} = 8.8 Hz), 4.54 (dq, 2H, CH, J_{HH} = 5.1 Hz, J_{HP} = 1.8 Hz); ^{13}C NMR δ 15.8 (d, Me, J_{CP} = 3.3 Hz), 24.6 (d, OCH(<u>C</u>H$_3$)$_2$, J_{CP} = 4.4 Hz), 66.4 (d, O<u>C</u>H(CH$_3$)$_2$, J_{CP} = 18.8 Hz), 73.8 (d, CH, J_{CP} = 6.6 Hz).

2-tert-Butoxy-4-5-dimethyl-1,3,2-λ^3*-dioxaphospholane (4) (mixture of isomers)*

To a solution of 0.31 g (2.01 mmol) of **5** in 20 mL of toluene at –78°C, was added 0.28 mL (2.01 mmol) of Et$_3$N. After the addition was complete, 0.19 mL (2.01 mmol) of *tert*-butanol in 0.80 mL toluene was added dropwise with a syringe over 30 min. The mixture let to reach ambient temperature, and the resultant triethylammonium chloride was filtered off. The ^{31}P NMR spectrum showed two signals in a 60/40

ratio corresponding to the *cis* and *trans* isomer respectively.^{31}P NMR δ 144.4 ppm (*cis*), and 136.0 ppm (*trans*).

*2-tert-Butoxy-t4-t5-dimethyl-1,3,2-λ^3-dioxaphospholane (**trans-4**)*

The mixture of isomers of compound **4** was distilled under vacuum (44°C/1 Torr) to give exclusively *trans*-**4**. ^{31}P NMR δ 136.0 ppm; ^{1}H NMR δ 1.18 (d, 6H, Me, $J_{HH} = 5.9$ Hz, $J_{HP} < 0.7$ Hz), 1.39 (s, 9H, OC($C\underline{H}_3$)$_3$), 4.55 (m, 2H, C$\underline{H}$, $J_{HH} = 5.9$ Hz, $J_{HP} = 2.0$ Hz); ^{13}C NMR δ 15.8 (d, Me, $J_{CP} = 3.3$ Hz), 31.1 (d, OC($\underline{C}H_3$)$_3$, $J_{CP} = 8.8$ Hz), 73.4 (d, CH, $J_{CP} = 7.7$ Hz), 75.5 (d, C(CH_3)$_3$, $J_{CP} = 8.8$ Hz).

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