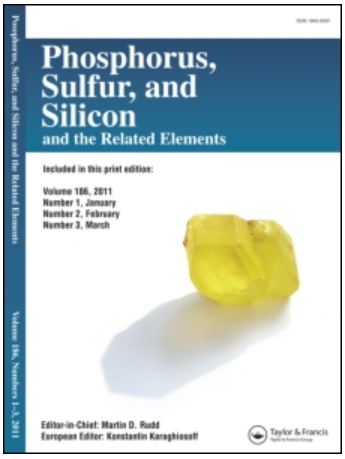

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Synthesis and Study of the Thermal Epimerization of r -2-Ethoxy- cis -4- cis -5-Dimethyl-1,3,2-λ 3 -Dioxaphospholane Using 31 P NMR

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SYNTHESIS AND STUDY OF THE THERMAL EPIMERIZATION OF *r*-2-ETHOXY-*cis*-4-*cis*-5-DIMETHYL-1,3,2-λ^3-DIOXAPHOSPHOLANE USING ^{31}P NMR

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The exclusive synthesis of r-*2-ethoxy-* cis-*4-* cis-*5-dimethyl-1,3,2-*λ^3-*dioxaphospholane (*cis-***1***) is reported. The kinetic measurements of the epimerization of* cis-***1*** *to* trans-***1*** *were performed by* ^{31}*P NMR from 50 to 80°C in toluene. The energy of activation (*E_a*) of the epimerization process was calculated from Arrhenius plot. The thermodynamic parameters of the transition state led us to conclude that the activation barrier of the inversion at phosphorus is driven by the enthalpy and by a large and negative entropy of activation.*

Keywords: 1,3,2-λ^3-dioxaphospholanes; inversion at phosphorus; kinetic studies; synthesis; thermodynamic parameters of the transition state

INTRODUCTION

Multinuclear NMR spectrometers have eliminated the serious limitation to the widespread utilization of phosphorus NMR due to the low sensitivity of phosphorus nucleus (0.066) as compared to proton nucleus.

Therefore nowadays ^{31}P NMR spectroscopy is largely applied to the characterization and the study of reactions of a great variety of phosphorus compounds.[1–2]

The triply-connected phosphorus atom is a highly-reactive center. Some well known reactions using trivalent phosphorus compounds

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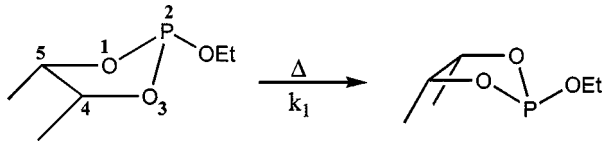

cis-**1** *trans*-**1**

FIGURE 1 The thermal equilibration of five membered ring phosphite **1**.

are the Arbuzov- and Wittig- reactions.[3] Moreover, substitution reactions at tricoordinate phosphorus have been exploited in oligonucleotide synthesis,[4–5] since they present attractive alternatives in the phosphotriester approach.[6]

Among cyclic trivalent phosphorus compounds, phosphites have been the subject of intensive investigation.[7–10] From these studies it is well known that five membered ring *cis* phosphites are not configurationally stable; therefore, the synthetic approaches to obtain them have led, unavoidably, to mixtures of *cis* and *trans* isomers wherein the *trans* isomer predominates.[11–13]

This work reports on the exclusive synthesis of *r*-2-ethoxy-*cis*-4-*cis*-5-dimethyl-1,3,2-dioxaphospholane (*cis*-**1**) (Figure 1) and the kinetic studies of its epimerization to the *trans* isomer.

RESULTS AND DISCUSSION

The synthesis of *cis*-**1** was carried out by the addition of triethylamine to a solution of *r*-2-chloro-*trans*-4-*trans*-5-dimethyl-1,3,2-λ^3-dioxaphospholane **2** in toluene at -78°C, followed by a very sluggish and dropwise addition of dry ethanol. Assignments of stereochemistry of *cis*-**1** and *trans*-**1** have been performed by ^{31}P, ^{1}H, and ^{13}C NMR spectroscopy.[14–18] In ^{31}P NMR spectra, the signal for the *cis* isomer is shifted downfield relative to the *trans* isomer [*cis*-**1**, 148.7 ppm; and *trans*-**1** 136.6 ppm].

This behavior can be explained by the δ-effect which results from the *syn* interaction between the ethoxy substituent at phosphorus and the ring methyl-groups at C_4 and C_5.

The kinetic studies of the epimerization of *cis*-**1** to *trans*-**1** were performed by ^{31}P NMR spectroscopy from 50 to 80°C in toluene. The measurements were carried out by quantifying the area ratio of the ^{31}P NMR signals for the *cis* and *trans* isomers at various times and at 6 different temperatures. Plotting the data points (about 10–18 data points) for each kinetic curve in the form ln c(*cis*) vs. time (see an example in Figure 2b), we obtained straight lines with good values of

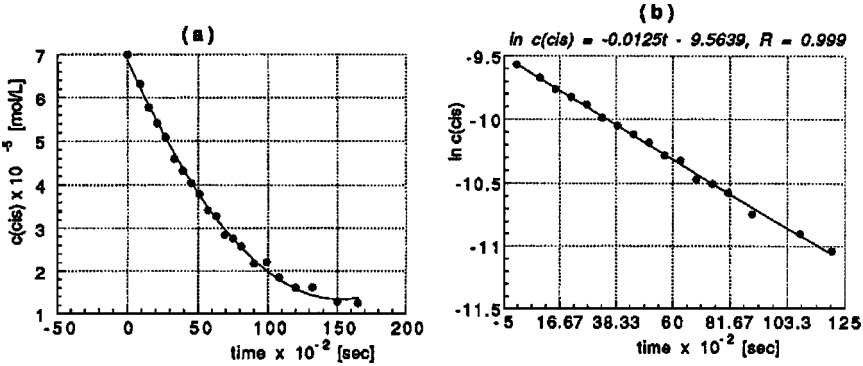

FIGURE 2 The epimerization *cis*-**1** to *trans*-**1** at 60°C: (a) kinetic curve; (b) first order treatment of the kinetic curve.

regression ($R > 0.98$), indicating that the isomerization experiments follow a first order kinetics for inversion at phosphorus. The rate constants (k_1) of the process were obtained from the slopes of the curves (Table I).

According to Eq. 1, a semilogarithmic plot of the rate constants k_1 against the inverse of temperature gave a straight line (Arrhenius plot). The energy of activation (E_a) of the *cis*-to-*trans* epimerization was calculated from the slope of the line and the frequency factor A from Eq. 1 (Table II). The thermodynamic parameters of the transition state ($\Delta H^{\ddagger}$, $\Delta S^{\ddagger}$, $\Delta G^{\ddagger}$) were evaluated with Eqs. 2–4[3] (see Table II).

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

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

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

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

TABLE I Rate Constants and Half-Life Times for the Epimerization *cis*-to-*trans* of Compound **1**

Compound	Temp. (°C)	k_1 (s^{-1})10^4	$t_{1/2}$ (h)
1	50	0.45 ± 0.01	4.28
	55	1.00 ± 0.01	1.93
	60	1.20 ± 0.02	1.60
	65	1.90 ± 0.03	1.01
	70	2.70 ± 0.06	0.71
	75	4.3 ± 0.1	0.45

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

Activation parameters	Compound **1**
ln A	19.8
E_a (kcal mol^{-1})	19.1 ± 1.2
$\Delta H^{\ddagger}$ (kcal mol^{-1})	19.5 ± 0.8
$-\Delta S^{\ddagger}$ (e.u.)[a]	22.0 ± 2.2
$\Delta G^{\ddagger}$ (kcal mol^{-1})[a]	26.9 ± 1.0

[a]at 60°C.

According to Table II, the activation barrier of the epimerization process is not only driven by the enthalpy ($\Delta H^{\ddagger} = 19.5$ kcal/mol), but also for unfavorable entropy of activation ($\Delta S^{\ddagger} = -22.0$ e. u.). The large and negative entropy of activation indicates that on going from the ground to the transition state, an extensive restriction in the degrees of freedom must be considered.

CONCLUSION

The synthesis of pure anancomeric *r*-2-ethoxy-4-*cis*-5-*cis*-λ^3-1,3,2-dioxaphospholane was achieved. The kinetic studies of the epimerization *cis*-**1** to *trans*-**1** led us to conclude that the process took place through phosphorus inversion. The barrier has an energy of activation of around 19 kcal/mol, a value which is closer to the barrier found in five membered ring phospholes (16 kcal/mol) than to the one found in five membered ring phosphines (38 kcal/mol).[19,20]

EXPERIMENTAL SECTION

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 Measurements

First-order rate constants for the *cis*-to-*trans* epimerization of **1** were determined by the change in the ratio of the isomers with time, and quantified by integration of their corresponding ^{31}P NMR signals. The

acquisition parameters were as follows: PD = 0.1 s, PW1 = 6.0 μs, 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 7 to 15 min. In the treatment of the data, the errors were calculated using a linear regression program.

Synthesis

All experiments were carried out under anhydrous conditions by using dry argon. Solvents and ethanol were dried by standard procedures, distilled and stored under argon. *meso*-2,3-Butanodiol (97%) was purchased from Aldrich and used without further purification. Phosphite *cis*-**1** was epimerized in crude form since attempts at isolation failed because of its sensibility to humidity.[7] The sample contained no starting material. The ^{1}H and ^{13}C NMR data for *trans*-**1** were taken after distillation of the crude material.

r-*2-Chloro*-trans-*4*-trans-*5-dimethyl-1,3,2-*λ^3-*dioxaphospholane (2)*[16]

To a solution of 2.54 g (28.2 mmol) of *meso*-2,3-butanediol in 15 mL of CH_2Cl_2, set in an ice bath, was added 3.87 g (28.2 mmol) of PCl_3. When the addition was completed the solution was stirred for additional 20 min while reaching ambient temperature. After removing the solvent, a short-path distillation gave at 32°C/2 mm Hg or 52°C/8 mm Hg, (66°C/15 mm Hg[10]) 3.52 g (81%) of the product as a colorless, fuming liquid. $\delta^{31}P = 168.2$ ppm.

r-*2-Ethoxy*-cis-*4*-cis-*5-dimethyl-1,3,2-*λ^3-*dioxaphospholane (1)*

To a solution of 0.34 g (2.20 mmol) of **2** in 20 mL of toluene at −78°C under argon was added 0.31 mL (2.20 mmol) Et_3N. Ethanol 0.13 mL (2.20 mmol) was then added drop wise with a syringe over 20 min. After the mixture reached ambient temperature, the triethylammonium chloride was filtered off and NMR tubes were filled via a syringe with 0.7 mL of the solution, and sealed with a cap and parafilm. $\delta^{31}P = 148.7$ ppm.

r-*2-Ethoxy*-trans-*4*-trans-*5-dimethyl-1,3,2-λ*^{3}-*dioxaphospholane (2)*

A sample of *cis*-**2** was distilled under vacuum (34°C / 2 Torr) to give a pure sample of *trans*-**2** isomer. ^{1}H NMR: δ 1.11 (d, 6H, Me, J_{HH} = 5.9 Hz, J_{HP} < 0.7 Hz), 1.16 (t, 3H, $OCH_2C\underline{H}_3$, J_{HH} = 6.9 Hz, J_{HP} < 0.7 Hz), 3.81 (dq, 2H, $OC\underline{H}_2CH_3$, 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, $OCH_2\underline{C}H_3$, J_{PC} = 4.4 Hz), 58.5 (d, $O\underline{C}H_2CH_3$, J_{CP} = 5.4 Hz), 74.2 (d, CH, J_{PC} = 7.7 Hz).

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REFERENCES

[1] L. D. Quin and J. G., Verkade Phosphorus-31 NMR Spectral Properties in *Compound Characterization and Structural Analysis* (VCH Publishers, New York, pp. 1–101. 1994).
[2] D. G. Gorenstein, *Progress in NMR Spectroscopy*, **16,** 1197 (1983).
[3] J. March, *Advanced Organic Chemistry* (Wiley, New York, 1985), 3rd. ed., pp. 845-fol.
[4] R. L. Letsinger, E. P. Groody, and T. Tanaka, *J. Am. Chem. Soc.*, **104,** 6805 (1982).
[5] M. D. Matteucci and M. H. Caruthers, *J. Am. Chem. Soc.*, **103,** 3185 (1981).
[6] M. J. Gait, H. W. D. Matthes, M. Singh, and R. C. Thomas, *J. Chem. Soc., Chem. Commun.*, 37 (1982).
[7] B. Gordillo, C. Garduño, G. Guadarrama, and J. Hernández, *J. Org. Chem.*, **60,** 5180 (1995).
[8] P. Haake, J. P. McNeal, and E. J. Goldsmith, *J. Am. Chem. Soc.*, **90,** 715 (1968).
[9] R. H. Cox and M. G. Newton, *J. Am. Chem. Soc.*, **94,** 4212 (1972).
[10] R. H. Cox, B. S. Campbell, and M. G. Newton, *J. Org. Chem.*, **37,** 1557 (1972).
[11] H. Goldwhite, *Chem. Ind.* (London), 494 (1964).
[12] B. Fontal and H. Goldwhite, *Tetrahedron*, **22,** 3275 (1966).
[13] J. Nielsen and O. Dahl, *J. Chem. Soc., Perkin Trans. II*, 553 (1984).
[14] M. J. Gallagher, *Stereochemical Analysis* (VCH Publishers, Deerfield Beach, FL, 1987), pp. 308-fol.
[15] W. G. Bentrude and H.-W. Tan, *J. Am. Chem. Soc.*, **98,** 1850 (1976).
[16] D. Z. Denney, G. Y. Chen, and D. B. Denney, *J. Am. Chem. Soc.*, **91,** 6838 (1969).
[17] G. Ponchoulin, J. R. Llinas, G. Buono, and E. J. Vincent, *J. Org. Magn. Reson.*, **8,** 518 (1976).
[18] D. Besserre and S. Coffi-Nketsia, *Org. Magn. Reson.*, **13,** 313 (1980).
[19] J. B. Lambert, *Top. Stereochem.*, **6,** 19 (1971).
[20] A. Rauk, L. C. Allen, and K. Mislow, *Angew. Chem. Int. Ed. Ingl.*, **9,** 400 (1970).