Optically Active Spirophosphoranes. Part VI.[1] Kinetics of Epimerization of the Chiral Skeleton Unit

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The diastereoisomeric spirophosphoranes (1M) and (1P) possess two elements of chirality, an optically active ligand derived from (+)-pseudoephedrine and the (±)-phospha^{V}spirononane system. The rates of epimerization of these compounds were obtained from a pure diastereoisomer [very likely (1M)] isolated by crystallization using the polarimetric kinetic method. Activation parameters at 278 K are: for (1M) ———➤ (1P); $\Delta G_1^{\ddagger} = 21\cdot44$ kcal mol^{-1}, $\Delta H_1^{\ddagger} = 19\cdot8$ kcal mol^{-1}, $\Delta S_1^{\ddagger} = -5\cdot7$ cal K^{-1}; for (1P) ———➤ (1M) $\Delta G_{-1}^{\ddagger} = 21\cdot10$ kcal mol^{-1}, $\Delta H_{-1}^{\ddagger} = 19\cdot4$ kcal mol^{-1}, $\Delta S_{-1}^{\ddagger} = -5\cdot9$ cal K^{-1} mol^{-1}. These results, compared with those obtained previously for (2M) ———➤ (2P), show that the change in the rate constant of epimerization can be large (133 : 1) even though the atoms surrounding phosphorus are the same. Comments on the possible structure of the transition state are presented.

INTRAMOLECULAR ligands can exchange positions around a pentaco-ordinate atom, not only in metal complexes,[2,3] but also in pentacovalent phosphorus derivatives.[4,5] Non-rigid pentaco-ordinate geometry was demonstrated essentially by dynamic n.m.r. spectroscopy.

In previous Parts,[1,6] we have shown that the availability of optically active spirophosphoranes offers a promising approach for the study of molecular stereolability by mutarotation: a second example is presented here to advance the understanding of the mechanism of pseudorotation processes.

RESULTS

(4′S,5′S)-4′,5′-Dihydro-3′,4′-dimethyl-5′-phenylspiro-(1,3,2-benzoxazaphos^{V}phole-2,2′-[1,3,2]-oxazaphos^{V}phole) (1) was prepared from o-aminophenol hydrochloride and (4S,5S)-2-dimethylamino-4-methyl-5-phenyl-1,3,2-oxazaphospholan derived from (+)-pseudoephedrine. The presence in the molecule of the additional chiral unit, the M or P helix, introduces the possibility of diastereoisomerism.

(1M)   (1P)
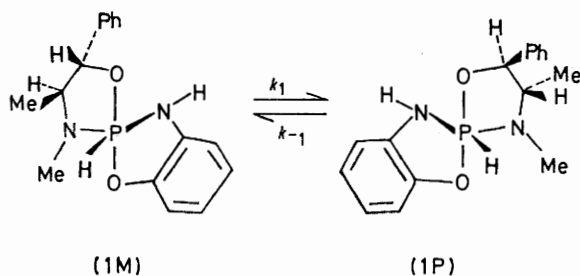
For this reason, the synthesis of (1) leads to the mixture of (1M) and (1P) in solution. Slow crystallization is accompanied by a second-order asymmetric transformation,[1,6,7] only one of the two isomers crystallizes, and as crystallization proceeds, the mobile equilibrium between (1M) and (1P) is displaced so that all the crystalline material is composed of a single epimer. We will give arguments leading to the assignment of structure (1M) for this epimer later. When these crystals are dissolved at room temperature in benzene, epimerization is rapid with an apparent half-time of reaction of ca. 8 min. At 278 K, epimerization is slow enough to observe the presence of a single diastereoisomer in the initial n.m.r. As the change of absolute configuration around phosphorus occurs [(1M) ⇌ (1P)], the ratios of intensities of non-equivalent signals for corresponding groups in (1M) and (1P) allow a kinetic study of the transformation. Due to the inaccuracy of determinations of the intensities by dynamic n.m.r., we studied the mutarotation phenomenon which is observed for a solution of (1M) by polarimetry. Polarimetric measurements on solutions when plotted against time, at different temperatures, fit an apparent first-order rate equation using a linear least square program or the classical graphic method. The results are collected in Table 1. To obtain the reversible first-order kinetic

TABLE 1

Apparent rate constants of epimerization of (1M) ⇌ (1P) at different temperatures

T/K	$10^3[(1)]$/M	$10^3(k_1 + k_{-1})$/s^{-1}	$t_{1/2}$/s
278·1	9·96	0·223	3120
283·0	29·1	0·428	1614
287·8	19·8	0·772	888
293·0	16·4	1·42	486

TABLE 2

Equilibrium constants between the two diastereoisomers (1M) ⇌ (1P) and free energy at different temperatures. Specific rotations of the corresponding two diastereoisomers

T/K	$K_e = [(1P)]/[(1M)]$ ^{e}	ΔG°/kcal mol^{-1} ^{b}	$[\alpha_{(1M)}]/^{\circ}$ ^{a}	$[\alpha_{(1P)}]/^{\circ}$ ^{a}	$[\alpha_{\infty}]/^{\circ}$ ^{a}
278·1	34·9/65·1 ^{d}	0,34$_4$	-260	$+229$	-89
283·1	35·2/64·8 ^{c}	0,34$_3$	-255	$+224$	-86
287·8	35·5/64·5 ^{c}	0,34$_2$	-254	$+215$	-87
293·0	35·7/64·3 ^{c}	0,34$_1$	-252	$+215$	-84
305·0	36·4/63·6 ^{d}	0,33$_8$			
328·0	37·4/62·6 ^{d}	0,33$_5$			

^{a} [α] is for λ 436 nm. ^{b} The mean values of the other thermodynamic parameters are $\Delta \bar{H}^{\circ} = 0\cdot396$ kcal mol^{-1}, $\Delta \bar{S}^{\circ} = 0\cdot18$ cal K^{-1} mol^{-1}. ^{c} Interpolated data. ^{d} Experimental data. ^{e} Error in K_e is ca. $\pm 1\%$.

[1] Part V, J. F. Brazier, A. Cachapuz Carrelhas, A. Klaebe, and R. Wolf, *Compt. rend. C*, 1973, **277**, 183.

[2] J. S. Wood, *Progr. Inorg. Chem.*, 1972, **16**, 227.

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[4] R. Luckenbach, ' Dynamic Stereochemistry of Pentacoordinate Phosphorus and Related Elements,' G. Thieme, Stuttgart, 1973, and references therein.

[5] D. Hellwinkel, in ' Organic Phosphorus Compounds,' eds. G. M. Kosolapoff and L. Maier, Wiley-Interscience, New York, 1972, vol. 3, ch. 5B.

[6] A. Klaebe, J. F. Brazier, F. Mathis, and R. Wolf, *Tetrahedron Letters*, 1972, 4367.

[7] J. D. Morrison and H. S. Mosher, 'Asymmetric Organic Reactions,' Prentice-Hall, Englewood Cliffs, 1971, p. 24.

TABLE 3

Rate constants and activation parameters of the transformation $(1M) \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} (1P)$

T/K	$10^5 k_1/s^{-1}$	$10^5 k_{-1}/s^{-1}$	$\Delta G_1^{\ddagger\,a}$	$\Delta H_1^{\ddagger\,a}$	$\Delta S_1^{\ddagger\,a}$	$\Delta G_{-1}^{\ddagger\,a}$	$\Delta H_{-1}^{\ddagger\,a}$	$\Delta S_{-1}^{\ddagger\,a}$
278·1	7·78	14·5	21·44	19·84	−5·7	21·10	19·45	−5·9
283·1	15·0	27·7	21·47	19·83	−5·7	21·12	19·44	−5·9
287·8	24·7	49·8	21·48	19·82	−5·7	21·14	19·43	−5·9
293·0	51·0	91·8	21·51	19·81	−5·7	21·17	19·42	−5·9

a $\Delta G^{\ddagger}$ and $\Delta H^{\ddagger}$ in kcal mol^{-1}, $\Delta S^{\ddagger}$ in cal K^{-1} mol^{-1}. Error in $\Delta H^{\ddagger}$ is ca. 2% and in $\Delta S^{\ddagger}$ is ca. 20%.

parameters, we needed to determine the concentrations of the two diastereoisomers at equilibrium, which was achieved by the integration of n.m.r. signals at three temperatures, over several days, to check the equilibrium position accurately. Because of the slight temperature dependence of the equilibrium constant, the temperature range for this determination was larger than that for the kinetic studies, and leads to the mean thermodynamic parameters: $\Delta \bar{H}_0 = 0.396$ kcal mol^{-1}, $\Delta \bar{S}_0 = 0.185$ cal K^{-1} mol^{-1}. The actual K_e values needed for the kinetic treatment were interpolated (Table 2).

N.m.r. data, associated with polarimetric measurements on pure (1M) solutions and equilibrated solutions lead to the specific rotation of the non-isolated diastereoisomer (1P). The temperature dependence of the first-order rate constants k_1 and k_{-1}, calculated from the data in Tables 1 and 2 were analysed by the Eyring plot equation with the transmission coefficient taken equal to 1. The results are in Table 3.

DISCUSSION

The experimental results are discussed in terms of molecular stereolability without bond breaking. This assumption is based on a large quantity of experimental data on spirophosphoranes essentially obtained by dynamic n.m.r.[8] However, in our particular models, the phosphorus substituent is a hydrogen atom and a
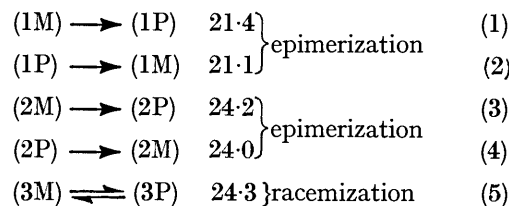

SCHEME
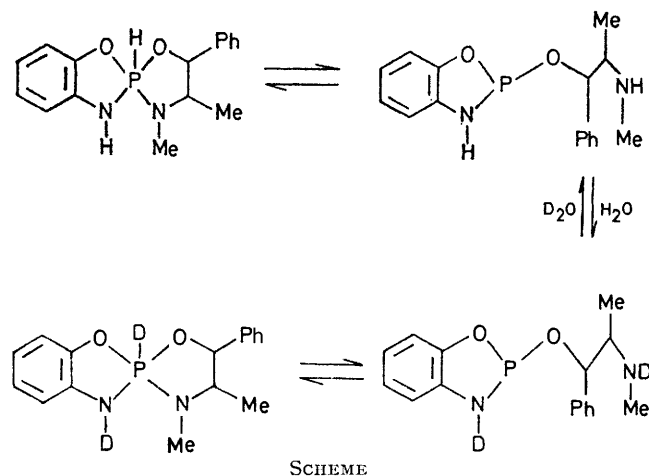
tautomeric equilibrium $P^V \rightleftharpoons P^{III}$ cannot be ruled out and actually exists in particular cases.[9,10] Proof

* Epimerization via irregular permutational processes, involving heterolytic breakage of the phosphorus–oxygen bond of the benzophospholan ring and polar transition state is ruled out by (i) the low value of the activation entropy and (ii) epimerization studies in polar solvents. In pyridine at 30°, the rate constant is four times lower than in benzene. The assumption of a polar transition state would involve a large increase in the rate constant.

that such an equilibrium does not interfere with molecular stereolability studied here is given by the absence of any exchange P^V–H $\longrightarrow P^V$–D which would occur as in the Scheme.*

If we consider the three available sets of thermodynamical data concerning spirophosphoranes having the same direct co-ordination environment (two oxygens, two nitrogens, and one hydrogen) [(1M) $\rightleftharpoons$ (1P), (2M) $\rightleftharpoons$ (2P),[5] (3M) $\rightleftharpoons$ (3P)[8]] it is clear, to a first approximation, that the inner atoms play the main role[11] in determining the range of $\Delta G^{\ddagger}$ (in kcal mol^{-1}) [equations (1)—(5)]. These values are well separated

$$(1M) \longrightarrow (1P) \quad 21\cdot4 \left.\right\}\text{epimerization} \quad (1)$$
$$(1P) \longrightarrow (1M) \quad 21\cdot1 \left.\right. \quad (2)$$
$$(2M) \longrightarrow (2P) \quad 24\cdot2 \left.\right\}\text{epimerization} \quad (3)$$
$$(2P) \longrightarrow (2M) \quad 24\cdot0 \left.\right. \quad (4)$$
$$(3M) \rightleftharpoons (3P) \quad 24\cdot3 \}\text{racemization} \quad (5)$$

from those for different inner atom systems such as (4) and (5) with activation free energy values of ca. 17·9 and 15·6 kcal mol^{-1}, respectively. Nevertheless, even with five identical sets of atoms directly connected to phosphorus, the range seems relatively large, i.e., at the same temperature, the rate constant of the epimerization (1P) $\longrightarrow$ (1M) is 133 times larger than that for (2M) $\longrightarrow$ (2P). The difference in $\Delta G^{\ddagger}$ can be of course balanced between (i) the stability of the ground state and (ii) the more or less constrained structures of the transition state. We have no experimental data concerning the former. But it is worth noting that the standard free energy difference ΔG^0 between (2M) and (2P) is small in spite of the large strain release of the substituents on going from (2P) to (2M).† So the main part of $\Delta(\Delta G^{\ddagger})$ can be ascribed to the transition state and we will later use this reasonable assumption. In the energy scale, we assume that the trigonal bipyramid intermediate involved in the epimerization process (i.e. the highest in energy) has one ring in a diequatorial position with the hydrogen atom attached in the usually

† Owing to the difference of occupancy of the acute (120°) and the obtuse (240°) dihedra, the latter are defined by the planes of the two rings; in (2M), two phenyl and two methyl groups are in the obtuse dihedra, whereas in (2P) they are in the acute one.

[8] D. Houalla, M. Sanchez, L. Beslier, and R. Wolf, Org. Magnetic Resonance, 1971, 3, 45.

[9] M. Sanchez, J. F. Brazier, D. Houalla, and R. Wolf, Bull. Soc. chim. France, 1967, 3930.

[10] M. Sanchez, J. Ferekh, J. F. Brazier, A. Munoz, and R. Wolf, Roczniki Chem., 1971, 45, 131.

[11] J. I. Dickstein and S. Trippett, Tetrahedron Letters, 1973, 2203.

unfavourable axial position, if we keep in mind the electronegativity rules.* The second ring contains

(2M)   (2P)

(3M)   (3P)
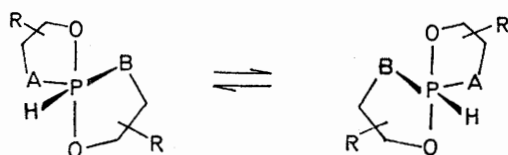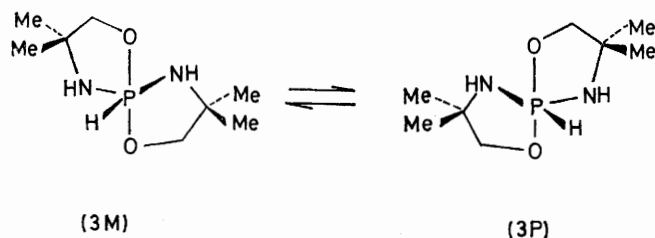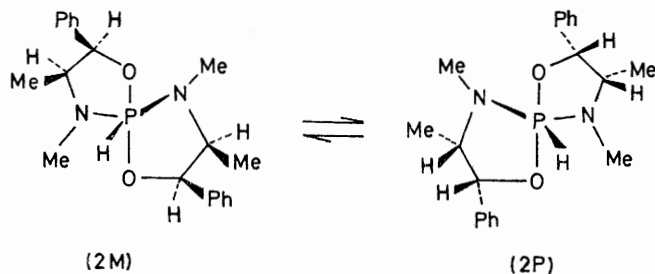

(4) A = NH, B = O
(5) A = B = O

normal axial and equatorial bonds according to the same rules.[13] Due to the lack of symmetry in each ligand, there are four such intermediates A—D. One can assume that the structure of the transition state is not far in energy from these intermediates. Molecular models help in understanding the interplay of the various factors by comparing systems (1) and (2). (i) The removal of one of the methyl groups directly connected to nitrogen introduces a large strain release. (ii) When the ephedrine ligand is diequatorial, the *trans*-position of the substituents in the pseudo-(*threo*) derivatives also leads to a less crowded intermediate than in the ephedrine one. These two factors appear to account for the increase in the rate constant on going from (2) to (1). However, another factor has the opposite effect; it seems more difficult for an amino-

* The recently postulated high apicophilicity of hydrogen [12] conflicts with this point of view.

† *Added in proof:* The origin of the releasing effect in (1) may be due to the comparative barrier to rotation between P–N(alkyl) and P–N(aryl): *cf.* the statement ' the resistance to P–N bond rotation makes a major contribution to the Berry rearrangement barrier in R_2NPF_4 molecules ' (E. L. Muetterties, P. Meakin, and R. Hoffman, *J. Amer. Chem. Soc.*, 1972, **94**, 5674).

phenol ligand to lie in the diequatorial position owing to the shortening of the C–C intracyclic bond and to the absence of conformational flexibility. It seems that this obstacle is overcome by the two former factors.†

Arguments for the Assignment of Structure (1M) *to the Isolated Enantiomer.*—The study of more than 20 optically active spirophosphoranes [14] enables us to lay down rules which allow the assignment of the helix skeleton of an isolated derivative. First, from X-ray diffraction,[15] isomer (2M) was isolated from the equilibrium (2M) ⇌ (2P). The study of the epimerization by n.m.r. spectroscopy, leads to the production of two rules. (i) The spin–spin coupling constant of the proton directly bound to phosphorus (J_{H-P}) is always smaller in the more crowded isomer.† (ii) The observed signal of the methyl group or the hydrogen connected to the nitrogen atom of one ring which are deshielded when the phenyl group in the other ring is *endo* (in the acute dihedra †) is shifted downfield. A third method of attribution comes from the polarimetric studies; the transformation from a minus to a plus helical structure is accompanied by an increase of the algebraic

A   B

C   D
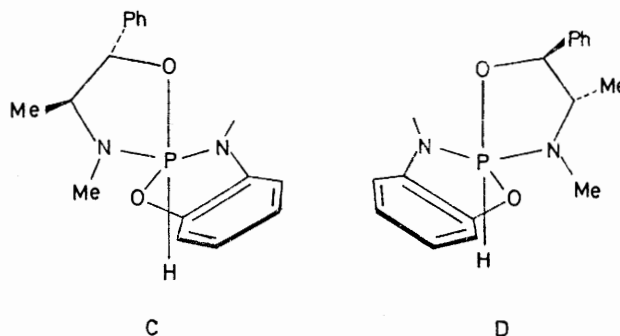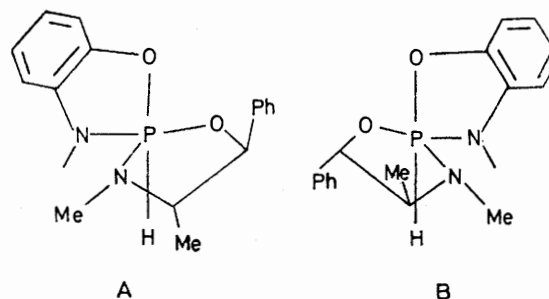
value of the rotation of the solution. This has been established by the study of quasi-enantiomers in this series.[16] The three rules are convergent and lead to the same assignment.

[12] R. K. Oram and S. Trippett, *J.C.S. Perkin I*, 1973, 1300.
[13] E. L. Muetterties, W. Mahler, K. J. Packer, and R. Schmutzler, *Inorg. Chem.*, 1964, **3**, 1298.
[14] J. F. Brazier, Thèse de Doctorat ès Sciences, Université Paul Sabatier, Toulouse, 1973.
[15] G. Newton and J. E. Collier, Abstracts, Summer Meeting of American Crystallographic Association, Iowa State University, Ames, 1971, no. 5, p. 105.
[16] R. Contreras, J. F. Brazier, A. Klaebe, and R. Wolf, *Phosphorus*, 1972, **2**, 67.

EXPERIMENTAL

100 MHz [1]H N.m.r. spectra were taken with a Varian HA 100 instrument for C_6D_6 solutions with tetramethylsilane as internal standard. Polarimetric measurements were taken with a Perkin-Elmer 141 instrument to within $0.002°$ in a temperature-controlled cell (± 0.02 °C).

($4'S,5'S$)-$4',5'$-Dihydro-$3',4'$-dimethyl-$5'$-phenylspiro-($1,3,2$-benzoxazaphos[V]phole-$2,2'$-[$1,3,2$]-oxazaphos[V]phole) was formed by refluxing ($4S,5S$)-2-dimethylamino-4-methyl-5-phenyl-$1,3,2$-oxazaphospholan (0.01 mol) and o-aminophenol hydrochloride (0.01 mol) in the presence of triethylamine (0.1 mol) in benzene (100 ml) under nitrogen. The dimethylamine generated was titrated to follow the progress of the reaction and at completion the mixture was filtered to separate triethylammonium chloride. The *product* (40%), m.p. $88—92°$, was purified by recrystallization in benzene (Found: C, 63.6; H, 6.35; N, 9.2; P, 9.85. $C_{16}H_{19}N_2O_2P$ requires C, 63.55; H, 6.35; N, 9.25; P, 10.25%), compound (1M) δ 8.14 (d, $J_{\text{H-P}}$ 793 Hz, PH), 4.94 (d, $J_{\text{H-N-P}}$ 19 Hz, 3-H), 4.23 (q, $J_{\text{H-C-C-H}}$ 8.4, $J_{\text{H-C-O-P}}$ 1.6 Hz, $5'$-H), 2.54 (d, $J_{\text{H-C-P}}$ 11 Hz,

NCH$_3$), and 0.75 (d, $J_{\text{H-C-C-H}}$ 6.1 Hz, CCH$_3$), compound (1P) δ 8.24 (d, $J_{\text{H-P}}$ 798 Hz, PH), 4.68 (d, $J_{\text{H-N-P}}$ 20.5 Hz, 3-H), 4.40 (q, $J_{\text{H-C-C-H}}$ 7.4, $J_{\text{H-C-O-P}}$ 2.4 Hz, $5'$-H), 2.60 (d, $J_{\text{H-C-N-P}}$ 10.1 Hz, NCH$_3$), and 0.78 (d, $J_{\text{H-C-C-H}}$ 6.1 Hz, CCH$_3$).

The [1]H N.m.r. spectrum of the crystallized product recorded immediately after the compound has been dissolved in C_6D_6 at *ca.* 5°, exhibits only one diastereoisomer, (1M), and on allowing the solution to warm, the signals of the second isomer appear and become more intense as those of (1M) decrease until equilibrium is reached. The equilibrium constants were determined, at different temperatures, by careful surface and electronic integration on well separated signals (accuracy $\pm 2\%$).

The apparent rates of epimerization (1M) $\rightleftharpoons$ (1P) were obtained from the plot of log ($\alpha_\infty - \alpha_t$) against time (where α_t is optical rotation of solution at time t). Good linear relationships were obtained. Extrapolated and calculated rotation values are: for (1M) $[\alpha]_{436}^{20} = -252°$, for (1P) $[\alpha]_{436}^{20} = +215°$.