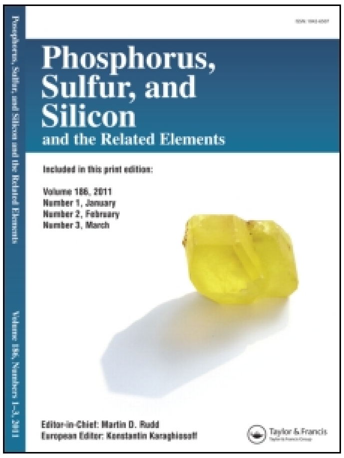

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MUTAROTATION ARISING FROM STEREOLABILE PENTACOORDINATED PHOSPHORUS †

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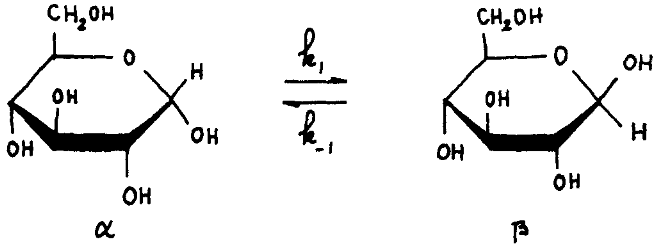
The purpose of this paper is to show that optical rotation is a convenient method for studying the intramolecular stereolability in pentacoordinated species, particularly phosphorus derivatives. In chemistry, it is difficult to present a completely new idea and we will deal with this topic under several headings.



glucose epimerization.

REVERSIBLE UNIMOLECULAR REACTION

$$\underset{(a-x)}{A} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \underset{(b+x)}{B}$$

$$k_1 + k_{-1} = \frac{1}{t} \ln \frac{x_e}{x_e - x}$$

$$k_1 + k_{-1} = \frac{1}{t} \ln \frac{\alpha_0 - \alpha_\infty}{\alpha_t - \alpha_\infty}$$

$x = x_e$ for $t = t_\infty$

$\alpha_t =$ experimental rotation.

FIGURE 1

I.

Dubrunfaut[1] (Paris, 1846) made the first kinetic observation in chemistry, in observing the change with time

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† Plenary Lecture. The Vth International Conference of Organic Phosphorus Chemistry, Gdansk, Poland, September 1974.

of the optical rotation of glucose as it is seen in Figure 1. Dubrunfaut knew very much less about the reaction than is shown, and it took more than half a century to gather the information shown here. We take this opportunity to recall the formula concerning the reversible unimolecular reaction. We see that the sum $k_1 + k_{-1}$ can be obtained from the optical rotation as a function of time. For the calculation of the k_1 and k_{-1}, the equilibrium constant of the reaction, at the same temperature, is required. To calculate the thermodynamic parameters of the same reaction, it is necessary to know the variation of the equilibrium constant with temperature.

II.

A second idea comes from the Hudson isorotation rule[2] (which was first advanced in 1909), that is, an optical superposition holds fairly accurately for many anomeric O-glucosides in which the only structural difference is the configuration on carbon C_1. We have used a similar idea to determine absolute configuration at the phosphorus atom.[3]

III.

We know that the change of configuration on the C_1 carbon proceeds by bond breakage and the intermediacy of an aldehyde. In our case we will demonstrate that the phosphorus epimerization is going on without bond breakage so our research is connected in this way with the large amount of results obtained in the biphenyls, which owe their optical activity to restricted rotation around a bond.

Figure 2 has some sentimental meaning because we have selected early examples studied by chemists now well known in organophosphorus chemistry.[4-6] As it is always difficult to present the principles of stereochemistry in pentacoordination in a short space, for readers less familiar with this field we have selected a model which helps one to understand quickly. We present, in Figure 3, a hinge which hangs by a thread. If the two conjoined pieces of metal make between them an acute angle of 120° we have a model of a trigonal bipyramid (TBP) with two axial 1,2 and three equatorial 3,4,5 positions. The hinge at the left is a chiral object in the sense that its mirror image is not superimposable on the original. It can be seen that if one flips the left model, one racemizes it. But if we mark the 1–P–3 plane of the model with a colored spot and the same for the mirror image, that is, if we can distinguish the two faces of at least one plane, the two models are no longer enantiomers since, if one flips the first model, we do not get the mirror image. The spot which was on the roof, say, is now in the attic of the house. There is a good analogy between the hinge and the spirophosphoranes. It is, however, an oversimplified analogy and we must not go too far and create a wrong impression. Here, to racemize when you flip, you permutate two equatorial bonds, but on a TBP you obtain the same result by permutation of two axial bonds; on a hinge you cannot. There is a second weakness for another reason: in the flipping process, two equatorial bonds approach each other very closely, a process which is not chemically possible.

Of course, if we intend to study the stereolability of pentacovalent phosphorus derivatives, we need first optically active compounds containing P^V with a definite configuration and this only recently became possible. This is also true for any pentaligated atom.

In a well known article on specification of molecular chirality, by Cahn, Ingold, and Prelog in *Angew. Chem.*, 1966,[7] the authors said that they knew of no molecule whose chirality depends on that of a configurationally stable, chiral, quinqueligated atom. In the same year, Hellwinkel published an article[8] on the first optically active pentaarylphosphorane shown in Figure 4. In this system the absolute configuration around phosphorus is obliterated by fluxional isomerization, and as the author says himself "this is actually a mixture of two rapidly equilibrating, diastereoisomeric, trigonal bipyramidal species."[9] The synthesis of P^V optically active derivatives constitutes the central part of our communication. In Figure 5, for the purposes of demonstration, we show in detail the simplest molecule we have synthesized, which contains only two chiral units: one chiral carbon and the spirosystem around the phosphorus. In a two-step chemical reaction, we introduce two different bidentate ligands in a TBP. The first is N-methylaminophenol which spans an axial and equatorial bond on the TBP, the nitrogen atom being placed in the equatorial plane following the electro-

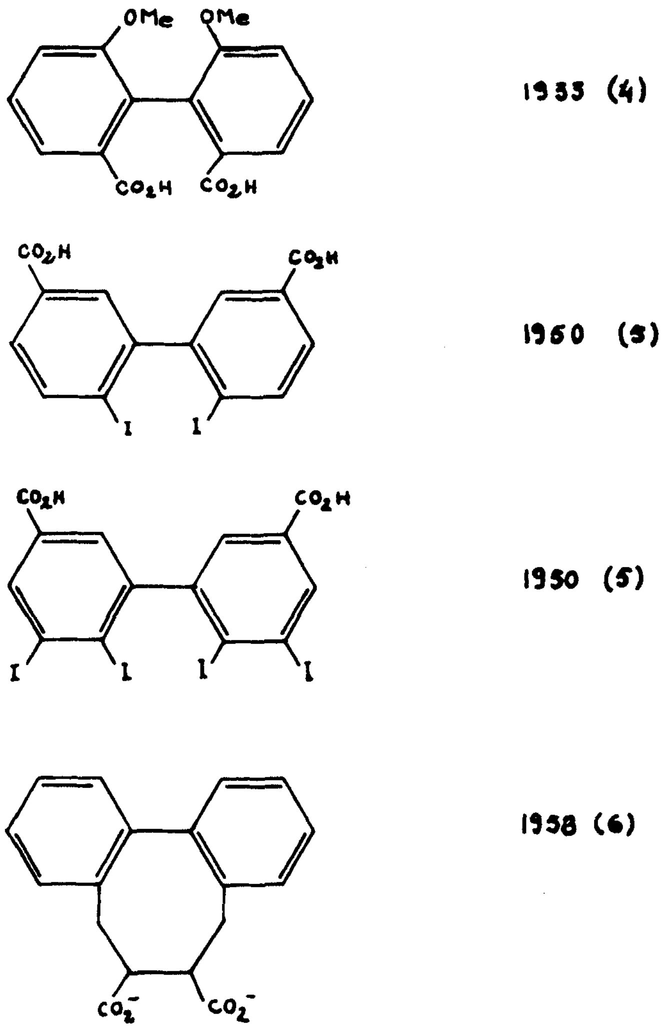
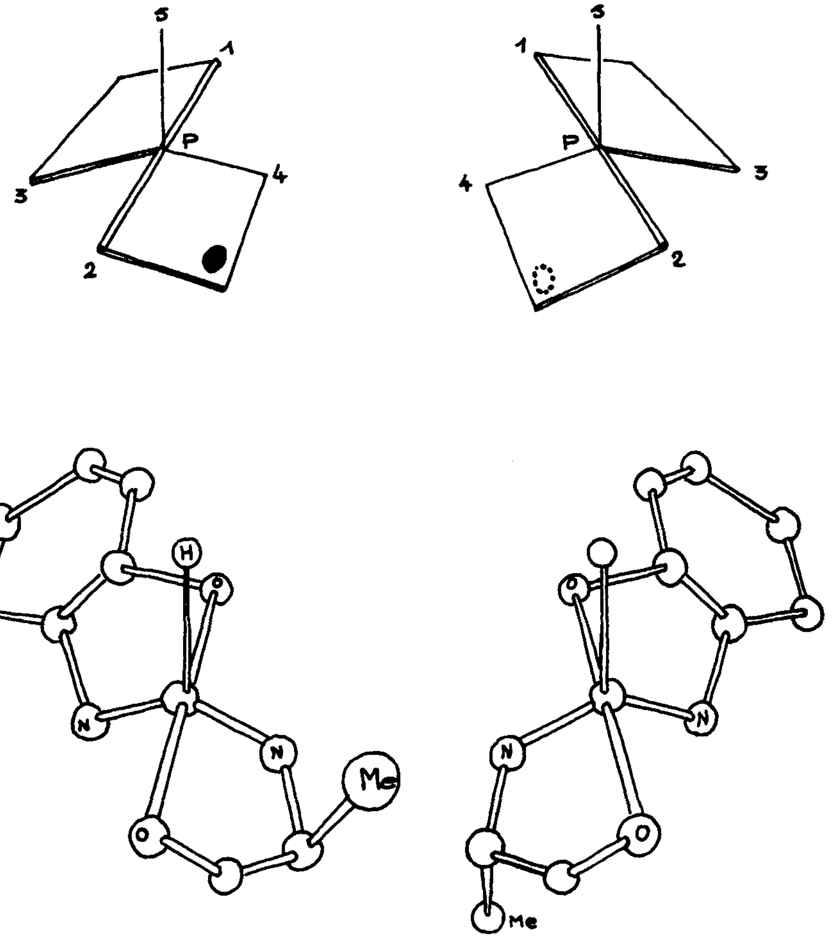


FIGURE 2

negativity rule. Two free equatorial positions remain, one being occupied by an hydrogen atom. In one model (upper left) the hydrogen atom is near the observer; in the second, remote from him. If we use a racemic mixture of alaninol, we have two ways to construct the spirophosphorane with the S derivative using the free bond far from or near the observer. The two molecules obtained are diastereoisomers and are optically active. Diastereoisomerism can be seen by observing the different distances between C-Me and H-P in each model. They are optically active because each one contains:

1) a given configuration of the skeleton;
2) a definite configuration for the chiral carbon.



compound 13

FIGURE 3

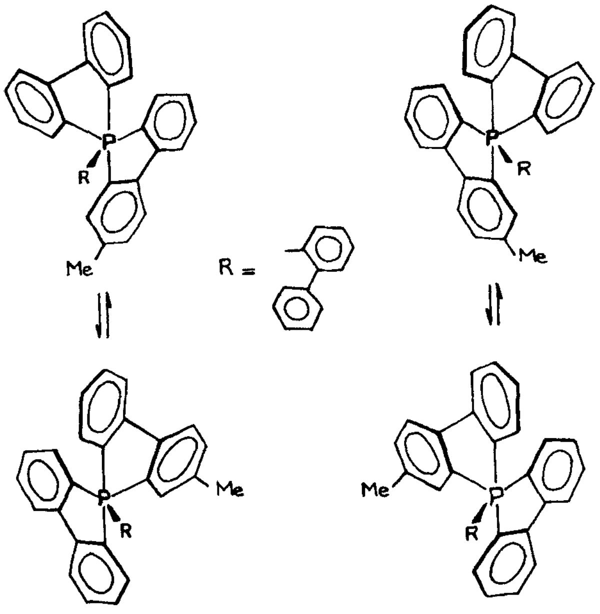
With R alaninol, we can construct two other molecules, and in Figure 5 the diagonal pairs are enantiomers. It is obvious that if the reaction is conducted starting with an optically active alaninol in the preparative mixture, we will obtain only a pair of diastereoisomers (each one being optically active). The same molecules appear after a convenient rotation about the O-P-O axis. In this situation, it is easier to define the skeletal chiral unit around the phosphorus atom. The helical model is suitable for this. If we neglect molecular details and retain only the molecular frame, it possesses the three necessary elements:

a) a helical axis, C_2, along the phosphorus hydrogen bond;

b) the pitch; here it is four times the distance between phosphorus and the straight line which joints the two nitrogen atoms;

c) the helical sense. For example, in following the helical line in M (Figure 5) between N and O in the clockwise sense, there is a corresponding axial translation directed towards the observer; it is a left-handed helix. With model P, the axial translation is away from the observer; it is a right-handed helix.

There is no limit to imagining derivatives in this series, and with the 8 ephedrines and norephedrines there are 72 possible isomers derived from them.[10]



Hellwinkel (1966).

FIGURE 4

Now, what about the two diastereoisomers we have in our preparative mixture? Not only were we able to isolate a pure, optically active diastereoisomer, but a slow crystallization is accompanied by second order asymmetric transformation; only one of the two isomers crystallizes and, as crystallization proceeds, the mobile equilibrium between the two possible configurations at phosphorus is displaced so that all crystalline material is composed of a single epimer (Figure 6).[11] When these crystals are dissolved at a sufficiently low temperature, the epimerization is slow enough to observe, on the initial nmr spectrum, the presence of a single diastereoisomer. As time goes on, change of absolute configuration around the phosphorus occurs, and the ratios of intensities of non-equivalent signals for corresponding groups allows a kinetic study of the transformation. Due to the inaccuracy of the determinations of the intensities by nmr on a dynamic system, and as we deal with optically active derivatives, we used the polarimetric counterpart of the epimerization, that is the *mutarotation* phenomenon which is observed on the solution of the isolated crystals.

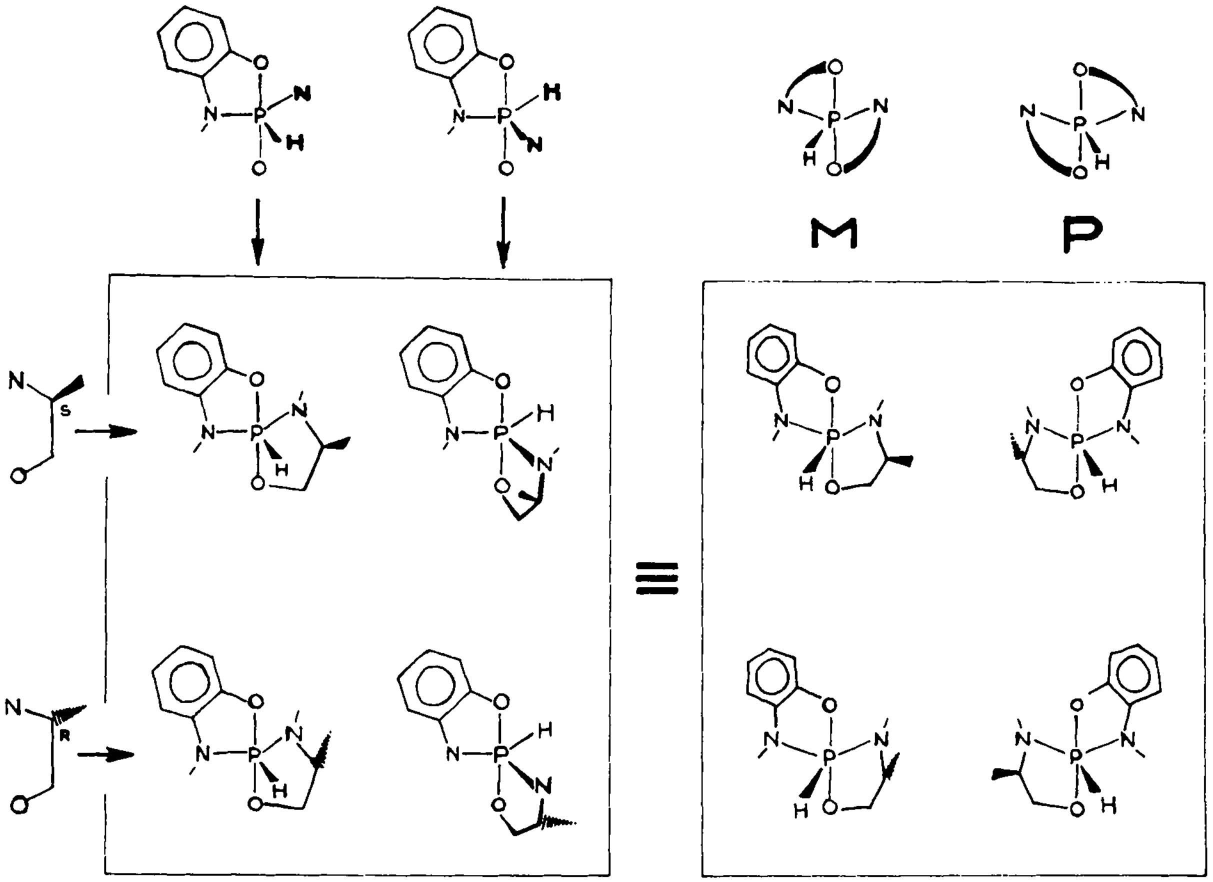


FIGURE 5

The polarimetric measurements on solutions as a function of time at different temperatures fit the rate equation of apparent first order reaction [ln $(\alpha_t - \alpha_\infty)$ vs. time] using a linear least-squares program or the classical graphic method. This was done on the 13 pairs of derivatives shown in Figure 7. To obtain the reversible first order parameters, we needed to determine the concentrations of the two diastereoisomers at equilibrium; this was achieved by integration of nmr signals at one temperature for all the pairs over a period of several days to check the equilibrium state accurately. In several cases, the determination of equilibrium constant was made at different temperatures with a range larger than the one we needed with the kinetic studies, and the data led us to the mean thermodynamic parameters

$$\ln K_e = -\frac{\overline{\Delta H_0}}{R}\,\frac{1}{T} + \frac{\overline{\Delta S_0}}{R}$$

where $\overline{\Delta H_0} = 0.396$ kcal/mole; $\overline{\Delta S_0} = 0.185$ cal. K^{-1}/mole in the case of pair 9 (Figure 7).

In Figure 8 the equilibrium values observed for twelve systems are presented. The main comment concerns the close stability of the two diastereoisomers. The largest value of ΔG_0 is 1.4 kcal, corresponding to a 12/88 equilibrium for the spirophosphoranes **3**. These results contain quite interesting information concerning the conformation of such molecules. When we construct a model, we notice that, depending on the fold of the pentagonal cycle, there exist situations in which the acute dihedra can be overcrowded. The fact that ΔG_0 is small in almost all examples shows that such a situation is avoided in this type of molecule indicating that, in actual conformation, the substituents tend to lie in the extension of the plane of the ring. We will see that this is true for the x-ray structure of the one example G. Newton et al.[12] have examined (Figure 9).

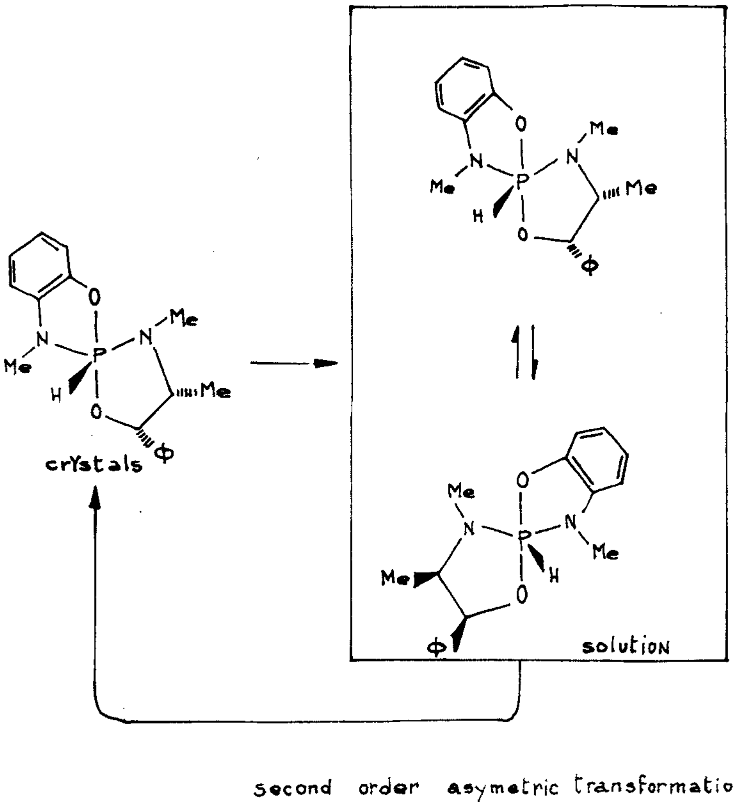


FIGURE 6

Among other comments, we note that in one case the stability of the two diastereoisomers is exactly the same in benzene (compound **11**). For compounds **5**, **6**, and **12** the diastereoisomer isolated in crystal form is the less stable in solution. A last comment: the isolation of a unique, optically active form is decided first by the relative solubility of the two diastereoisomers in the chosen solvent. Therefore, in changing the latter or the conditions of crystallization, we have a chance of isolating the other isomer. We partly succeeded in one case (compound 7) but obtained only a crystalline mixture situated on the other side of the equilibrium; we have checked the identity of the kinetic rate in both directions.

The value of the equilibrium constant is influenced by change of temperature or solvent as shown in Figure 10. As we can see, particularly with basic solvents, the equilibrium is strongly displaced to the prejudice of the diastereoisomer isolated in crystalline form. With this tool in hand, we have tried to obtain information on the question of the stereolability of spirophosphoranes.

One of the most interesting questions we want to answer deals with the influence of basic solvents on the stereomutation of the spirophosphoranes. This study is exciting due to the variety of influences we can imagine before doing the experiments. The study was conducted with compound **11**; the choice being determined not only by an easier synthesis, but also by the good stability necessary to support polarimetric measurements, sometimes over several days. Among the possible influences on comparative stereolability of the molecule in benzene, pyridine, and methyl pyridines, we can consider several likely interactions (Figure 11).

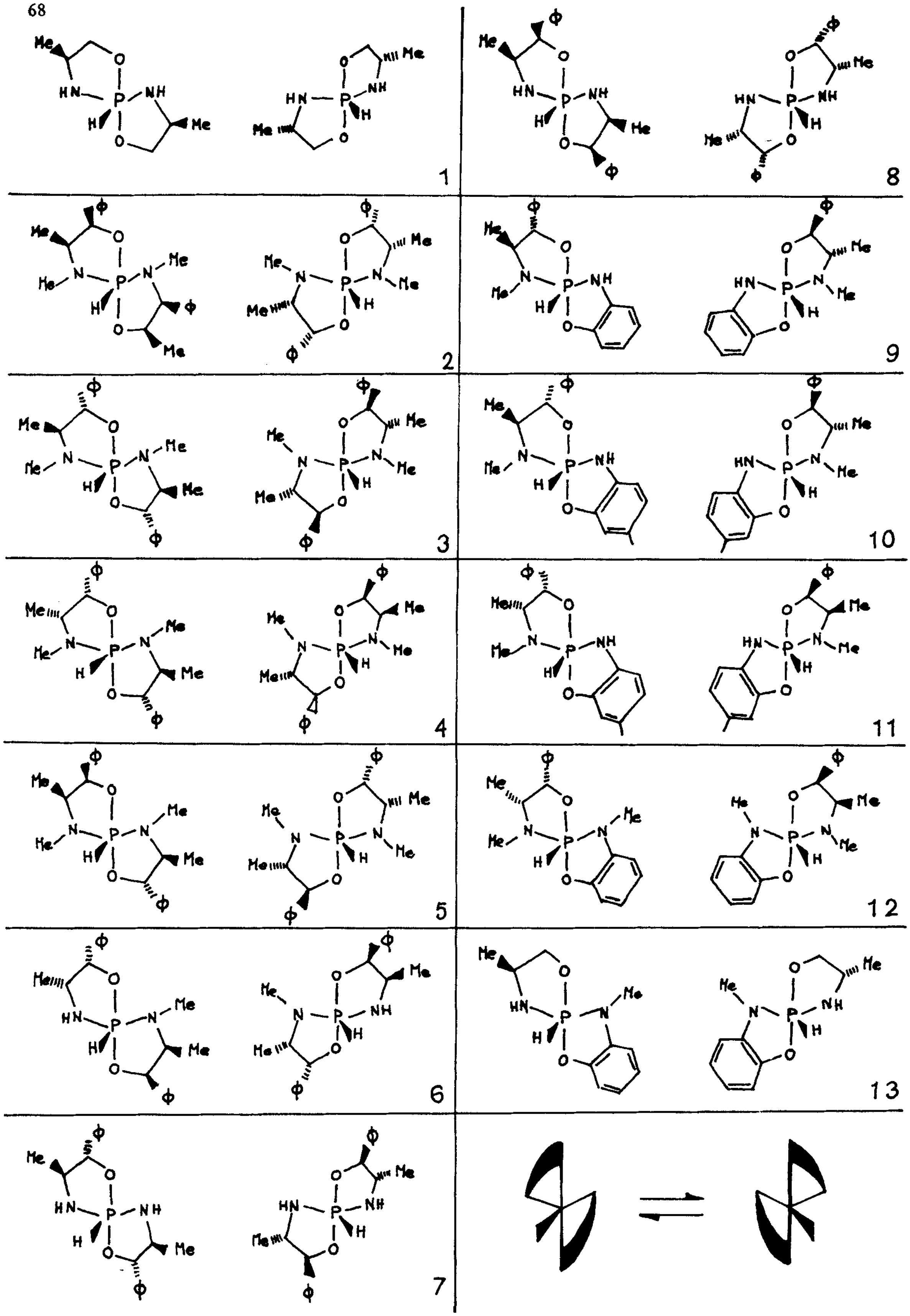
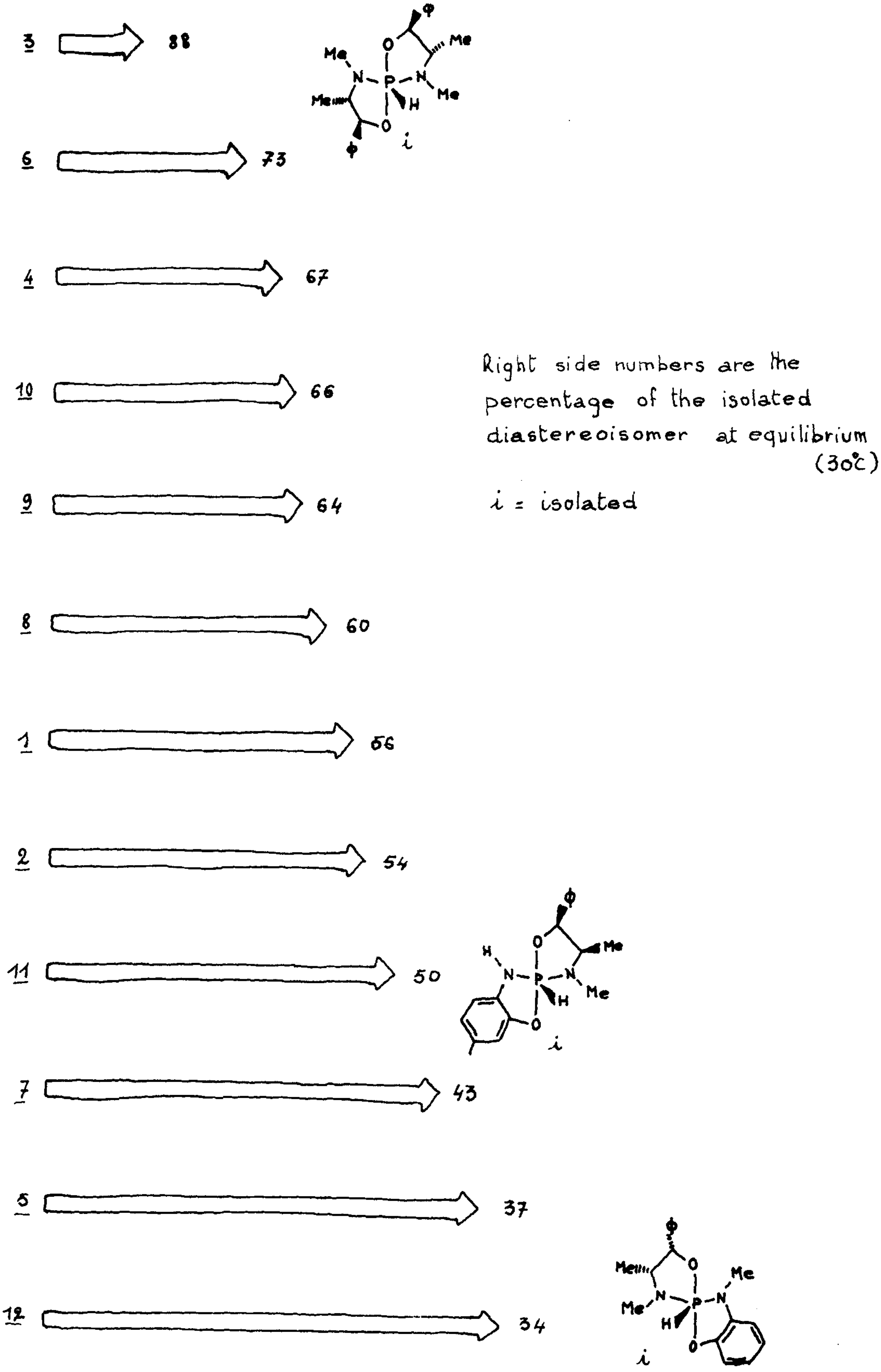


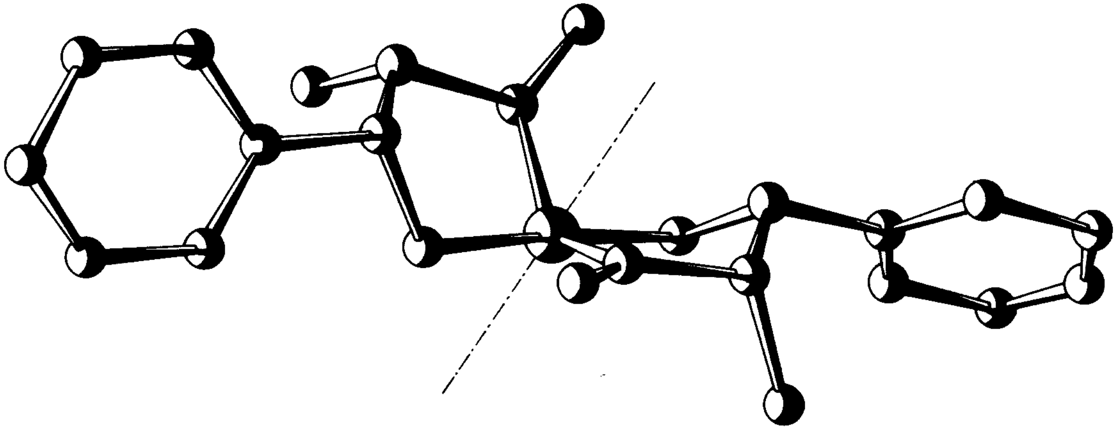
FIGURE 7



Right side numbers are the percentage of the isolated diastereoisomer at equilibrium (30°C)

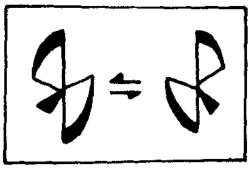
i = isolated

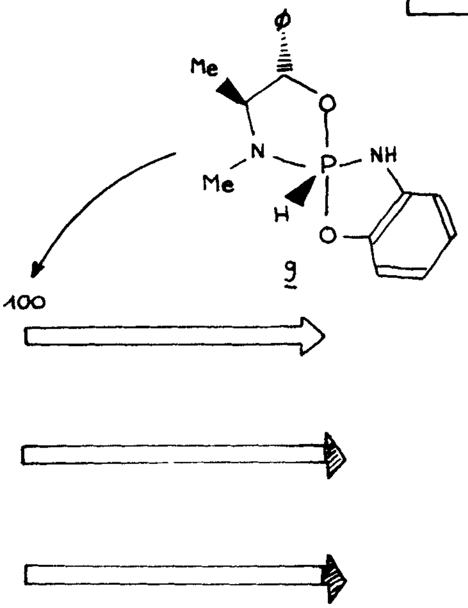
FIGURE 8



X rays structure of 2 according to G. Newton and al. (12)

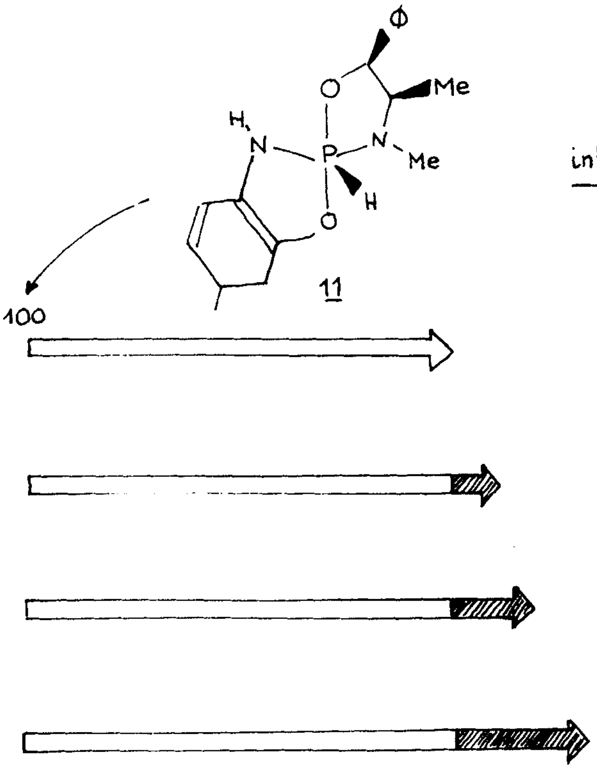
FIGURE 9



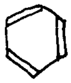
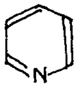
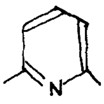


influence of temperature on K_e

%	t° C
65.1	5.1
63.6	32.0
62.6	55,0



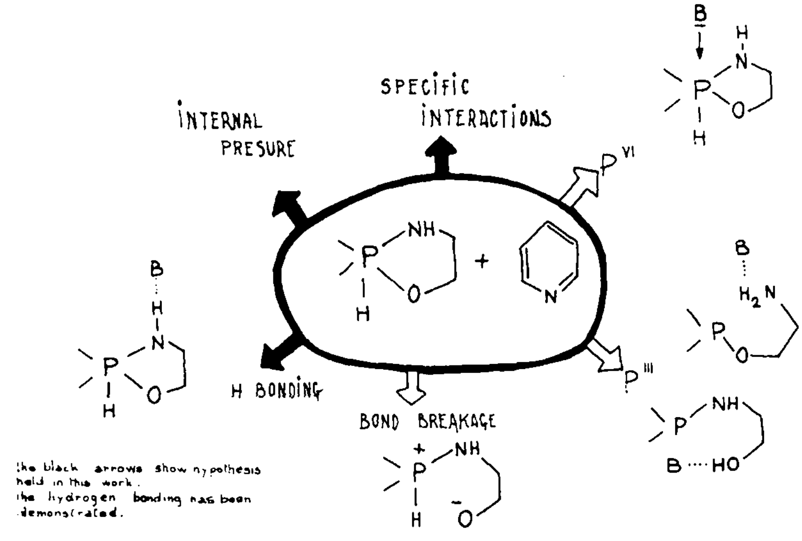
influence of solvent on K_e

%	solvent
50	
45	
40	
33	

The dashed part of arrows corresponds to equilibrium displacement under influence of temperature or solvents.

% = percentage of the isolated isomer at equilibrium

FIGURE 10



the black arrows show hypothesis held in this work.
the hydrogen bonding has been demonstrated.

FIGURE 11

First: a formation, or partial formation, of a hexacoordinated compound. Such an interaction between a spirophosphorane and pyridine is known in the case of tetraoxyspirophosphoranes in which the ligands are pyrocatechol.[13] In our spirophosphorane the absence of this interaction was checked by a comparative measurement of the chemical shift of ^{31}P in benzene and in pyridine. In this latter case, even at −40°, we did not observe any significant modification of the chemical shift towards the high field (+ 57 vs. H_3PO_4) going from benzene to pyridine; therefore, in the compound studied we can conclude that such an interaction is absent.

Second hypothesis: it is known that many spirophosphoranes with a P–H bond give an equilibrium mixture, $P^V \rightleftharpoons P^{III}$,[14] which is sensitive to the nature of the solvent; the presence of a P^{III} form cannot be completely precluded, and we have checked the absence of this latter form by heavy water deuterium exchange. After several minutes the hydrogen of the NH bond is completely exchanged, but after 24 hours there is still no exchange at the PH bond. We conclude that even if the P^{III} form is present in minute quantity, it is not involved in the isomerization.

Third hypothesis: if we now look at the experimental results (Figure 12), we observe that the process slows down in going from benzene to pyridines as solvent, by a factor which can reach 3. This result excludes several other processes; particularly those which imply a bond breakage and which occur through a polar transition state, because in this latter case one would expect an increase of the rate constant, often by a factor of several orders of magnitude.

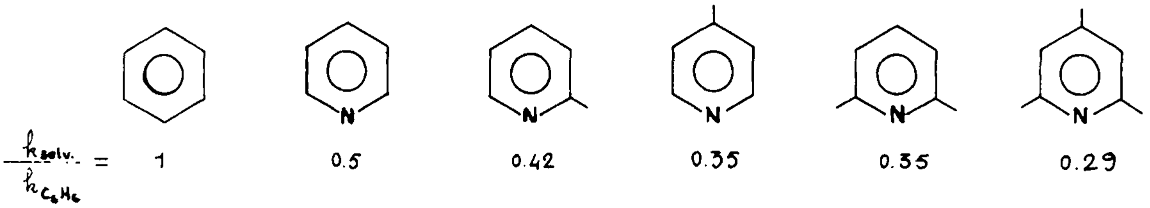
All these data are in agreement with an epimerization of phosphorus without rupture of any bond. The explanation of the observed decrease in rate entails at least factors A and B:

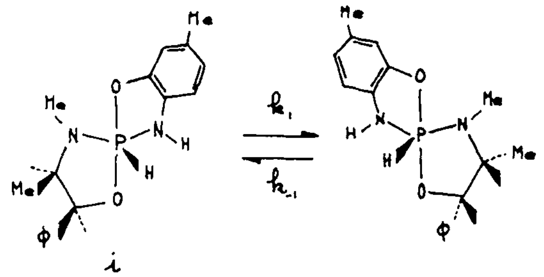
A) the main one is a hydrogen bonding between HN and pyridine, which has been proved in three ways:

i) such an interaction must decrease when the temperature is raised; This is true in our case. For example, at 7.4°C we have for each diastereoisomer of **11** the following ratios for k_1 and k_{-1}:

$$\frac{k_{1\,C_6H_6}}{k_{1\,C_5H_5N}} = 1.66 \; ; \qquad \frac{k_{-1\,C_6H_6}}{k_{-1\,C_5H_5N}} = 2.54 \; ;$$

values which become at 35.6°C:





in benzene at 80 °C

$k_1 = k_{-1} = 37.3 \cdot 10^{-3}$ mn^{-1}.

$\Delta G^{\ddagger} = 22.1$ Kcal mol^{-1}.

FIGURE 12

$$\frac{k_{1\,C_6H_5}}{k_{1\,C_5H_5N}} = 1.45 \quad ; \quad \frac{k_{-1\,C_6H_6}}{k_{-1\,C_5H_5N}} = 1.77$$

The sensitivity of the polarimetric measurements is particularly evident.

ii) In the nmr spectrum, the chemical shift of H–N is largely influenced by the presence of pyridine. In pure C_6D_6, N–H is 4.46. It becomes, still in deuterated benzene, 5.45 for a molar ratio of compound **11**/ C_5D_5N = 1, and 7.44 for a molar ratio = 0.1. When the last solution is warmed, the N–H line is shifted towards high field. The pyridine effect disappears at 70°C.

iii) This interaction was also confirmed by ir spectroscopy. Compound **11**, in CCl_4, shows a single N–H band (ν_{N-H} = 3471 cm^{-1}) corresponding to a free N–H stretch (3438 in benzene). When pyridine is added gradually to this solution, the frequency of this band is unaffected but a second band (ν_{N-H} = 3220 cm^{-1}) appears and increases in intensity at the expense of the free N–H band. In pure pyridine, the free ν_{N-H} at is still present at 3447 cm^{-1} and the associated ν_{N-H} at 3190 cm^{-1}.

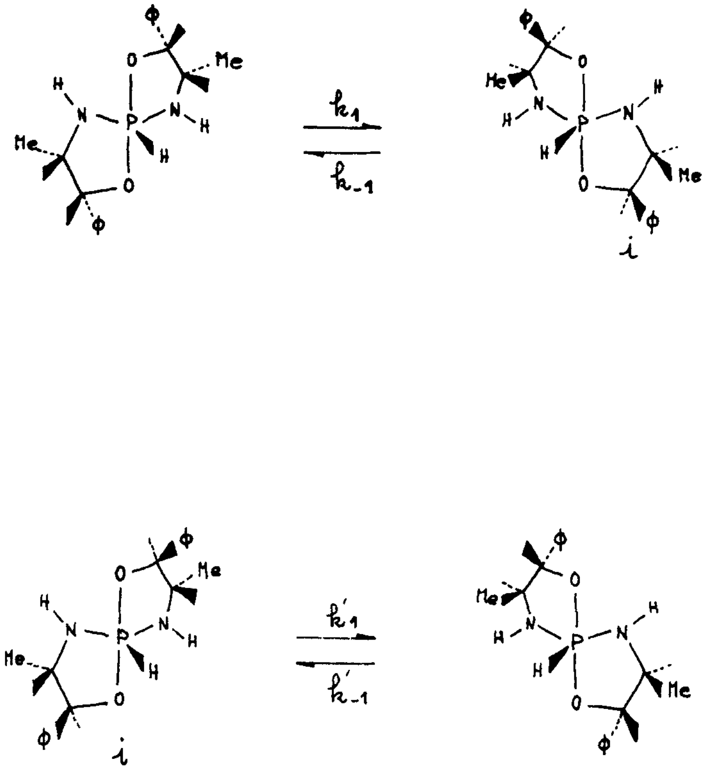
B) This hydrogen bonding being proved, several other factors are not excluded, such as internal pressure in liquids[15] and a specific interaction between pyridine and the transition state. In this latter structure, even without bond breakage, the repartition of charges, or electron transfer along the bonds, have completely original values compared with those in the fundamental state. That such phenomena could occur was demonstrated by kinetic measurements in benzene and pyridine on a neighbor derivative not containing an NH bond: **12**

k_{app} at 30° in benzene 8.35×10^{-3} min^{-1}

k_{app} at 30° in pyridine 14.27 min^{-1} .

Thus the rate constant increased by about 80% proving the interplay of several factors.

The results on a set of similar derivatives enable us to gather some information about the factors which influence the transition barrier in the stereomutational process (we have only just begin in this field and we will give here only a tentative interpretation).



$\frac{k'_1}{k_1} = 2.7$

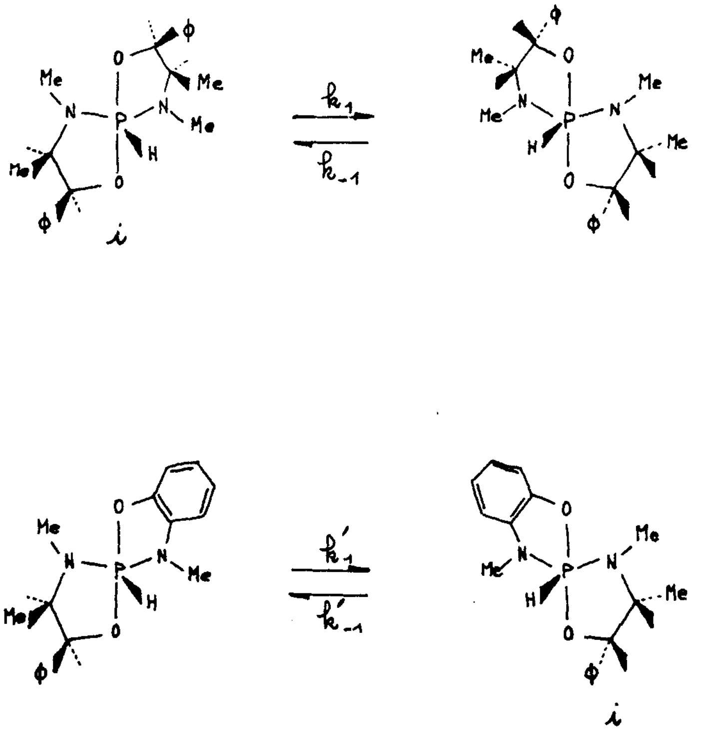
$\frac{k_{-1}}{k'_{-1}} = 3.3$

FIGURE 13

1) Figure 13 shows the influence of the absolute configuration of a choral carbon atom introduced in one ring of a spirophosphorane. It is obvious to forecast lowering of the energy of the transition state, i.e. an acceleration of the process, in going from an erythrow (*cis*) to a threo (*trans*). The change observed is in the right direction, but when a kinetic process is tripled on the thermodynamic scale it corresponds to only 0.3 kcal. Therefore, we need to repeat the observation in several neighbor models.

2) We have also considered the role which can be played by the amino phenol taking the place of an ethanolamine (Figure 14). In our discussions, to forecast the influence of that replacement, we thought that it would clearly slow down the process for at least two reasons: the lack of any conformational flexibility in the aminophenol, and the shortening of the lengths of bonds C–C, and very likely P–N and P–O, all acting to hinder the stereomutational process. It is not true (see Figure 14). An attractive explanation proposed by several authors is concerned with restricted rotation around the P–N bond; this hypothesis will be checked. We recall the sentence of Muetterties and coworkers who proposed this idea: "The resistance to P–N bond rotation makes a major contribution to the Berry rearrangement barrier in R_2NPF_4 molecules."[16]

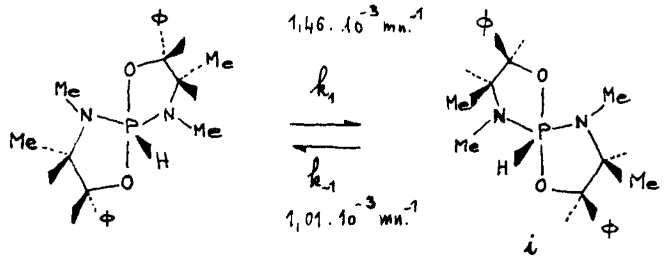
3) In Figure 15 the two compounds are shown for which the rate constant has the minimum and maximum values. In examining the structures, it is apparent that the presence of one or two methyl groups

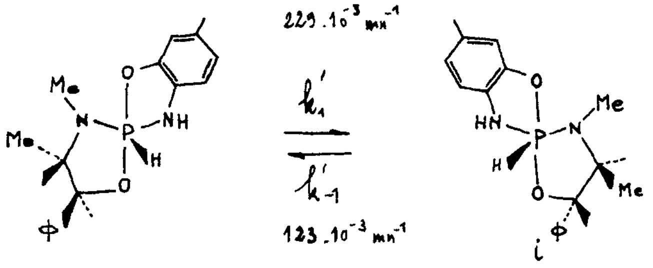


$$\frac{k'_1}{k_1} = 2.3$$

$$\frac{k'_{-1}}{k_{-1}} = 2.9$$

FIGURE 14





directly connected to nitrogen plays a major role on the value of the $\Delta G^{\ddagger}$. It is not surprising that such a modification on an atom close to the phosphorus will bring an important modification of the rate constant.

In conclusion, the mutarotation offers a very sensitive and accurate method for studying the intramolecular process of isomerization in pentacoordination, not only in the field of covalent compounds but also in coordination chemistry.[17] We conclude by emphasizing that the results were obtained in a research group, and, besides the authors, I wish to thank R. Contreras and M. R. Marre for their contributions to our progress.

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