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# Magnetic non-equivalence in phosphate esters. Solvent effects on the $^1$H NMR spectrum of dibenzyl 2-pyridylphosphate

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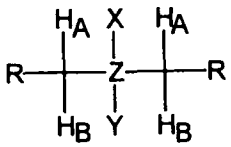
**Abstract**

Methylene protons of benzyl groups in dibenzyl 2-pyridylphosphate show strong magnetic non-equivalence in $CDCl_3$, while the effect is absent in benzene-$d_6$ solutions. The non-equivalence is explained by the intramolecular N → P interactions leading to the "quasi trigonal bipyramidal" geometry of the substrate, observed in solid state, as determined by X-ray diffraction.

*Keywords:* NMR spectroscopy, Solvent effect, Phosphate ester

## 1. Introduction

The magnetic non-equivalence of the methylene protons ($H_A$, $H_B$) located in the vicinity of a chiral or prochiral centre is a well-recognized phenomenon [1] and includes some examples of the system **1**:




**1**

In organophosphorus chemistry (**1**, Z = P), observation on "doubling the resonance signals" of the β- and γ-methyl groups in the ester functions of organic phosphates was reported over thirty years ago [2]. Williamson and Griffin [3] observed the magnetic non-equivalence of the O-methylene protons in the $^1$H NMR spectra of three out of nine compounds of the type $(EtO)_2P(X)Y$ and explained the different chemical shifts of those protons in terms of the ethoxyl groups being attached to the P atom bearing three different substituents. For eight phosphonium ions of the structure $(PhCH_2)_2PXY^+$ the benzyl methylene hydrogens of five substrates showed non-equivalence in the $^1$H NMR spectra recorded in $CDCl_3$ [4]. For one substrate the effect disappeared in DMSO-$d_6$ solution, while the temperature variation showed a negligible effect on the spectra. The most comprehensive

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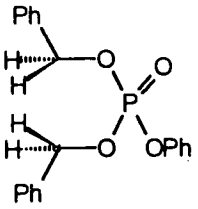
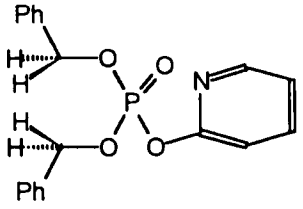
study on the subject was carried out by Hall et al. [5], who examined $^1$H NMR spectra of 22 organophosphorus substrates in various solvents and at a variable temperature. Only three non-chiral compounds of the type $(EtO)_2P(X)Y$ showed the magnetic non-equivalence of the ethoxyl methylene groups; for $MeP(S)(OEt)_2$ the chemical shift difference varied in a series of solvents from $\Delta\delta_{AB} = 10.0$ Hz (in $C_6D_6$) to $\Delta\delta_{AB} = 6.3$ Hz (in DMSO-$d_6$). The results were interpreted in terms of "intrinsic" non-equivalence, combined with the conformational distributions.

We have recently found that the $^1$H NMR spectra of some dibenzyl arylphosphates differ dramatically when recorded in two different solvents. In this paper we report the magnetic non-equivalence of the benzyl methylene groups in two closely related esters, dibenzyl phenyl (**2a**) and dibenzyl 2-pyridyl (**2b**) phosphate.




**2a**




**2b**

## 2. Experimental

### 2.1. Preparation of 2a

Triethylamine (3.49 ml, 25 mmol) was added dropwise, with stirring and cooling to 5°C, to a solution of phenol (2.35 g, 25 mmol) and dibenzyl phosphite (6.56 g, 25 mmol) in dry tetrachloromethane (16 ml). The reaction mixture was stirred overnight at room temperature, filtered, and the solvent was removed from the filtrate under reduced pressure. The product was purified by column chromatography (silica gel, $CHCl_3$/EtOH, 9:1) yielding pure **2a**, a colourless oil (54%). $^1$H NMR ($CDCl_3$) $\delta$ 5.10 (4H, d, $J_{HP} = 8.3$ Hz), 7.11–7.36 (15H, m); $^{31}$P NMR $\delta$ – 5.58. Analysis. Calculated for $C_{20}H_{19}O_4P$: C, 67.8; H, 5.4. Found: C, 66.9; H, 5.5

### 2.2. Preparation of 2b

Prepared as **2a** from 2-hydroxypyridine (2.38 g, 25 mmol) and dibenzyl phosphite (6.56 g, 25 mmol) and purified by column chromatography (silica gel, $CHCl_3$/EtOH, 4:1) and recrystallized from ether; white solid (83%); m.p. 61.5–62.5°C. $^1$H NMR ($C_6D_6$) $\delta$ 5.24 (4H, d, $J_{HP} = 8.2$ Hz), 6.42 (1H, dd, $J_{HH} = 7.2$, 5.1 Hz), 6.74 (1H, d, $J_{HH} = 8.2$ Hz), 6.92 (1H, dt, $J_{HH} = 8.2$, 7.2, Hz), 7.05–7.12 (6H, m), 7.25–7.28 (4H, m), 7.99 (1H, dd, $J_{HH} = 5.1$, 2.0 Hz); $^{31}$P NMR $\delta$ – 5.50; $^{13}$C NMR ($CDCl_3$) $\delta$ 70.1 (d, $J_{CP} = 5.4$ Hz), 113.2 (d, $J_{CP} = 7.7$ Hz), 120.8 (s), 128.0 (s), 128.5 (s), 135.7 (d, $J_{CP} = 7.7$ Hz), 140.0 (s), 147.9 (s), 157. 6(s).

NMR spectra (structural assignments and non-equivalency) were recorded on a Bruker AC300 spectrometer at a probe temperature of 30°C. Chemical shifts are given relative to $SiMe_4$ ($^1$H, $^{13}$C) as an internal standard and 85% $H_3PO_4$ ($^{31}$P) as an external standard. Variable-temperature measurements were carried out using a Varian Unity 400 spectrometer incorporating a Varian VT control unit. A temperature array was set between 25 and 60°C, using 5°C increments with a 300 s delay for thermal equilibration. NMR simulations were carried out using a Varian Unity 400 spectrometer with an IPX SPARC station data system; the LAOCOON program incorporated in the Varian VNMR software package was used.

### 2.3. Crystal structure determination

Accurate unit cell parameters were obtained by the least-squares method from the position of 25 selected centred reflections on an Enraf Nonius CAD4 diffractometer with Mo $K\alpha$ radiation using a graphite monochromator. Corrections for the observed crystal decay were applied, and intensities were also corrected for Lorentz and polarization effects. No absorption correction was applied. The structure was solved by standard Patterson and Fourier methods [6]. Refinement was done by a full-matrix least-squares method [7]. Atomic scattering factors were taken from the literature [8].

Table 1
Crystal data and processing parameters for ester **2b**

| Data/parameter | Value used |
|---|---|
| Empirical formula | $C_{19}H_{18}NO_4P$ |
| Molecular weight (g mol$^{-1}$) | 355.33 |
| Crystal dimension (mm) | 0.21 × 0.23 × 0.27 |
| Space group | *PT* |
| Cell dimensions: *a* (Å) | 5.822 (1) |
| *b* (Å) | 9.188 (1) |
| *c* (Å) | 17.389 (2) |
| $\alpha$ (deg) | 76.82 (1) |
| $\beta$ (deg) | 85.07 (1) |
| $\gamma$ (deg) | 79.51 (1) |
| *Z* | 2 |
| Volume (Å$^3$) | 889.6 |
| *D* (calc.) (g cm$^{-3}$) | 1.308 |
| $\mu$ (cm$^{-1}$) | 1.35 |
| Radiation ($\lambda$, Å) | 0.7107 |
| *T* (°C) | 22 |
| *F* (000) | 372.00 |
| Scan type ($\omega/2\theta$) | 1:0 |
| Scan range (deg) | $3 \leqslant \theta \leqslant 30$ |
| Zone collected: *h* | −8, 8 |
| *k* | 0, 12 |
| *l* | −24, 24 |
| Maximum scan speed (deg min$^{-1}$) | 5.49 |
| Maximum scan time (s) | 60 |
| Scan angle ($\omega + 0.34 \tan\theta$) (deg) | 0.70 |
| Aperture size (mm) | 1.4 × 4.0 |
| Reflections collected | 5376 |
| Decay (%) | 11.8 (corrected) |
| Unique reflections used ($> 3\sigma(I)$) | 2872 |
| $R_{int}$ | 0.017 |
| Parameters refined | 227 |
| Maximum positional shift/esd | 0.002 |
| Residual electron density (*e* Å$^3$) | |
| Maximum | 0.304 |
| Minimum | −0.418 |
| $U_{iso}$(H) (Å$^2$) | 0.134 (5) |
| *R* | 0.072 |
| $R_w$ | 0.056 |

The non-hydrogen atoms were refined anisotropically and the hydrogen atoms were placed in idealized positions with a common isotropic thermal parameter that was also included in the refinement. Convergence was reached using a $\sigma^{-2}(F_0)$ weighting scheme. Crystal data and processing parameters are given in Table 1. The tables showing the structure factors, coordinates, and anisotropic thermal parameters have been deposited with the B.L.L.D. as Supplementary Publication No. SUP 26562 (16 pages).

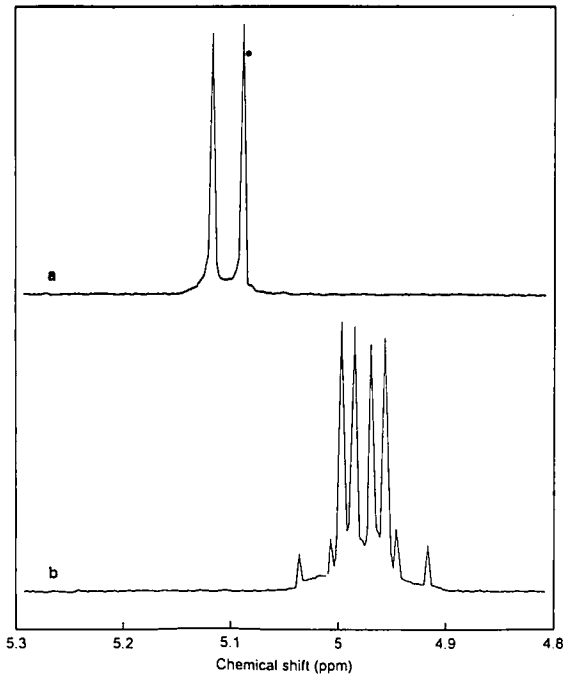



Fig. 1. $^1$H NMR spectrum of the methylene protons of dibenzyl phenylphosphate (**2a**) in: (a) chloroform-*d*; (b) benzene-$d_6$.

## 3. Results and discussion

Sections of the $^1$H NMR spectra (300 MHz) of **2a** and **2b** in $CDCl_3$ and in $C_6D_6$ are shown in Figs. 1 and 2, respectively. For each substrate in one solvent a "deceptively simple" signal of the methylene protons was observed: for **2a** in $CDCl_3$ (d, $J_{HP} = 8.3$ Hz), and for **2b** in $C_6D_6$ (d, $J_{HP} = 8.2$ Hz). On the other hand, **2a** in $C_6D_6$ showed the pattern expected for two ABX systems (two dd, $J_{HP} = 8.6$, 8.8 Hz; $J_{gem} = 11.7$ Hz), and for **2b** the ABX pattern (two dd, $J_{HP} = 7.8$, 8.2 Hz, $J_{gem} = 11.7$ Hz) was observed in $CDCl_3$. The reverse solvent effect indicated essentially different structural effects responsible for the observed behaviour. Ester **2a** belongs to a group of phosphate derivatives where no specific, intramolecular interactions are possible, and numerous compounds of that type have been studied before. Magnetic non-equivalence, as demonstrated in the $^1$H NMR spectra, seems to be a very subtle function of the substituents at phosphorus, as well as of solvation effects. For example, no non-equivalence of

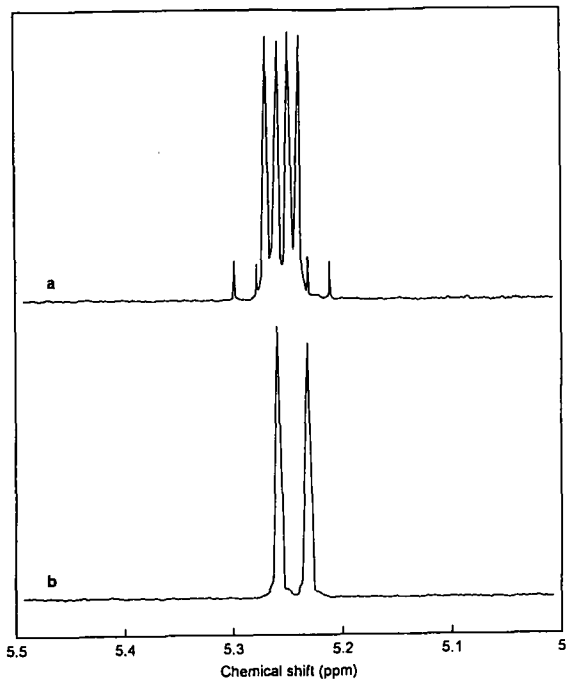



Fig. 2. $^1$H NMR spectrum of the methylene protons of dibenzyl 2-pyridylphosphate (**2b**) in: (a) chloroform-*d*; (b) benzene-$d_6$.

methylene protons was observed for diethyl phenylphosphate [2], but it was observed for diethyl phosphorochloridate [5]. It was concluded that for a substantial difference in the chemical shifts ($\Delta\delta_{AB}$) to exist, "... the potentially anisotropic sensor protons must be influenced by a highly unsymmetrically substituted phosphorus atom." [5]. We believe that **2a** belongs to that "general" type of phosphate, where the non-equivalence results from the fact that each $OCH_2$ group is located in the vicinity of phosphorus bearing three different substituents (phosphoryl oxygen, phenoxy group, and the second benzyloxy substituent). In a low-polarity solvent ($C_6D_6$) the environment of the individual methylene protons is sufficiently different, so the expected signal, consisting of two doublets of doublets, is observed. In the more polar chloroform, in agreement with previous observations of the decrease of $\Delta\delta_{AB}$ with the solvent's polarity [5], the difference is too small to give rise to an observable ABX pattern, and the "deceptively simple' signal is obtained.

We propose, however, that the pyridyl ester **2b** belongs to a different group of substrates, and that the observed non-equivalence is a consequence of specific, highly solvent-dependent, intramolecular interactions. Since the non-equivalence is observed in a more polar but non-aromatic solvent ($CDCl_3$), and not in a less polar but aromatic solvent ($C_6D_6$), we conclude that the specific solvation effects are capable of breaking those intramolecular interactions that are responsible for the non-equivalence. Because of such a dramatic difference in the $^1$H NMR spectra of **2b** in $CDCl_3$ and in $C_6D_6$, we were interested in the magnitude of the solvent effects on the chemical shift difference ($\Delta\delta_{AB}$) in the $CH_AH_B$ system of **2b**. In order to obtain the $\Delta\delta_{AB}$ value, simple simulation experiments were carried out for the methylene protons. For $CDCl_3$ as a medium, the methylene protons' signal can be described as an $A_2B_2X$ system. Simulation of that system requires estimated values of both $J_{H(A)P}$ and $J_{H(B)P}$ coupling constants. Those values should, in principle, be obtainable from the H-coupled $^{31}$P NMR spectrum of **2b** in $CDCl_3$; a signal consisting of two triplets is expected as a first-order approximation. The experimental spectrum revealed, however, partial overlap of signals yielding a broad quintet, from which the $J_{HP}$ values could not be accurately determined. The $^1$H NMR spectrum (Fig. 2), on the other hand, allowed us to estimate both coupling constants as $J_{H(A)P} = 8.12$ Hz, and $J_{H(B)P} = 7.76$ Hz. Using those two $J$ values, simulation of the $A_2B_2X$ system resulted in a spectrum which corresponded with the experimental spectrum to a reasonable degree (Fig. 3). From the simulation experiment a chemical shift difference of $\Delta\delta_{AB} = 23$ Hz (in $CDCl_3$) was obtained indicating a significant difference in the molecular environment of the two methylene protons. In addition, the geminal coupling constant, $J_{AB} = -10.5$ Hz was obtained, which is in reasonable agreement with the value estimated from the experimental spectrum, and with typical $J_{gem}$ values reported in the literature [9]. The temperature effect on the non-equivalence in **2b** was studied in $CDCl_3$ up to 60°C and was found to be negligible, in accordance with earlier reports for other systems [4,5,10].

In order to account for the observed magnetic non-equivalence of the methylene protons in **2b**, the following hypotheses were considered.

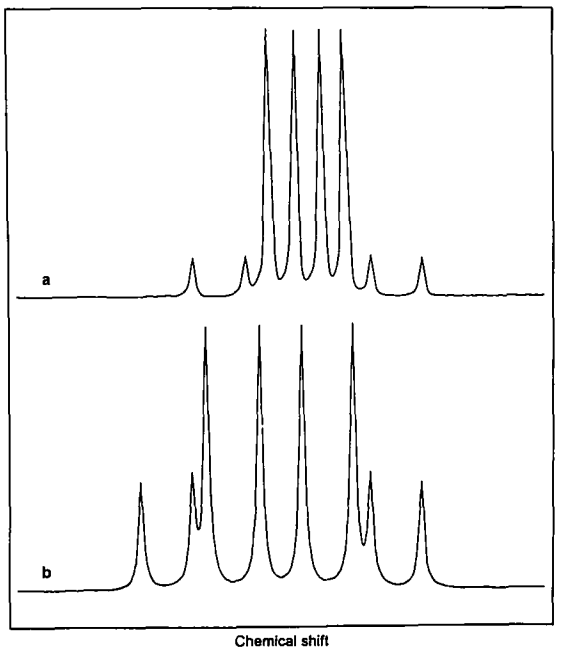



Fig. 3. $^1$H NMR spectrum of the methylene protons of dibenzyl 2-pyridylphosphate (**2b**) in chloroform-*d*: (a) experimental spectrum; (b) simulate spectrum.

(i) Intermolecular interactions

Hudson et al. [11] found that dialkyl α-hydroxyalkylphosphonates exist in the solid state as intermolecularly hydrogen-bonded dimers, and suggested that the bonding may persist in solvents of low polarity. Although the same authors showed that the observed chemical shift non-equivalence results not from H-bonding but from the chirality of the α-C atom, they pointed out that the restricted rotation due to the intermolecular association might also be responsible for the effect. Following the same argument, the non-equivalence in **2b** could, in principle, be the result of a dimeric association via two N → P intermolecular interactions operating in the $CDCl_3$ solution. The $^1$H NMR spectrum of **2b** in $CDCl_3$ does not, however, show any changes with concentration, so the "dimerization" hypothesis was therefore disregarded.

(ii) Intramolecular ring stacking

Self-association of nucleotides via ring stacking of nucleobases is an important phenomenon [12], and since the molecule of **2b** contains three aromatic groups in a flexible framework, such interactions are conceivable for **2b**. A Dreiding model of **2b** revealed a possibility of such ring stacking with the pyridyl ring located between two phenyl groups. Such a structure would impose non-equivalence of the molecular environment of the methylene hydrogens, with one hydrogen of each group located "inside", and the other "outside", the ring-stacked system. This explanation was also discarded because of the observed solvent effect on the chemical shift of the pyridyl protons in **2b**. When pyridine itself is transferred from $CDCl_3$ to $C_6D_6$, the signals of β-H and γ-H undergo a much stronger upfield shift than that of α-H; the effect was explained [13] by a differential shielding of the α,β,γ-hydrogens by solvating benzene molecules (the effect being absent in $CDCl_3$). When moving **2b** from $CDCl_3$ to $C_6D_6$, we observed almost the same change of the $\delta_H$ values for the pyridyl hydrogens as for pyridine, so the explanation postulated for **2b** in $CDCl_3$, a structure involving the pyridyl group "solvated" intramolecularly by two phenyl rings (a situation similar to that existing in benzene solution), had to be discarded.

(iii) Intramolecular N → P donor–acceptor interaction.

We have previously demonstrated [14] the existence of intramolecular interactions between nitrogen and phosphorus atoms in the 8-quinolylphosphate system leading to the distortion of the geometry at phosphorus due to a cyclic arrangement of the N–C–C–O–P linkage. The possibility of a similar (in this case, four-membered) N → P interaction in **2b** was investigated by determining the structure of **2b** by single crystal X-ray diffraction. Fig. 4 depicts a perspective view of the molecule with atomic nomenclature, while Table 2 lists selected bond lengths, bond angles, and dihedral angles.

According to a general effect observed for phosphate triesters [14], the geometry at the phosphorus atom in **2b** deviates from a regular tetrahedron in a sense of smaller O–P–O angles involving ester P–O bonds (98.2–106.4°) and larger angles involving the phosphoryl group (114.6–118.3°). Superimposed on that effect, however, is a secondary effect involving the interaction between the

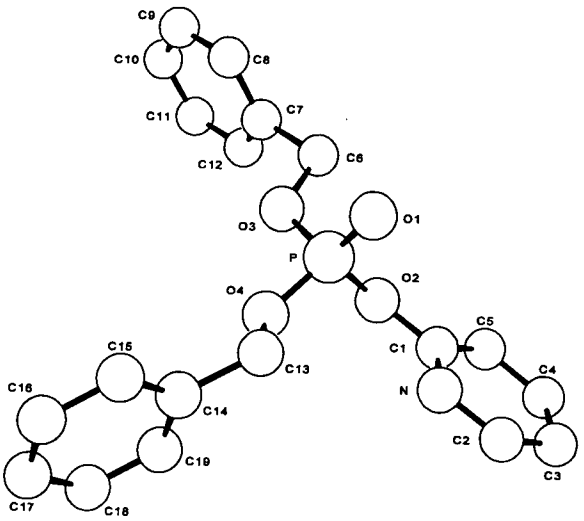



Fig. 4. Crystal structure of dibenzyl 2-pyridylphosphate (**2b**).

nucleophilic pyridyl nitrogen and the electrophilic phosphoryl centre. The N···P non-bonded distance in **2b** is 3.010 Å, while the corresponding sum of van der Waals radii is 3.4 Å [15]. This "short contact" clearly indicates N → P intramolecular interaction and is expected to change the geometry of the phosphorus centre towards that of a trigonal bipyramidal. Analysis of the molecular parameters given in Table 1 confirm the postulated structural effect. The observed dihedral angles, $P-O_2-C_1-N$ (30.65°; ideal 0°) and $P-O_2-C_1-C_5$ (−152.04°; ideal-180°), are an indication of the tendency of nitrogen to locate itself in the vicinity of phosphorus in a quasi four-membered ring. The angles $O_3-P-O_2-C_1$ (173.04°; ideal 180°) and $O_4-P-O_2-C_1$ (−85.62°; ideal-90°) suggest the 'quasi apical" and 'quasi equatorial" positions of the two benzyloxy groups. These conclusions are corroborated by the slightly longer $P-O_3$ bond (1.563 Å) than the $P-O_4$ bond (1.542 Å), as well as by the bond angles $O_1-P-O_2$ (114.6°), $O_1-P-O_4$ (117.7°), and $O_2-P-O_4$ (106.4°), tending towards the ideal value of 120°, and the angles $O_2-P-O_3$ (98.7°) and $O_3-P-O_4$ (98.2°) approaching the ideal value of 90°. As a result of these intramolecular effects, the geometry of **2b** can be presented (in an exaggerated form) by Fig. 5.

Table 2
Selected molecular parameters of dibenzyl 2-pyridylphosphate **2b**

| | |
|---|---|
| *Bond distances (Å)* | |
| $P-O_1$ | 1.453(3) |
| $P-O_2$ | 1.595(3) |
| $P-O_3$ | 1.563(3) |
| $P-O_4$ | 1.542(3) |
| $O_2-C_1$ | 1.394(5) |
| $O_3-C_6$ | 1.462(4) |
| $O_4-C_{13}$ | 1.442(4) |
| *Bond angles (deg)* | |
| $O_1-P-O_2$ | 114.6(2) |
| $O_1-P-O_3$ | 118.3(2) |
| $O_1-P-O_4$ | 117.7(2) |
| $O_2-P-O_3$ | 98.7(2) |
| $O_2-P-O_4$ | 106.4(2) |
| $O_3-P-O_4$ | 98.2(2) |
| *Torsional angles (deg)* | |
| $P-O_2-C_1-N$ | 30.6(0.5) |
| $O_3-P-O_2-C_1$ | 173.1(0.3) |
| $O_4-P-O_2-C_1$ | −85.6(0.4) |
| $P-O_2-C_1-C_5$ | −152.0(0.4) |

In chloroform solution, **2b** may retain its "quasi trigonal bypyramidal" geometry found in the solid state. That geometry necessarily results in a strong molecular non-equivalence of the methylene groups ("quasi apical" and "quasi equatorial"). Fast (on the NMR time-scale) pseudorotation should lead to an exchange of both benzyloxy substituents, but the individual $H_A$ and $H_B$ atoms of each methylene group will always exist in a different molecular environment, leading to the observed non-equivalence in the $^1H$ NMR spectrum. In benzene all aromatic groups in **2b** (including the pyridyl ring) should be effectively solvated (intermolecular ring stacking), so the stabilization of the system via the donor–acceptor interactions leading to the geometry shown in Fig. 5 is no longer necessary. The chemical shift differences for the methylene hydrogens of two benzyloxy groups should

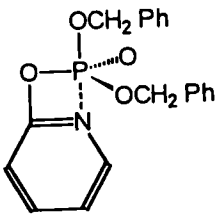



Fig. 5. "Quasi trigonal bypiramidal" geometry of **2b**.

therefore be reduced to such degree that no magnetic non-equivalence would be observed in the $^1H$ NMR spectrum.

## Acknowledgements

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