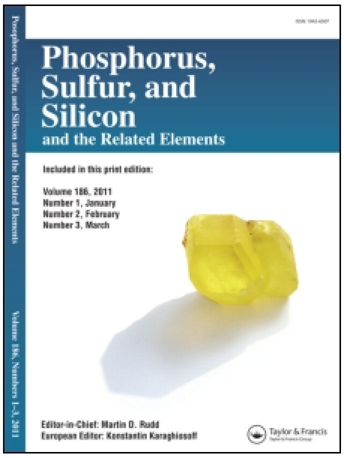

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A NON-SYMMETRICAL DIESTER OF 1(R)-AMINO-1-PHENYLMETHANEPHOSPHONIC ACID. PART II. THE DETERMINATION OF ABSOLUTE CONFIGURATION AT THE CHIRAL PHOSPHORUS CENTER BY ^{1}H NMR STUDIES

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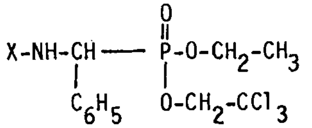
The diastereoisomers of the ethyl-2,2,2-trichloroethyl diester of optically active 1-amino-1-phenylmethanephosphonic acid derivatives were examined by ^{1}H NMR and IR methods. The configuration of the phosphorus atom in each diastereoisomer was determined on the basis of conformational analysis using ^{1}H NMR spectra. Calculations of the location of the methylene protons in the trichloroethyl group as a function of dihedral angles were performed and compared with the experimental values.

Recently[1] we described the synthesis and separation of a diastereoisomeric mixture of non-symmetrical 1(R)-amino-1-phenylmethanephosphonic acid diester **1**



$$\text{X-NH-}\underset{C_6H_5}{\underset{|}{CH}}\text{—}\underset{\text{O-CH}_2\text{-CCl}_3}{\underset{|}{\overset{O}{\overset{\|}{P}}}}\text{-O-CH}_2\text{-CH}_3$$

1

where:

X = Z-benzyloxycarbonyl group a
PHT—phthalyl group b
HCl—hydrochloride c

A number of organophosphorus compound with a center of chirality at the phosphorus atom have been described[2] but until now no data on aminophosphonic acid derivatives have been available. Remarkable differences in the ^{1}H NMR spectra of two diastereoisomers of the diester were observed. These differences were the basis for the determination of the configuration at the phosphorus atom. Sidhal and Prohaska[3] described ^{1}H NMR spectra of diastereoisomeric mixtures of compounds containing a chiral phosphorus atom. The differences in the chemical shift of selected protons in the diastereoisomers were attributed to discrete rotational isomers with relatively large energy barriers separating them. In this paper two diastereoisomeric series "A" and "B" of *N*-derivatized 1(R)-amino-1-phenylmethanephosphonic acid ethyl-2,2,2-trichloroethyl diester were examined. The compounds in the two series have the same configuration at the chiral carbon center (R) but differ in configurations at the phosphorus atom. The ^{1}H NMR spectra of series

"A" compounds showed sizeable differences compared with series "B" compounds. The differences were especially pronounced for protons of the ester groups ($\Delta\delta \sim 0.4$ ppm for **1a**). These rather large differences might be explained, as Sidhal and Prohaska did, by the existence of perferred conformers due to the interactions of the large substituents at the phosphorus atom with those on the α-carbon. This study extends this reasoning to assigning the absolute configuration at the phosphorus atom. In the case of *N*-benzyloxycarbonyl derivatives the protons of the trichloroethyl group appear as ABX patterns (where X is ^{31}P). Although, it is true that an ABX pattern would be observed for two geminal protons which are close to a chiral center, such a pattern was observed only for the *N*-benzyloxycarbonyl derivatives over a wide range of temperatures (−60 to +60°C). The other derivatives showed a simple A_2X pattern. This difference in patterns can be explained by the additional rotational hindrance in *N*-benzyloxycarbonyl derivatives due to the intramolecular hydrogen bonding of the amide proton to the phosphoryl oxygen. This type of bonding in this class of compounds has been described in the literature;[4] however its intra- versus intermolecular character has not been determined. In the IR spectra of *N*-benzyloxycarbonyl 1(R)-amino-1-phenylmethanephosphonic acid ethyl-2,2,2-trichloroethyl diester a peak at 3260 cm^{-1}, characteristic of amides where N—H is engaged in intramolecular hydrogen bonding is observed as opposed to 3400–3500 cm^{-1} for non-H-bonded forms. Unlike the ABX pattern seen for **1a**, in the *N*-phthalyl derivatives **1b**, the methylene protons of the trichloroethyl group were obtained as simple doublets ($J^3_{PH} = 7$ Hz) in both diastereoisomers. A probable explanation is due to the free rotation about the P—O and O—C bonds. Hydrogen bonding as in the *N*-benzyloxycarbonyl derivatives which restricted rotation is not possible. In *N*-benzyloxycarbonyl derivatives as a result of the restricted rotation about P—C_α bond, hindered rotation about P—O—C bonds is also observed.

This causes each methylene proton of the trichloroethyl group to have quite different environments and thus different chemical shifts ($\Delta\delta$ 0.6 ppm for isomer "A"; $\Delta\delta$ 0.2 ppm for isomer "B"; see Table II). In support of this conclusion is the observation that the ABX pattern for the proton of the trichloroethyl group of *N*-benzyloxycarbonyl derivatives is reduced to an A_2X pattern ($J^3_{PH} = 7$ Hz), when the spectra are run in trifluoroacetic acid where intramolecular hydrogen bonding cannot exist. Taking note of these observations, and with the use of molecular models, two preferred conformational isomers can be suggested (Figure 1). Protons

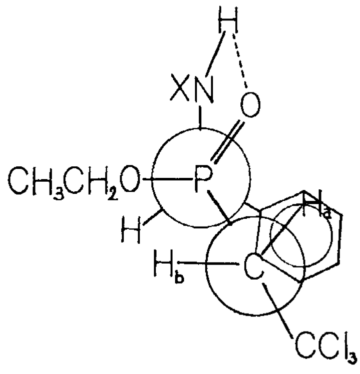


FIGURE 1

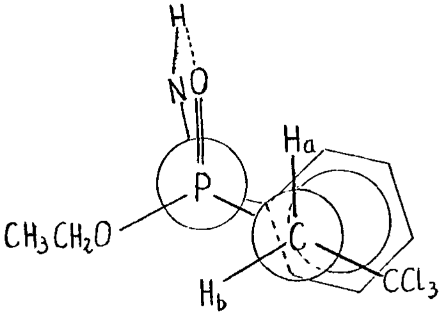


FIGURE 2

in the plane of the benzene ring will resonate at lower field while the protons axial to the ring will resonate at a higher applied field. The following predictions are obtained.

	CH_3—CCl_3	CH_3—CH_3
PHT	$\delta_I > \delta_{II}$	$\delta_I < \delta_{II}$
HCl	$\delta_I < \delta_{II}$	$\delta_I > \delta_{II}$
Z	$\delta_I < \delta_{II}$	$\delta_I > \delta_{II}$

Comparison of the predicted relationship of the chemical shifts deduced from anisotropy of the benzene ring effect and the experimental values (Table I) allows us to conclude that isomers in series "A" have the same configuration at the phosphorus atom as the proposed Structure I, i.e. (R; R) and isomer series "B" as the Structure II, i.e., (R; S).

In order to confirm this hypothesis, the calculation of the location of the trichloroethyl group's protons (coordinates ρ and Z), in relation to the benzene ring, as a dihedral angles (Figure 2) function were performed for *N*-benzyloxycarbonyl derivatives. Using tables[5] of shielding effects produced by ring currents in the benzene ring, the values of this effect were attributed to each pair of coordinates

$$\delta'_{H_a} = f(\rho_{H_a}; Z_{H_a}) \qquad \delta'_{H_b} = f(\rho_{H_b}; Z_{H_b})$$

Values of δ' were added to the average chemical shift for the trichloroethyl groups $\bar{\delta} = 4.30$ ppm (found for derivatives without the benzene ring attached to the α-carbon atom) and the pair of chemical shift were obtained.

$$\delta_{H_a} = \bar{\delta} + \delta'_{H_a} \qquad \delta_{H_b} = \bar{\delta} + \delta'_{H_b}$$

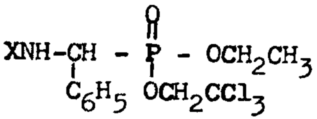
for respective angles α, β, γ and δ.

The calculations were performed for preferred conformational angles, over the range $\pm 30°$ in $5°$ steps, taking into consideration the existence of the intramolecular hydrogen bond.

The chemical shift of H_a and H_b which were found from ^1H NMR spectra run at $-60°C$ are respectively for isomer "A" $\delta_{H_a} = 4.24$ ppm and $\delta_{H_b} = 3.37$ ppm, and for isomer "B" $\delta_{H_a} = 4.54$ ppm and $\delta_{H_b} = 4.35$ ppm. The calculations for isomer I (Figure 1) gave values of chemical shifts similar to the one obtained from isomer Z "A"'s spectrum ($\delta_{H_a} = 4.26$ ppm and $\delta_{H_b} = 3.56$ ppm) for only one set of dihedral angles ($\alpha = 100°$; $\beta = -10°$; $\gamma = -60°$; $\delta = -60°$; $\omega = 60°$).

TABLE I

Proton resonance data



$$XNH\text{-}\underset{C_6H_5}{CH}\text{-}\overset{O}{\underset{OCH_2CCl_3}{\overset{\|}{P}}}\text{-}OCH_2CH_3$$

$[\alpha]_D^{20}$	X	Ph δ(ppm)	NH δ (ppm)	CHP δ (ppm)	CH_2—CCl_3 δ (ppm)	$\underline{CH_2}CH_3$ δ (ppm)	$CH_2\underline{CH_3}$ δ (ppm)
9.1 $CHCl_3$	Z A	7.25 s	6.60–6.95 m	5.31 d-d J_{HH} = 9.5 Hz J_{HH} = 22 Hz	3.62–4.47 ABX system	3.92–4.30 m	1.22 t J_{HH} = 8 Hz
0 $CHCl_3$	Z B	7.25 s	6.35–6.75 m	5.30 d-d J_{HH} = 10 Hz J_{PH} = 22.5 Hz	4.20–4.75 ABX system	3.60–4.20 m	1.05 t J_{HH} = 7 Hz
8.0 Ch_3OH	HCl A	7.57–8.12 m	9.32–10.00 NH_3^+ m	5.45 d J_{PH} = 19 Hz	4.90 d J_{PH} = 8 Hz	4.51 d-q J_{HH} = 7 Hz J_{PH} = 7 Hz	1.54 t J_{HH} = 7 Hz
−7.0 CH_3OH	HCl B	7.59–8.07 m	9.32–10.30 NH_3^+ m	5.45 d J_{PH} = 18 Hz	5.16 d J_{PH} = 9 Hz	4.33 d-q J_{HH} = 7 Hz J_{PH} = 7 Hz	1.35 t J_{HH} = 7 Hz
−81.5 $CHCl_3$	PHT A	7.17–7.95 m	—	5.80 d J_{PH} = 26 Hz	4.77 d J_{PH} = 7 Hz	4.23 d-q J_{HH} = 7 Hz J_{PH} = 7 Hz	1.21 t J_{HH} = 7 Hz
−48.0 $CHCl_2$	PHT B	7.17–7.95 m	—	5.87 d J_{PH} = 26 Hz	4.47 d J_{PH} = 7 Hz	4.29 d-q J_{HH} = 7 Hz J_{PH} = 7 Hz	1.17 t J_{HH} = 7 Hz

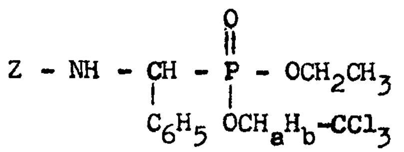
The chemical shifts for isomer II (Figure 1) for dihedral angles ($\alpha = 80°$; $\beta = 120°$; $\gamma = 60°$; $\delta = -60°$; $\omega = 60°$) were almost identical to values found from isomer Z "B" 's spectrum ($\delta_{H_a} = 4.56$ ppm and $\delta_{H_b} = 4.36$ ppm).

These results confirmed the hypothesis that isomer "A" has the configuration illustrated by Structure I (R; R) and isomer "B" by Structure II (R; S). As a result the proton of the trichloroethyl group of isomer Z "A" are in an environment with a considerably higher gradient of magnetic field (near the benzene ring) and a great variation of $\delta_{H_a} - \delta_{H_b}$ values with temperature can be expected.

In contrast protons of the trichloroethyl group in isomer Z "B" are far from the benzene ring so they are in a region of low gradient of magnetic field and a small variation of $\delta_{H_a} - \delta_{H_b}$ values can be expected. These predictions are in good agreement with the experimental data (see Table II).

TABLE II

Results of calculation of ABX system



$$Z-NH-\underset{C_6H_5}{\underset{|}{CH}}-\overset{O}{\overset{\|}{\underset{OCH_aH_b-CCl_3}{\underset{|}{P}}}}-OCH_2CH_3$$

	T °C	−60	−50	−40	−30	0	20	60
Isomer A	$\delta_{H_a} - \delta_{H_b}$ Hz	69.7	69.3	63.4	57.2	50.0	47.0	39.1
	$\delta_{H_a} - \delta_{H_b}$ ppm	0.87	0.87	0.79	0.72	0.62	0.59	0.49
Isomer B	$\delta_{H_a} - \delta_{H_b}$ Hz	13.7	13.7	13.8	13.9	15.0	15.6	15.6
	$\delta_{H_a} - \delta_{H_b}$ ppm	0.171	0.171	0.172	0.174	0.188	0.195	0.195

EXPERIMENTAL

The preparation of all the compounds was described by Szewczyk *et al.*[1] ^1H NMR spectra were recorded at temperatures between −60°C and +60°C using Tesla BS 80 $CDCl_3$ with HMDSO as internal standard and in DMSO and TFA with HMDSO as external standard. IR Spectra were obtained with UR 10 Zeiss, Jena in CCl_4 for c = 0.2 mol/l : 0.1 mol/l : 0.05 mol/l : 0.02 mol/l : 0.01 mol/l : 0.005 mol/l. Calculations were made using a Data Point 5500 computer.

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