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N.M.R. NONEQUIVALENCE OF DIASTEREOISOMERIC DIALKYL PHOSPHITES

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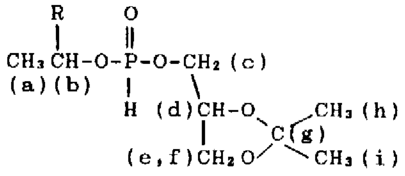
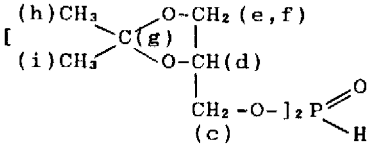
Summary: *N.m.r. (^1H, ^{13}C, ^{31}P) spectra of three dialkyl phosphites existing as diastereomeric mixtures were analysed in order to demonstrate the n.m.r. nonequivalence caused by the chirality of the XYP(O)H centre. In all cases, ^{31}P, ^{13}C, and to a lesser extent, ^1H n.m.r. showed the expected splitting, indicating configurational stability of the phosphorus atom.*

^{31}P n.m.r. nonequivalence of diastereoisomeric diesters of dithiophosphoric acid, $(RO)_2PS_2H$, has been used for determination of the enantiomeric excess of chiral alcohols.[1] For other systems in which chiral centres are the source of nonequivalence in the ^{31}P n.m.r. spectra, very few reports concern derivatives of the type XYP(O)H. The exceptions are alkyl alkylphosphinates, R(OR')P(O)H, for which the magnetic nonequivalence of the phosphorus atoms was observed when a chiral centre was located either in the phosphinate (R),[2] or in the alcohol (R')[3] moiety. In the same system, the nonequivalence of the diastereotopic protons was reported for ester groups,[4,5] but for benzylarylphosphine oxides the methylene protons gave rise only to doublet of doublets,[6] indicating negligible difference in the chemical shifts of these diastereotopic atoms. Mixed dialkyl phosphites (RO)(R*O)P(O)H, (1), derived from a racemic alcohol, R*OH, should exist as diastereomeric pairs of two racemates, while a phosphite containing two moieties of a racemic alcohol, $(R^*O)_2P(O)H$, (2), should give rise to a mixture of one racemate and two diastereomeric meso forms. Since the hydrogen exchange at the $X_2P(O)H$ fuction is believed [6] to proceed with retention of configuration, stereochemical relations existing in systems (1) and (2) should be revealed in their n.m.r. spectra. It was reported, however,[7] that the phosphite of the type (1) [R = 3-(isopropylamino)propyl; R* = 2,3-(isopropylidenedioxy)propyl] gives rise to only one signal (d, $^1J_{PH}$ 733 Hz) in the ^{31}P n.m.r. spectrum. On the other hand, trialkyl phosphite $MeOP(OR^*)_2$ shows two signals in its ^{31}P n.m.r. spectrum.[8] Recent work on the synthesis of glycerophospholipids [9] showed the magnetic nonequivalence ($\Delta\delta$ = 0.22 ppm) of phosphorus atom in the two diastereomeric phosphites derived from ethanoloamine and 1,2-dipalmytoylglycerol.

We described recently [10] a simple method for the preparation of mixed and symmetrical phosphites *via* the Ti(IV) - mediated transesterification of dialkyl phosphites. In this paper we report the full analysis of the n.m.r. (^{1}H, ^{13}C, ^{31}P) spectra of the two mixed and one symmetrical phosphites prepared [11] by the transesterification method: ethyl 2,3-(isopropylidenedioxy)propyl phosphite, (1a); isopropyl 2,3-(isopropylidenedioxy)propyl phosphite, (1b); bis-[2,3-(isopropylidenedioxy)propyl phosphite, (2a).



1a, R = H;
1b, R = CH$_3$



2a

The n.m.r. spectroscopic data obtained for compounds 1a, 1b, and 2a are given in the Table.

Since all substrates contain a large number of similar hydrogen atoms of the O-C-H functions, the multiplicity and the partial overlap of the signals of these protons complicated unambigous determination of the nonequivalence of the individual atoms. The protons of the individual isopropylidene methyl groups, with the exception of one group in (2a), give rise to a single signal in the ^{1}H n.m.r. spectrum. The P-H protons, however, located directly at one of the chiral centers, show magnetic nonequivalence by significant broadening of both parts of the doublets for (1a) and (1b), and by splitting the signal of the P-H proton of (2a) into three doublets with the expected intensity ratio. The magnetic nonequivalence of diastereomers is much better demonstrated by ^{13}C n.m.r. spectroscopy. Most of the carbon atoms in mixed phosphites (1a) and (1b) give separate signals for both diastereomers, with the average value of $\Delta\delta$ 0.12 ppm. Similarly, carbon atoms in the diastereomers of (2a) show magnetic nonequivalence (av. $\Delta\delta$ 0.05 ppm), although in most cases splitting into two, not the expected three signals is observed. Only the ring carbon (e), vicinal to the chiral centre at C(d), gives rise to three signals in the 1:2:1 ratio.

The magnetic nonequivalence of phosphorus atom is clearly demonstrated for all three phosphites. In all cases the expected splitting of the ^{31}P n.m.r. signal (and the expected intensity ratio) is observed;

the chemical shift difference for individual stereoisomers being 0.17 - 0.18 ppm for mixed phosphites (1), and 0.27 - 0.28 ppm for (2a). The observed nonequivalence of phosphorus was retained upon addition of triethylamine to the $CDCl_3$ solutions of the substrates, as well as for their solutions in methanol-d_4. This result supports the earlier view[6] that the H-D (or H-H) exchange at the $(RO)_2P(O)H$ centre occurs with retention of configuration.

Table. N.m.r. data for 1a, 1b, 2a; $CDCl_3$; chemical shifts in ppm, relative to TMS (^{1}H, ^{13}C) or trimethyl phosphate (^{31}P); coupling constants in Hz.[12]

	1a	1b	2a
^{1}H			
(a)	1.28,t,$^{3}J_{HH}$ 7.0	1.30,d,$^{3}J_{HH}$ 5.6	
(b)	4.11,m[a]	4.71,m[a]	
(c)	4.01,m[a]	4.01,m[a]	4.05,m[a]
(d)	4.25,m[a]	4.26,m[a]	4.27,m[a]
(e)	3.76,m[a]	3.76,m[a]	3.76,m[a]
(f)	4.01,m[a]	4.01,m[a]	4.05,m[a]
(h)	1.27,s	1.29,s	1.308,s
(i)	1.35,s	1.37,s	1.383,s 1.386,s
P-H	6.81,d(broad), $^{1}J_{HP}$ 704	6.81,d,(broad), $^{1}J_{HP}$ 701	6.89,three d(1:2:1) δ 0.007; $^{1}J_{HP}$ 717
$^{13}C\{^{1}H\}$			
(a)	16.1,d,$^{3}J_{CP}$ 6.0	23.7,d,$^{3}J_{CP}$ 4.6	
		23.9,d,$^{3}J_{CP}$ 4.6	
(b)	61.8,d,$^{2}J_{CP}$ 5.4	71.2,d,$^{2}J_{CP}$ 6.0	
(c)	65.2,d,$^{2}J_{CP}$ 6.3	65.0,d,$^{2}J_{CP}$ 6.1	65.4,d,$^{2}J_{CP}$ 6.5
	65.5,d,$^{2}J_{CP}$ 6.3	65.4,d,$^{2}J_{CP}$ 6.1	
(d)	74.0,d,$^{3}J_{CP}$ 6.4	74.0,d,$^{3}J_{CP}$ 6.3	74.0,d,$^{3}J_{CP}$ 5.9
	74.1,d,$^{3}J_{CP}$ 6.4	74.1,d,$^{3}J_{CP}$ 6.3	74.1,d,$^{3}J_{CP}$ 5.9
(e)	65.72,s	65.82,s	65.73,s
	65.75,s[b]	65.88,s[b]	65.78,s
			65.81,s[b]
(g)	109.8,s	109.8,s	109.9,s
	109.9,s	109.9,s	110.0,s
(h)	25,0,s	25.1,s	25.1,s
	25.1,s	25.6,s	25.2,s
(i)	26.6,s	26.6,s	26.6,s
$^{31}P\{^{1}H\}$	5.63, 5.81 (1:1)	4.23, 4.40 (1:1)	6.19, 6.46, 6.72 (1:2:1)

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[a] Partial overlap of signals due to hydrogens b,c,d,f made multiplicity determination difficult. Fine structure was however observed indicating magnetic nonequivalence of the methylene and methine hydrogen atoms.

[b] The observed values of $\Delta\delta$ for carbon e in substrates 1a, 1b, 2a, are 2.3, 4.5, and 3.0 Hz, respectively. They are clearly too large for the ^{4}J(CCCOP) coupling, particularly that we found no splitting of the Γ-carbon atom signal in the ^{13}C n.m.r. spectrum of di-n-butyl phosphite.

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11. 1,2-Isopropylidene glycerol (4 mol eq.) was added to $Ti(OiPr)_4$ or $Ti(NEt_2)_4$ (1 mol eq.) in dry benzene, and the volatile components were removed under reduced pressure. Dialkyl phosphite (1 mol eq.) in benzene was added, and the solutions were incubated at 40°C for 4 days. After the aqueous work-up, the products were purified by "bulb to bulb" distillation. Mixed phosphites (1a), (1b) were obtained as first fraction (oven temp. 110°C/0.1 mm), and phosphite (2a) as a second fraction (oven temp. 150°C/0.1 mm). All products gave elemental analysis results (C,H), as well as i.r. and mass spectra in agreement with expected structures.
12. N.m.r. assignments were made by detailed comparison of the n.m.r. spectra of the products with those of the substrates (dialkyl phosphites, 1,2-isopropylidene glycerol), and by the use of the 2D COSY and HETCOR experiments (FT Bruker AC 300 spectrometer).

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