Phosphoramides. Part 9.[1] An Attempt to describe the Mechanism in the Reaction of Benzyl Alcohols with Hexamethylphosphoric Triamide

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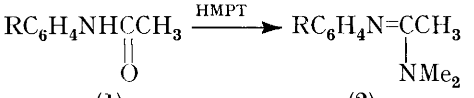
The reactions of *p*-methoxybenzyl alcohol, *m*-nitrobenzyl alcohol, and diphenylmethanol with hexamethylphosphoric triamide (HMPT) at 190—210 °C to form *NN*-dimethylbenzylamines were followed by quantitative ^{13}C n.m.r. spectroscopy and were found to be autocatalysed. A competition experiment between *m*-nitrobenzyl alcohol and diphenylmethanol with HMPT, and the observed quenching of the reaction by addition of NaOAc to the reaction mixture, indicated the metaphosphate anion as a reactive intermediate. Mono- and bis-*p*-methoxybenzyl phosphates, which were believed to be formed from the corresponding alcohol and metaphosphate, were detected in the ^{13}C and ^{31}P spectra of the reaction mixture. The intermediately formed benzyl phosphates were believed to undergo an S_N1 or an S_N2 substitution reaction with dimethylamine present in the reaction mixture yielding the *NN*-dimethylbenzylamines.

HEXAMETHYLPHOSPHORIC TRIAMIDE (HMPT) is a versatile reagent capable of both dehydrohalogenation [2] and dehydration [3] and a variety of other reactions.[4] Although few attempts have been made to clarify the mechanisms of these reactions, which are still obscure, an early investigation showed that reaction of the amide (1) with HMPT at 210 °C to give the amidine (2) was autocatalysed; the catalyst, which was thought to be *NNN'N'*-tetramethylphosphorodiamidic acid,[5] was found to be formed at a similar rate to that for disappearance of the amide (1). The reaction rate was given by equation (1)



$$RC_6H_4NHC(=O)CH_3 \xrightarrow{HMPT} RC_6H_4N{=}C(CH_3)NMe_2$$

(1) (2)

$$\text{rate} = k[AcNHC_6H_4R]([AcNHC_6H_4R]_0 - [AcNHC_6H_4R]) \quad (1)$$

where $[AcNHC_6H_4R]_0$ is the initial concentration of compound (1). In the dehydration of tertiary alcohols with HMPT at reflux temperature, evidence has been found for a carbonium ion mechanism,[6,7] but for other alcohols this does not seem to be the case.[8,9] In the reaction of alcohols, ROH, with HMPT the alkyl *NNN'N'*-tetramethylphosphorodiamidate, $RO{\cdot}PO(NMe_2)_2$ (3), was thought to be formed in the initial step. This suggestion was supported by isolation of (3; R = 2-adamantyl) in 15% yield in the reaction of 2-adamantol with HMPT.[10] In the reaction of benzyl alcohol (4) with HMPT to give *NN*-dimethylbenzylamine (5) the phosphorodiamidate (3; R = benzyl) was also believed to be a reaction intermediate.[3,9] This was supported by the observation that independently prepared (3; R = benzyl) could be decomposed at 230—240 °C to give the amine (5).[3] In the present work the reaction of benzyl alcohols with HMPT has been reinvestigated in order both to identify the reaction intermediates as well as to obtain kinetic results upon which reliable reaction mechanisms could be based.

$$\underset{(4)}{PhCH_2OH} \xrightarrow{HMPT} \underset{(5)}{PhCH_2NMe_2}$$

Quantitative ^{13}C *N.M.R. Measurements.*—For our investigation of the reaction of benzyl alcohols with HMPT we were looking for a direct spectroscopic method. Quantitative ^{13}C n.m.r. measurements were thought to be attractive since collapse of spectral lines are rare. There are several problems with this technique however because of the nuclear Overhauser effect (n.O.e.). These problems can be avoided, however, by using the gated decoupling technique first suggested by Freeman *et al.*[11] or by adding paramagnetic species to the samples.[12] A weakness of the first method is associated with extended waiting periods which result in an overlong accumulation time.

In our investigation we found that not only was there no improvement in the accuracy upon the addition of paramagnetic ions to the samples, but rather the reverse in that, because of the reduction in signal-to-noise ratio, such additions should be avoided.

Several difficulties in quantitative ^{13}C n.m.r. measurements can be eliminated by introducing an internal reference compound. This procedure is based upon the assumption that the n.O.e. effects do not change during the reaction and that the changes in relaxation times are equivalent for all carbon atoms. These assumptions are likely to be fulfilled if the viscosity is equivalent in all samples.[13]

The ^{13}C n.m.r. spectra of a reaction mixture of benzyl alcohols (BA), and HMPT were recorded in normal FT mode as a function of time. Normal noise decoupling of the protons were used. The peak height was used instead of the integrals because numerical integration by the computer is too inaccurate. Since diphenyl ether (DPE), does not react with HMPT, this molecule was introduced to the reaction mixture as an internal reference. In order to minimize the uncertainties the sum of the intensities of all the strong signals in the spectrum was used. The concentration of BA is then given by

$$[BA] = K\frac{\sum_i I^i_{BA}}{\sum_j I^j_{DPE}} \quad (2)$$

in which I^i_{BA} and I^j_{DPE} are intensities of strong lines in the spectra of benzyl alcohols and diphenyl ether, respectively.

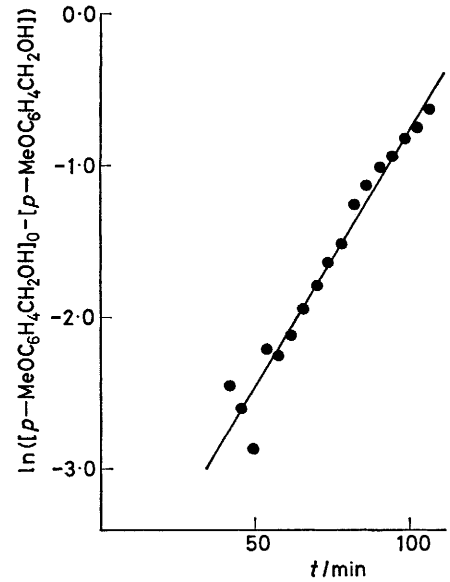


FIGURE 1 Plot of ln($[p\text{-MeOC}_6\text{H}_4\text{CH}_2\text{OH}]_0 - [p\text{-MeOC}_6\text{H}_4\text{CH}_2\text{OH}]$) *versus* time at 200 °C. The initial conditions are: $[p\text{-MeOC}_6\text{H}_4\text{CH}_2\text{OH}]_0 = 0.655$ mol kg^{-1} and $[(\text{C}_6\text{H}_5)_2\text{O}] = 0.134$ mol kg^{-1} in HMPT. Induction period of the autocatalysed reaction ≈40 min

The value of K can be evaluated from spectra of standard solutions with known concentrations. The uncertainty of [BA] for *p*-methoxybenzyl alcohol decreases from 18 to 6% when three strong lines * instead of two were used in equation (2) for both BA and DPE.

Figure 1 shows a plot of ln ($[\text{BA}]_0 - [\text{BA}]$) *versus* time for the reaction of *p*-methoxybenzyl alcohol with HMPT at 200 °C. The plot shows a very good approach to a straight line, which can be explained as due to an autocatalysed reaction following expression (3) in which

$$-\frac{\mathrm{d}[\text{BA}]}{\mathrm{d}t} = k([\text{BA}]_0 - [\text{BA}]) \qquad (3)$$

$[\text{BA}]_0$ is the initial concentration. The rate constants given in Table 1 for other benzyl alcohols were found likewise.

TABLE 1

Rate constants for autocatalysed reactions of benzyl alcohols with HMPT

Alcohols	t/°C	Induction period (min)	10^4k/s^{-1}
$p\text{-MeOC}_6\text{H}_4\text{CH}_2\text{OH}$	190	60	2.6
$p\text{-MeOC}_6\text{H}_4\text{CH}_2\text{OH}$	200	40	5.7
$p\text{-MeOC}_6\text{H}_4\text{CH}_2\text{OH}$	210	0	8.4
$p\text{-MeOC}_6\text{H}_4\text{CH}_2\text{OH}$ + NaOAc	200		~0
$p\text{-MeOC}_6\text{H}_4\text{CH}_2\text{OD}$	200	0	5.4
$m\text{-O}_2\text{NC}_6\text{H}_4\text{CH}_2\text{OH}$	200	0	6.9
Ph_2CHOH	200	100	3.8

RESULTS AND DISCUSSION

^{31}P N.m.r. spectra were found to give invaluable information about possible phosphorus reaction intermediates. A typical hydrogen undecoupled ^{31}P n.m.r. spectrum of the reaction mixture of *p*-methoxybenzyl alcohol and HMPT is illustrated in Figure 2. HMPT was used both as solvent and reagent and is therefore represented by the strong peak A showing couplings with the protons of HMPT. The singlets D and E are due to pyrophosphate and trimetaphosphate ions, respectively. Peak B consists of a triplet [$^3J(^{31}\text{P-H}) = 4.9$ Hz], in agreement with a mono-*p*-methoxybenzyl phosphate, where the methylene protons couple to the phosphorus atom. Similarly peak C was found to be a quintet [$^3J(^{31}\text{P-H}) = 5.9$ Hz], which was assigned to bis-(*p*-methoxybenzyl) phosphate. The pyrophosphate D has previously been isolated as bis(dimethylammonium) dihydrogen pyrophosphate, $(\text{Me}_2\text{NH}_2)_2\text{H}_2\text{P}_2\text{O}_7$, which at the end of the reaction was found, in agreement with the literature,[14] to form an insoluble oily layer. Since dimethylamine is formed during the reaction the above mentioned benzyl phosphates would be expected to exist in the reaction mixture as their mono-dimethylammonium salts.

Confirmation of the above mentioned assignments was obtained from the ^{31}P n.m.r. spectra of the reaction mixture, since the chemical shift of ^{31}P in the benzyl phosphates was affected both by addition of concentrated HCl or NaOH. Upon addition of concentrated HCl $p\text{-MeOC}_6\text{H}_4\text{CH}_2\text{OPO}_3\text{H}^-$ was protonated to give $p\text{-MeOC}_6\text{H}_4\text{CH}_2\text{PO}_3\text{H}_2$; this was reflected by a change in the chemical shift of 4.7 p.p.m. towards higher field for phosphorus (see Table 2). The same species could be deprotonated by addition of 40% NaOH, whereupon the phosphorus nuclei was found 2.8 p.p.m. to lower field in the spectrum. $(p\text{-MeOC}_6\text{H}_4\text{CH}_2\text{O})_2\text{PO}_2^-$ was found as such both in the reaction mixture and when 40% NaOH was added; it was, however, protonated upon addition of

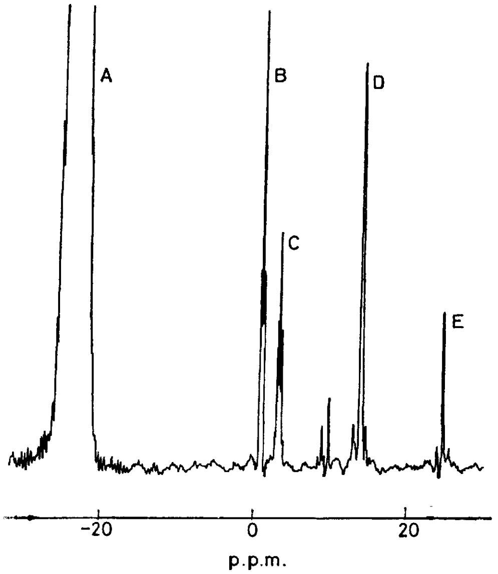


FIGURE 2 Proton undecoupled ^{31}P n.m.r. spectrum of the reaction mixture from $p\text{-MeOC}_6\text{H}_4\text{CH}_2\text{OH}$ and HMPT after 250 min at 190 °C when 77% of the alcohol had disappeared. A, HMPT; B, $p\text{-MeOC}_6\text{H}_4\text{CH}_2\text{OPO}_3\text{H}^-$; C, $(p\text{-MeOC}_6\text{H}_4\text{CH}_2\text{O})_2\text{PO}_2^-$; D, pyrophosphate; E, trimetaphosphate

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* The chemical shifts (p.p.m.) of the lines used in diphenyl ether were: $C(2)$: 118.8; $C(4)$: 124.0; and $C(3)$: 130.4 and in *p*-methoxybenzyl alcohol: CH_2OH: 63.2; $C(2)$: 128.4 and $C(1)$: 134.8.

TABLE 2

^{31}P Chemical shifts of intermediates found in the reaction mixture of p-$MeOC_6H_4CH_2OH$ and HMPT at 190 °C

	Reaction mixture	Reaction mixture + conc. HCl	Reaction mixture +40% NaOH
p-$MeOC_6H_4CH_2OPO_3H_2$	0.3	5.0	−2.5
(p-$MeOC_6H_4CH_2O)_2PO_2H$	2.8	5.3	2.4
$H_4P_2O_7$	13.5	17.0	11.6

concentrated HCl, when the chemical shift of the phosphorus atom shifted 2.5 p.p.m. towards higher field. Similarly it was concluded that the pyrophosphate, found as $H_2P_2O_7^{2-}$, could be converted into $H_4P_2O_7$ or $P_2O_7^{4-}$, depending on whether HCl or NaOH was added to the reaction mixture. The phosphate ions formed by addition of NaOH could be converted into their protonated forms by addition of HCl and *vice versa*, as could easily be followed by ^{31}P n.m.r. spectroscopy. Two small doublets were found in the ^{13}C spectrum of the reaction mixture of p-$MeOC_6H_4CH_2OH$ and HMPT at 65.9 and 66.6 p.p.m. both with $^2J(^{31}P–C) = 5$ Hz. These signals were assigned to the benzylic carbons of p-$MeOC_6H_4CH_2OPO_3H^-$ and (p-$MeOC_6H_4CH_2O)_2PO_2^-$, where couplings to phosphorus atoms are possible. Surprisingly, the benzyl phosphorodiamidate (3), previously assumed to be an intermediate in the reactions of benzyl alcohols with HMPT could not be detected. This species should easily be recognized in the ^{31}P n.m.r. spectra because of coupling between the phosphorus atom and the dimethylamino-protons.

In Figure 3 the concentrations of p-$MeOC_6H_4CH_2OPO_3H^-$ and (p-$MeOC_6H_4CH_2O)_2PO_2^-$ are given during the reaction. The formation and disappearance of the benzyl phosphates with simultaneous transformation to benzylamine strongly indicates that the benzyl phosphates are reaction intermediates. It is known that the metaphosphate ion (7) is formed as an intermediate in the hydrolysis of the pyrophosphate (6) at an adequate pH value.[15] Since the pyrophosphate (6) was observed during the reaction of the benzyl alcohol (8; R = p-MeO) with HMPT we can similarly assume the intermediate formation of the metaphosphate anion (7), which can react with benzyl alcohol (8) to produce the monobenzyl phosphate (9). The dibenzyl phosphate (10) is believed to be formed from (9) in a similar mechanism. Phosphate ions are known to be good leaving groups in S_N1 and S_N2 reactions so that benzylamine (11) can easily be produced from the phosphates (9) and (10) by reaction with the dimethylamine released from the dimethylammonium ion. The phosphoric acid produced during the reaction is believed to react with HMPT so that more pyrophosphate is formed. pH dependence in the formation the metaphosphate (7) from pyrophosphate (6) was also demonstrated here. At 200 °C the reaction of p-$MeOC_6H_4CH_2OH$ with HMPT was complete within 2 h, but addition of NaOAc (concentrations: 0.652 mol kg^{-1} p-$MeOC_6H_4CH_2OH$ and 0.338 mol kg^{-1} NaOAc) effectively quenched the reaction. After 46 h only 12% of the benzyl alcohol had disappeared. This is in agreement with the observation that the pyrophosphate (6) is stable to hydrolyses *via* the metaphosphate (7) in alkali media. Using HMPT as a solvent at reflux temperature, it is possible to reduce the side reactions of HMPT by addition of NaOAc. If KOH is added precautions should be taken to prevent possible auto-oxidations.[16]

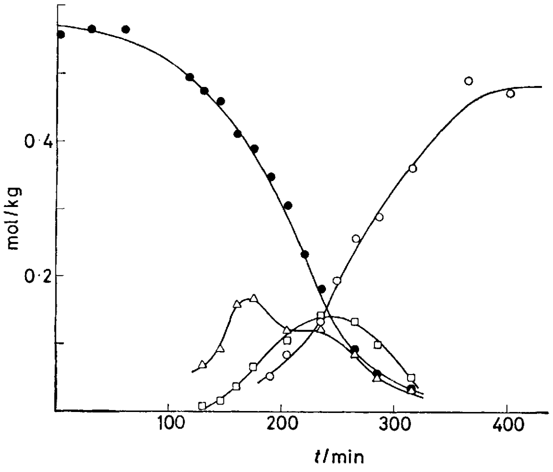
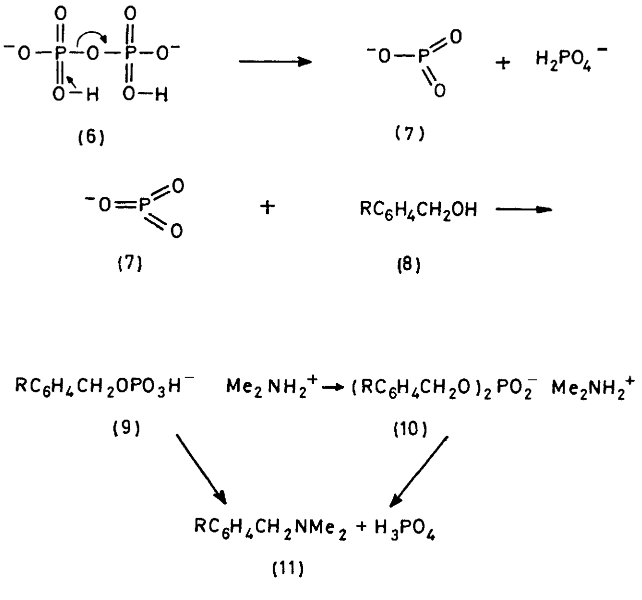
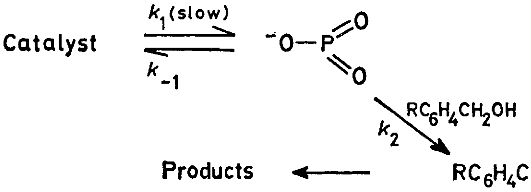


FIGURE 3 Reaction of p-$MeOC_6H_4CH_2OH$ (●) with HMPT at 190 °C, p-$MeOC_6H_4CH_2NMe_2$ (○), p-$MeOC_6H_4CH_2OPO_3H^-$ (△), (p-$MeOC_6H_4CH_2O)_2PO_2^-$ (□)





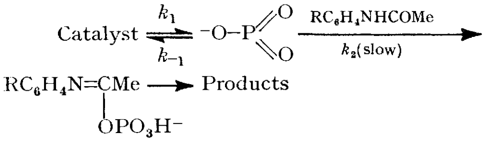
SCHEME 1

Although the reaction of benzyl alcohols with HMPT appear complex (see Figure 3) the initial stages of the reaction mechanism may be described by Scheme 1.

The catalyst is believed to be composed mainly of the pyrophosphate (6), which probably is in a rapid equilibrium with trimetaphosphate and the unidentified phosphates shown in the ^{31}P n.m.r. spectrum in Figure 2. If it is assumed that the rate of catalyst formation is equivalent to that for benzyl alcohol disappearance, a steady-state approximation for the metaphosphate PO_3^-, gives expression (4) for the reaction rate:

$$\text{rate} = \frac{k_1k_2[\text{BA}]([\text{BA}]_0 - [\text{BA}])}{k_{-1} + k_2[\text{BA}]} \qquad (4)$$

If the first step is rate-determining equation (4) is reduced to equation (3); this was confirmed experimentally. For the reaction of carboxamides the mechanism in Scheme 2 may be assumed similar to that given in Scheme 1. The rate expression given in equation (4) is also obtained here, except that the benzyl alcohol should be replaced by carboxamide. Since an oxygen atom of the carboxamide is a weak nucleophile compared with that of benzyl alcohol in the reaction with metaphosphate, it can be assumed that the second step in Scheme 2 is the rate-determining step. If so the rate expression is reduced to equation (1); this was experimentally found in the reaction of carboxamides with HMPT.[5]



SCHEME 2

The rate constants for the reaction of benzyl alcohols with HMPT at 200 °C are almost identical (Table 1). This behaviour is explained by the mechanism illustrated in Scheme 1, where formation of metaphosphate was assumed to be the rate-determining step, the influence of the benzyl alcohols in the rate constants being reduced to simple solvent effects. Lack of discrimination in reactions of metaphosphate (7) between different nucleophiles has been taken as the most compelling evidence for the operation of this type of mechanism.[15] A competition experiment between diphenylmethanol and *m*-nitrobenzyl alcohol is shown in Figure 4, where it is seen that the reaction is almost non-discriminating, preference for the less sterically hindered *m*-nitrobenzyl alcohol being small. A calculation based on all data points showed that *m*-nitrobenzyl alcohol reacts only 1.5 times as fast as diphenylmethanol, whereas several powers of ten would have been expected, if the reaction of benzyl phosphate (9) with the dimethylammonium ion had been the rate-determining step, or if a carbonium ion had been formed directly from the alcohols in an acid-catalysed process. No deuterium effect was observed in the reaction of p-$MeOC_6H_4CH_2OD$ with HMPT, which also indicated the lack of acid catalysis, benzyl alcohol being assumed to be the only source of hydrogens bonded to phosphate ions.

In the reaction of benzyl alcohol Arimatsu *et al.*[3] also observed formation of dibenzyl ether. The corresponding *p*-methoxybenzyl alcohol lead to the appearance of bis-(*p*-methoxybenzyl) ether (12) in the ^{13}C n.m.r. spectrum at 71.3 p.p.m. (CH_2). The identity of the compound was confirmed by isolation of the ether (12) from the reaction mixture. The formation was favoured by high temperature since the characteristic peak of the ether (12) at 71.3 p.p.m. was observed only in reactions at 200 °C and 210 °C and not at 190 °C. *p*-Methoxybenzaldehyde (13) was also formed by thermal decomposition of the ether (12) an observation previously recorded by Quelet and Allard.[17]

$$\underset{(12)}{(p\text{-}MeOC_6H_4CH_2)_2O} \xrightarrow{\text{heat}} \underset{(13)}{p\text{-}MeOC_6H_4CHO}$$

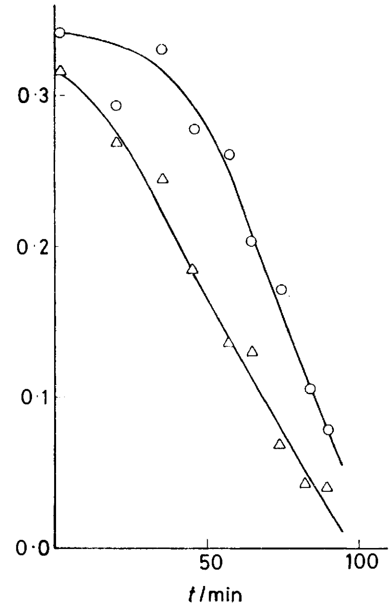


FIGURE 4 Competition reaction between m-$O_2NC_6H_4CH_2OH$ (△) and Ph_2CHOH (○) with HMPT at 200 °C

Finally the presence of the metaphosphate ion (7) in the reaction mixture explains why alkyl phosphates and not the alkyl phosphorodiamidate (3) are intermediates in the reaction of alcohols with HMPT. It also explains why weak nucleophiles such as alcohols and carboxamides react faster than phenol with HMPT. In the latter reaction the phosphorodiamidate (14) is formed,[18] since no 'water' can be split off with subsequent formation of a diphosphate catalyst and, therefore, only an $S_N2(P)$ mechanism is possible.

$$PhOH + O{=}P(NMe_2)_3 \longrightarrow \underset{(14)}{PhOP(O)(NMe_2)_2} + HNMe_2$$

EXPERIMENTAL

In all experiments commercial HMPT (Pierrefitte—Auby) was used. [Nasal tumours have been observed in rats exposed daily to 400 parts per billion (p.p.b.) HMPT after 8 months of exposure.[19]]

Kinetics.—The ^{13}C and ^{31}P n.m.r. spectra were recorded on a JEOL FX60 spectrometer with internal deuterium lock on water added to 1.3 ml aliquots of the reaction mixture, which was quenched by cooling to room temperature. 8K data points were used with a spectral width of 4 000 Hz. The flip angle was 60°, corresponding to a pulse length of 6 and 8 μs for carbon and phosphorus respectively. The repetition time was taken equal to the acquisition time. The disappearance of benzyl alcohols with initial concentration 0.5—0.8 mol kg^{-1} and the appearance of *NN*-dimethyl-*p*-methoxybenzylamine were followed by quantitative ^{13}C n.m.r. using 0.12—0.16 mol kg^{-1} diphenyl ether as an internal standard. The concentrations of mono- and bis-(*p*-methoxybenzyl) phosphates were determined from ^{31}P n.m.r. using the HMPT as internal reference for integration of peak intensities.

Products from the Reaction of p-*Methoxybenzyl Alcohol with HMPT.*—*p*-Methoxybenzyl alcohol (0.743 mol kg^{-1}) in HMPT with diphenyl ether (0.152 mol kg^{-1}) as internal standard for following the kinetics was heated at 210 °C for 70 min. The reaction mixture, which was allowed to cool to room temperature, was poured into 1M-NaOH (400 cm^3) and extracted with diethyl ether (3 × 100 cm^3). The diethyl ether phase was extracted with 4M-HCl (2 × 25 cm^3). The ether phase was then evaporated and subjected to preparative silica gel t.l.c. using diethyl ether-light petroleum (b.p. 40—60 °C) (1 : 2) for elution, by means of which bis-(*p*-methoxybenzyl ether (12), m.p. 38.5 °C (lit.,[17] m.p. 39 °C) and *p*-methoxybenzaldehyde, with n.m.r. and i.r. spectra similar to an authentic sample, were isolated. The HCl phase from above was made alkaline with 2M-NaOH and extracted with diethyl ether (2 × 100 cm^3). The diethyl ether phase was dried (K_2CO_3) and *NN*-dimethyl-*p*-methoxybenzylamine, b.p. 110—112 °C/15 mmHg (lit.,[15] b.p. 59 °C/0.75 mmHg) was obtained.

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