Kinetics and mechanism of tetrazole-catalyzed phosphoramidite alcoholysis

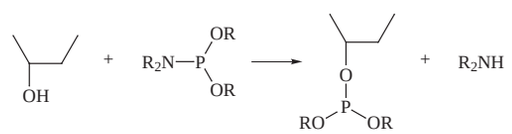
Erkki J. Nurminen,*[a] Jorma K. Mattinen[a] and Harri Lönnberg[b]

[a] *Department of Organic Chemistry, Åbo Akademi University, FIN-20500 Åbo, Finland*
[b] *Department of Chemistry, Turku University, FIN-20014 Turku, Finland*

Kinetics of the tetrazole-catalyzed reaction of diisopropyl *N*,*N*-diisopropylphosphoramidite (1b) with *tert*-butyl alcohol has been studied by ^{31}P NMR spectroscopy in THF, and the results obtained have been compared to those observed for the possible partial reactions involved, *viz*. the formation of diisopropyl tetrazolylphosphite (2b) and its subsequent alcoholysis. The stoichiometry of the processes was first examined with dimethyl *N*,*N*-diisopropylphosphoramidite (1a) in MeCN. The tetrazole-promoted disappearance of 1b is as fast in the absence and in the presence of the alcohol: the alcoholysis of 1b is zero-order in the concentration of alcohol and second-order in the concentration of tetrazole. The reaction of 1b with tetrazole is independent of the concentration of the tetrazolide anion and second-order in that of tetrazole, while the reverse reaction, aminolysis of 2b is first-order in the concentration of the amine. The alcoholysis of 2b is, in turn, first-order in the concentration of alcohol and second-order in that of tetrazole, but it also proceeds, although slowly, in the absence of tetrazole. The time-dependent product distribution of the alcoholysis of 1b shows intermediary accumulation of 2b, but at a lower level than could be predicted by applying the rate constants determined independently for the assumed partial reactions. Accordingly, tetrazole-catalyzed alcoholysis of 1b is shown to proceed at least mainly *via* 2b, but an additional pathway not involving 2b as an intermediate is proposed. Mechanisms of the partial reactions are discussed on the basis of the formal kinetics observed.

Introduction

Phosphoramidites are used as phosphitylation agents in the syntheses of various biomolecules, such as phospholipids, sugar phosphates and oligonucleotides (Scheme 1).[1,2] The displacement of the dialkylamino ligand by the entering hydroxy function is usually catalyzed by weak nitrogen acids, such as amine hydrohalides and azoles, tetrazole being the most extensively used activator. While the well-established synthetic methods usually give excellent yields, little work has been done to elucidate the underlying mechanisms. In particular, the lack of quantitative kinetic data that could be used to distinguish between mechanistic alternatives is obvious.

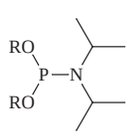


Scheme 1

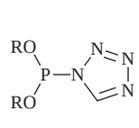
The role of the weakly acidic activators employed has several tentative explanations: they have been suggested to protonate either the phosphorus[3] or nitrogen[4,5] atom of the phosphoramidite, or to form a reactive H-bonded complex[6] where the proton is partially donated to the phosphorus atom and transferred to the nitrogen as the amine departs. According to quantum-chemical calculations,[7,8] protonation of the nitrogen atom favors the cleavage of the P–N bond and increases the susceptibility of phosphorus atom to nucleophilic attack. *N*-Protonation, however, has never been verified by a direct observation, whereas protonation of the phosphorus atom is observed when phosphoramidites are treated with a strong acid, such as HBF_4. These *P*-protonated cations have been found to be practically inert towards nucleophiles,[9] as suggested by theoretical calculations.[7,8]

Tetrazole[10] may play a dual role as an activator of phosphoramidite alcoholysis. It is generally assumed to serve as an acid catalyst but it is also known to attack trivalent phosphorus as a nucleophile: reactions of phosphoramidites with tetrazole give the corresponding tetrazolylphosphites that have been isolated and characterized.[11] Tetrazolylphosphites—unlike phosphoramidites—undergo uncatalyzed alcoholysis to phosphite triesters. This fact, together with the observed accumulation of tetrazolylphosphites during the tetrazole-catalyzed alcoholysis of phosphoramidites, has led to a proposal of tetrazole acting as a nucleophilic catalyst and the tetrazolylphosphite being an intermediate in the process,[3,11] but this theory has also been questioned.[1] Nevertheless, the kinetic evidence either in favor of or against nucleophilic catalysis by tetrazole is meager.

The present work is aimed at elucidating the roles that tetrazole and the entering alcohol play in the alcoholysis of simple model compounds, dialkyl *N*,*N*-diisopropylphosphoramidites (**1a**, **1b** and **1c**). Consequently, we studied the equilibrium and kinetics of the tetrazole-catalyzed reaction of **1a** and **1b** with methanol and *tert*-butyl alcohol by ^{31}P NMR spectroscopy, and compared the data obtained to those observed for the possible partial reactions involved, *viz*. reaction of **1a** with tetrazole and alcoholysis of the resulting tetrazolylphosphite (**2a**).



1a R = Me
1b R = Pr^i
1c R = Bu^t



2a R = Me
2b R = Pr^i
2c R = Bu^t

Results

Stoichiometry and equilibria

The stoichiometry and equilibrium of the reaction of dimethyl *N*,*N*-diisopropylphosphoramidite (**1a**) and tetrazole (TH) to

give tetrazolylphosphite (**2a**) and diisopropylamine (DIA) was investigated by allowing **1a** and **2a** to react with tetrazole and diisopropylamine, respectively [eqn. (1)]. The measurements

$$(MeO)_2PN(Pr^i)_2 + TH \rightleftharpoons (MeO)_2PT + HN(Pr^i)_2 \quad (1)$$

were carried out in acetonitrile (MeCN), in which solvent the equilibrium was reached rapidly after addition of reagents. The reagents were added in small portions and their effects on the reaction system were monitored by ^{31}P NMR spectroscopy.

Two reactions take place: nucleophilic substitution at trivalent phosphorus [eqn. (1)] and a protolytic reaction between tetrazole and diisopropylamine [eqn. (2)]. The ions of eqn. (2)

$$HN(Pr^i)_2 + TH \rightleftharpoons T^- + H_2N^+(Pr^i)_2 \quad (2)$$

form a salt, diisopropylammonium tetrazolide (DIAT), that is very sparingly soluble in MeCN and precipitates as white flakes. This indicates that the equilibrium of eqn. (2) is driven almost entirely to the right side. The salt formation is also very fast compared to the substitution reaction: when tetrazole was added to a mixture of **1a** and DIA, no substitution could be detected, only immediate formation of DIAT. A tertiary amine like *N*,*N*-diisopropylethylamine also prohibited the reaction between **1a** and TH. Similarly, no substitution occurred upon adding diisopropylamine to a mixture of **2a** and TH.

Two equivs. of TH are needed to convert **1a** quantitatively to **2a** as one tetrazole molecule serves as the entering nucleophile and the second one is consumed by salt formation with DIA. Since the diisopropylamine liberated is instantly protonated by TH, it is unable to attack phosphorus, and the reverse reaction is prevented. Analogously, conversion of **2a** to **1a** consumes 2 equivs. of DIA, one becomes bonded to phosphorus and the other forms DIAT with liberated tetrazole. **1a** is also obtained when 2 equivs. of a tertiary amine are introduced to a mixture of **2a** and DIAT: added *N*,*N*-diisopropylethylamine deprotonates diisopropylamine allowing it to displace tetrazole at the phosphorus. It is worth noting that in this case the reaction occurs with concomitant formation of a soluble salt, *N*,*N*-diisopropylethylammonium tetrazolide (DIEAT).

Phosphoramidite **1a** does not react with alcohol in the absence of tetrazole (or some other acid).[12] The mixture of **1a** and *tert*-butyl alcohol in MeCN remained unchanged for 2 h, whereas in the presence of 2 equivs. of tetrazole the alcoholysis is completed in less than 1 min even at −20 °C. The reaction is irreversible yielding dimethyl *tert*-butyl phosphite (**3a**) and DIAT [eqns. (2) and (3)]. Since tetrazole does not remain bonded to phosphorus in the final products, only 1 equiv. of tetrazole is now consumed. The tetrazolylphosphite **2a** undergoes an irreversible alcoholysis to **3a** even in the absence of tetrazole [eqn. (4)]. The irreversibility of the alcoholyses indicates that under these conditions the phosphite products are by far the thermodynamically most stable species.

$$(MeO)_2PN(Pr^i)_2 + Bu^tOH \longrightarrow (MeO)_2POBu^t + HN(Pr^i)_2 \quad (3)$$

$$(MeO)_2PT + Bu^tOH \longrightarrow (MeO)_2POBu^t + TH \quad (4)$$

Kinetics

General. The kinetic experiments were carried out in THF. Replacing MeCN with a less polar solvent retarded the reactions to such an extent that they could be followed by ^{31}P NMR spectroscopy. In addition, diisopropyl *N*,*N*-diisopropylphosphoramidite (**1b**) was used as a starting material instead of **1a** to further reduce the reaction rate. The corresponding *tert*-butyl derivative (**1c**) was not used since in the presence of tetrazole it underwent acid-catalyzed cleavage to 2-methylpropene and $(Pr^i)_2NP(O)H(OBu^t)$.

Table 1 ^{31}P NMR spectrometric data of the compounds identified during the equilibrium measurements and kinetic runs. Chemical shifts are given in ppm (70% H_3PO_4 as an external standard) and coupling constants in Hz.

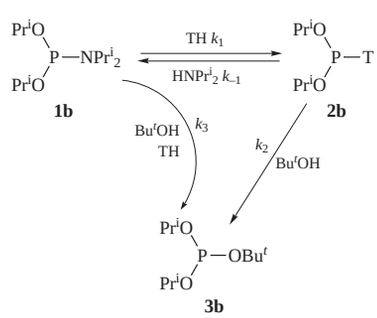
	MeO[a]	Pr^iO[b]	Bu^tO[b]
$(RO)_2P–NPr^i$	150.3 br m	143.1 br m	130.0 t J = 10.1
$(RO)_2P–T$	130.2 septet J = 11.0	126.0 t J = 9.1	—
$(RO)_2P–OBu^t$	136.7 septet J = 10.4	135.1 t J = 8.9	141.0 s —
$(RO)_3P$	141.4 decet J = 10.6	138.6 q J = 8.8	
$(RO)P(NPr^i_2)_2$	159.5 m	—	—
$(RO)_2P(O)H$	11.7 d septet J = 11.9 J = 694	4.3 d t J = 8.5 J = 687	−3.4 d J = 679
$(RO)_2P–(O)N(Pr^i)$	—	—	6.1 d t J = 18.3 J = 617

Solvent: [a] MeCN or [b] THF.

The four different reactions that were followed are depicted in Scheme 2: (i) reaction of **1b** with tetrazole in the absence of alcohol, (ii) reaction of the resulting tetrazolylphosphite (**2b**) with diisopropylamine, (iii) reaction of **2b** with *tert*-butyl alcohol, and (iv) reaction of **1b** with Bu^tOH in the presence of tetrazole.

Kinetic runs were performed at 19 °C. An attempt was made to monitor the reactions at −40 °C, but the kinetic behavior was severely distorted at such a low temperature, probably due to decreased solubilities of the components, especially tetrazole. The ^{31}P NMR spectrometric data of the compounds identified during kinetic runs and/or equilibrium measurements are given in Table 1. The measurements were performed at various initial concentrations of each reactant and catalyst to determine the reaction order with respect to each species by the method of initial rate. The initial rate of the disappearance of the phosphorus reactant was obtained by fitting an exponential curve to the observed time-dependent concentration points. The experimentally convenient pseudo-first-order conditions could not be used, since large excess of tetrazole or Bu^tOH makes the reactions too fast to be monitored.

In addition to the method of initial rates, integrated rate laws were also applied to obtain the rate constants (see Scheme 2),



Scheme 2

as described below for individual reactions. Since none of the reaction constituents could be used in sufficient excess to simplify the kinetics, third-order kinetics were usually observed. Owing to the complexity of rate equations and limited accuracy of ^{31}P NMR spectroscopic data, only approximate values could be obtained for the third-order rate constants. These values, however, were in moderate agreement with those calculated on the basis of the initial rate data, which means that the formal kinetics obeyed in the beginning of the reactions predict the

Table 2 Kinetic data of the reactions at different initial concentrations (mol dm^{-3}) of the reactants in THF at 19 °C: initial rates v_0 (mol dm^{-3} s^{-1}) and rate constants k (dm^6 mol^{-2} s^{-1} for reactions of **1b** and dm^3 mol^{-1} s^{-1} for reaction **2b** + DIA) calculated from the integrated rate equations

Reaction	$[\mathbf{1b}]_0$	$[\mathbf{2b}]_0$	$[TH]_0$	$[Bu^tOH]_0$	$[DIA]_0$	v_0	k
1b + TH	0.082	—	0.167	—	—	0.000 61	—
	0.069	—	0.240	—	—	0.001 06	0.43[a]
	0.084	—	0.325	—	—	0.002 72	0.40
	0.077	—	0.369	—	—	0.003 16	0.43
1b + Bu^{t}OH	0.080	—	0.162	0.303	—	0.000 39	0.29[b]
	0.069	—	0.148	0.485	—	0.000 41	0.36
	0.077	—	0.156	0.728	—	0.000 48	0.35
	0.073	—	0.152	0.971	—	0.000 68	0.48
	0.075	—	0.254	0.303	—	0.001 40	0.29
	0.073	—	0.244	0.485	—	0.001 18	0.32
	0.073	—	0.245	0.971	—	0.001 09	0.42
	0.070	—	0.344	0.303	—	0.002 82	0.42
	0.065	—	0.328	0.485	—	0.002 09	0.39
2b + DIA	—	0.076	—	—	0.495	0.000 17	0.004 4[c]
	—	0.069	—	—	0.718	0.000 20	0.003 9
	—	0.065	—	—	0.926	0.000 25	0.004 2
	—	0.059	—	—	1.232	0.000 30	0.004 0
2b + Bu^{t}OH	—	0.067	0.032	0.297	—	0.000 29	—
(Method 1)	—	0.072	0.107	0.303	—	0.000 72	—
	—	0.062	0.187	0.275	—	0.000 56	—
	—	0.066	0.038	0.466	—	0.000 56	—
	—	0.057	0.099	0.442	—	0.001 06	—
	—	0.070	0.148	0.485	—	0.001 67	—
	—	0.061	0.203	0.485	—	0.002 08	—
	—	0.066	0.030	0.952	—	0.001 39	—
	—	0.063	0.108	0.971	—	0.002 04	—

[a] k_1 obtained from eqn. (6). When calculated from initial rates, a value of 0.31 dm^6 mol^{-2} s^{-1} is obtained (Fig. 2). [b] k_3 obtained by eqn. (10). When calculated from initial rates, a value of 0.33 dm^6 mol^{-2} s^{-1} is obtained. [c] k_{-1} obtained from eqn. (7).

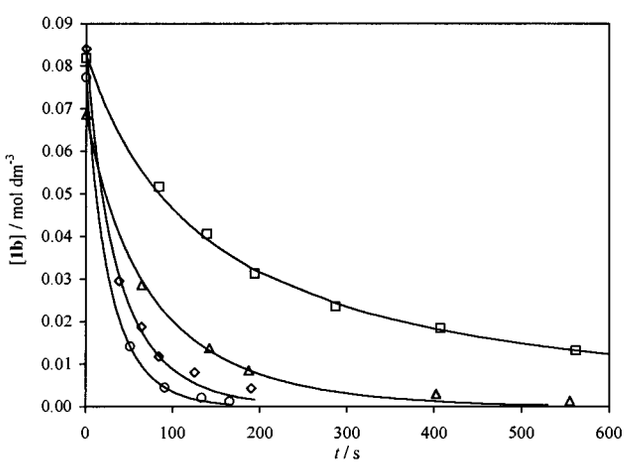


Fig. 1 Reaction of phosphoramidite **1b** with tetrazole at different initial concentrations of tetrazole (TH): the dependence of **[1b]** on time in THF at 19 °C. The curves refer to the following initial concentrations of tetrazole 0.167 mol dm^{-3} (□), 0.240 mol dm^{-3} (△), 0.325 mol dm^{-3} (◇) and 0.369 mol dm^{-3} (○).

behavior of the reaction system properly also during the late stages of the process.

Reaction of 1b with tetrazole. Fig. 1 shows the time-dependent concentration of phosphoramidite **1b** when reacted with a moderate excess of tetrazole. The dependence of the initial disappearance rate of **1b** [v_0 in eqn. (5)] on the initial

$$v_0 = \lim_{t\to 0}\left(\frac{\mathrm{d}[\mathbf{1b}]}{\mathrm{d}t}\right) = k_1[\mathbf{1b}]_0\,[TH]_0^n \qquad (5)$$

concentration of tetrazole was used to determine the reaction-order in the concentration of tetrazole. The linear dependence ($r = 0.997$) of $v_0/[\mathbf{1b}]_0$ on $[TH]_0^2$ (Fig. 2) indicates that the reaction is of second-order in the concentration of tetrazole, and the slope of the plot, 0.31 dm^6 mol^{-2} s^{-1}, equals the third-order rate constant of the process [see eqn. (5), $n = 2$]. The initial rates are listed in Table 2. The integrated rate equation for a reaction that consumes 1 equiv. of **1b** and 2 equivs. of TH (see the discussion of stoichiometry) and obeys the third-order rate law [eqn. (5)] may be expressed by [eqn. (6)].[13] The third-order rate constant k_1 is obtained as a slope of the linear dependence between the value of the right hand side of eqn. (6) and time. Insertion of observed concentrations in eqn. (6) gave with linear regression ($r > 0.98$ in each case) the rate constant values (Table 2) that are invariably somewhat greater than the one obtained by the initial rate method. In other words, according to the integrated equation method, the reaction proceeds 20–30% faster than expected on the basis of its initial rate.

$$k_1 t = \frac{1}{2[\mathbf{1b}]_0 - [TH]_0}\left(\frac{1}{[TH]} - \frac{1}{[TH]_0}\right) + \left(\frac{1}{2[\mathbf{1b}]_0 - [TH]_0}\right)^2 \ln\left(\frac{[\mathbf{1b}]_0[TH]}{[TH]_0[\mathbf{1b}]}\right) \qquad (6)$$

Reaction of 2b with diisopropylamine. The reverse reaction for the tetrazolylphosphite formation was studied by allowing the isolated and purified tetrazolylphosphite **2b** to react with DIA. The linear dependence of $v_0/[\mathbf{2b}]_0$ on $[DIA]_0$ (Fig. 3) suggests that the process is first-order with respect to both reactants, the second-order rate constant being 4×10^{-3} dm^3 mol^{-1} s^{-1}. Table 2 lists the initial rates and the second-order rate constants calculated by eqn. (7).

$$k_{-1}t = \frac{1}{[\mathbf{2b}]_0 - [DIA]_0}\ln\left(\frac{[\mathbf{2b}]_0[DIA]}{[DIA]_0[\mathbf{2b}]}\right) \qquad (7)$$

Reaction of 2b with *tert*-butyl alcohol. Alcoholysis of tetrazolylphosphite was studied by three methods: 1, **2b** was isolated and alcoholyzed in the absence of DIAT, 2, isolated **2b** was alcoholyzed in the presence of a small amount of DIAT in order to imitate the conditions of phosphoramidite alcohol-

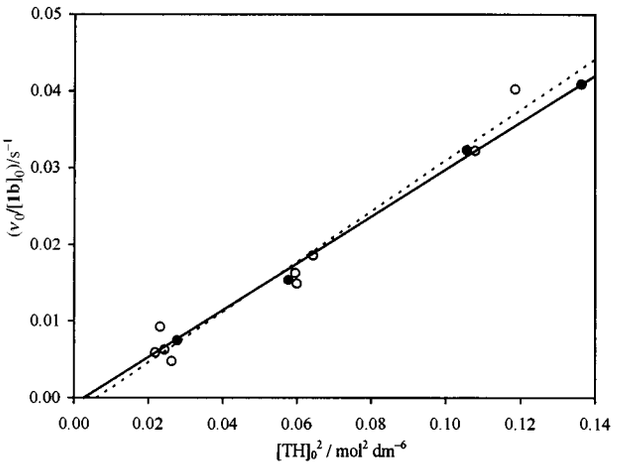


Fig. 2 Reaction of phosphoramidite **1b** with tetrazole (TH) (solid points and solid line) and reaction of **1b** with *tert*-butyl alcohol at different concentrations of TH (open dots and dotted line): the dependence of $v_0/[\mathbf{1b}]_0$ on $[TH]_0^2$ in THF at 19 °C [for v_0, see eqn. (5)]

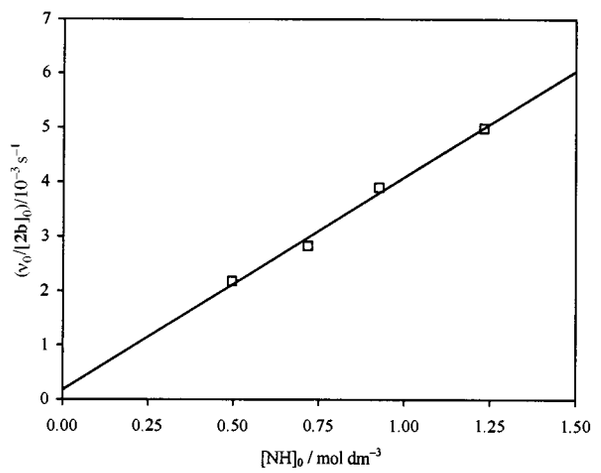


Fig. 3 Reaction of tetrazolylphosphite **2b** with diisopropylamine at different initial concentrations of the amine (NH): the dependence of $v_0/[\mathbf{2b}]_0$ on $[NH]_0$ in THF at 19 °C

ysis[14] and 3, **2b** was generated *in situ* from **1b**, and Bu^{t}OH was introduced to the resulting equimolar mixture of **2b** and DIAT. The rate of alcoholysis of **2b** depends both on the concentration of the alcohol and on that of tetrazole (Table 2). Furthermore, the salt efficiently accelerates the process that is more than 10-fold faster in the presence of DIAT than in its absence. Since methods 2 and 3 both have the medium saturated with DIAT, they give essentially the same results; the NMR data of method 3 are just more scattered due to the high amount of precipitated salt in the sample.

In the absence of the salt (method 1), runs at a constant initial concentration of tetrazole show linear dependence of $v_0/[\mathbf{2b}]_0$ on $[Bu^tOH]_0$ indicating that the reaction is first-order in the concentration of both reactants. The rate law of the tetrazole-catalyzed process may be expressed by eqn. (8).

$$-\frac{d[\mathbf{2b}]}{dt} = k_2[\mathbf{2b}][Bu^tOH] = (k_{2u} + k_{2c}[TH]^n)[\mathbf{2b}][Bu^tOH] \quad (8)$$

Initially, a linear dependence of $v_0/([\mathbf{2b}]_0[Bu^tOH]_0)$ on $[TH]_0^n$ should be observed [eqn. (9)]. Method 1 (Fig. 4) indicates the

$$k_{2u} + k_{2c}[TH]_0^n = \frac{v_0}{[\mathbf{2b}]_0[Bu^tOH]_0} \quad (9)$$

catalysis to be second-order in tetrazole concentration [eqn. (8),

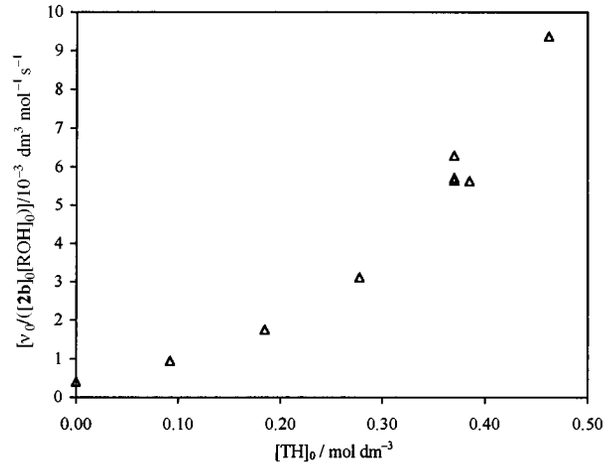


Fig. 4 Reaction of tetrazolylphosphite **2b** with *tert*-butyl alcohol in the absence of DIAT (method 1) at different initial concentrations of tetrazole (TH) and the alcohol (ROH): the dependence of $v_0/([\mathbf{2b}]_0[ROH]_0)$ on $[TH]_0$ in THF at 19 °C

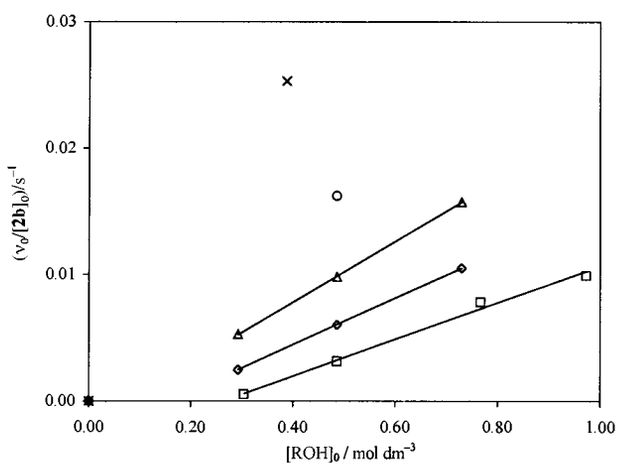


Fig. 5 Reaction of tetrazolylphosphite **2b** with *tert*-butyl alcohol in the presence of DIAT (method 2) at different initial concentrations of tetrazole (TH) and the alcohol (ROH): the dependence of $v_0/[\mathbf{2b}]_0$ on $[ROH]_0$ in THF at 19 °C. Initial concentrations of tetrazole are 0 mol dm^{-3} (□), 0.048 mol dm^{-3} (◇), 0.092 mol dm^{-3} (△), 0.139 mol dm^{-3} (○) and 0.185 mol dm^{-3} (×).

$n = 2$]. The kinetic parameters of the reaction are calculated to be $k_{2u} = 0.040$ dm^3 mol^{-1} s^{-1} and $k_{2c} = 3.5 \times 10^{-4}$ dm^9 mol^{-3} s^{-1}.

The results of methods 2 and 3 suggest that the reaction is first-order in the concentration of alcohol (Fig. 5). Surprisingly, the plots of $v_0/[\mathbf{2b}]_0$ *vs.* $[Bu^tOH]_0$ show a negative intercept as if a certain amount of alcohol would be required for the reaction to be able to proceed at all. The reason for this phenomenon remains obscure for the time being. The slopes of these linear plots are the observed rate constants k_2 for tetrazole-catalyzed alcoholysis [eqn. (8)]. As they are plotted against $[TH]_0$, the relationship in eqn. (9) is derived (Fig. 6). The dependence has a positive intercept (the detected k_2 value in the absence of TH is 0.014 dm^3 mol^{-1} s^{-1}) indicating the rate of alcoholysis in the absence of tetrazole. The tetrazole catalysis is second-order as is also observed in the absence of the salt (method 1). Method 2 gives the rate constant values $k_{2u} = 0.013$ dm^3 mol^{-1} s^{-1} and $k_{2c} = 1.42$ dm^9 mol^{-3} s^{-1} while method 3 yields $k_{2u} = 0.022$ dm^3 mol^{-1} s^{-1} and $k_{2c} = 1.27$ dm^9 mol^{-3} s^{-1}.

Reaction of 1b with *tert*-butyl alcohol in the presence of tetrazole. The rate for the reaction of **1b** with *tert*-butyl alcohol in the presence of tetrazole depends on the tetrazole concentration, but is entirely independent of the concentration of alcohol (Table 2). In fact, **1b** seems to disappear as fast in the absence of alcohol, *i.e.* when reacting with tetrazole under

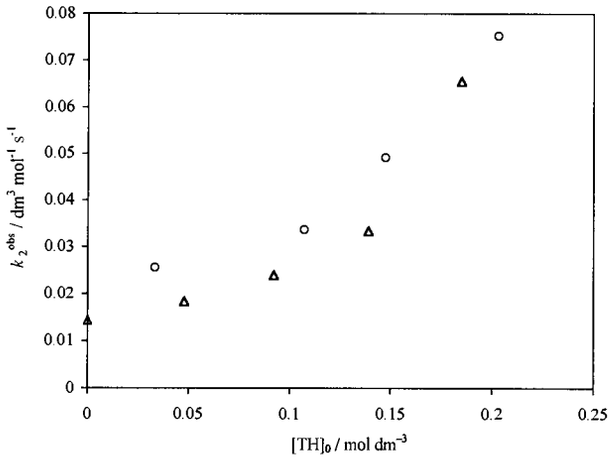


Fig. 6 Reaction of tetrazolylphosphite **2b** with *tert*-butyl alcohol in the presence of DIAT at different initial concentrations of tetrazole (TH) and alcohol (ROH): the dependence of the observed rate constant k_2 [eqn. (8)] on $[TH]_0$ in THF at 19 °C. Notation: △ = catalytic amount of DIAT (method 2), ○ = stoichiometric amount of DIAT (method 3).

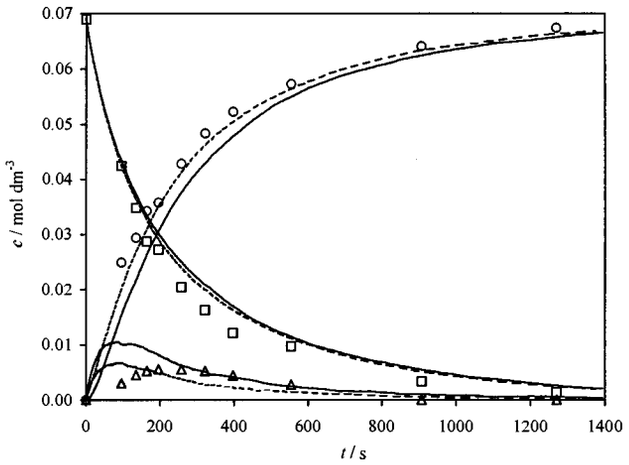


Fig. 7 Reaction of phosphoramidite **1b** with *tert*-butyl alcohol in the presence of tetrazole in THF at 19 °C: observed and simulated time-dependent concentration distributions of phosphorus(III) components. Initial concentrations are $[\mathbf{1b}]_0 = 0.069$ mol dm^{-3}, $[TH]_0 = 0.148$ mol dm^{-3} and $[ROH]_0 = 0.485$ mol dm^{-3}. Notation for observed data points is **1b** = □, **2b** = △ and **3b** = ○; solid lines indicate concentrations simulated by model 1 and dotted lines those simulated by model 2.

similar conditions. The plot of $v_0/[\mathbf{1b}]_0$ *vs.* $[TH]_0^2$ for the phosphoramidite alcoholysis closely resembles that of the corresponding tetrazolysis (Fig. 2) and gives a value of 0.33 dm^6 mol^{-2} s^{-1} for the third-order rate constant ($r = 0.97$). This agrees, within the limits of experimental error, with the value observed for the tetrazolysis.

For a reaction that consumes 1 equiv. of **1b** and 1 equiv. of TH (see the discussion on stoichiometry), and obeys the third-order rate law [eqn. (5), $n = 2$], the integrated rate equation may be expressed by eqn. (10).[13] Insertion of the observed data in

$$k_3 t = \frac{1}{[\mathbf{1b}]_0 - [TH]_0}\left(\frac{1}{[TH]} - \frac{1}{[TH]_0}\right) + \left(\frac{1}{[\mathbf{1b}]_0 - [TH]_0}\right)^2 \ln\left(\frac{[\mathbf{1b}]_0[TH]}{[TH]_0[\mathbf{1b}]}\right) \quad (10)$$

eqn. (10) yields by linear regression ($r > 0.97$ in each case) rate constant values that range from 0.29 to 0.48 dm^6 mol^{-2} s^{-1}, being thus in a reasonable agreement with the constant (0.33 dm^6 mol^{-2} s^{-1}) obtained by the initial rate method. As in the case of tetrazolysis, the reaction appears to proceed 20–30% faster than the initial rates predict.

An intermediary accumulation of **2b** is observed during the alcoholyses of **1b**, in particular at low alcohol concentrations. When more than 10 equivs. of *tert*-butyl alcohol were used, **2b** did not appear any more. One should bear in mind, however, that small amounts of **2b** are difficult to detect owing to broadening of the ^{31}P resonance signal in THF.[11b] An illustrative example of observed time-dependent distributions is depicted in Fig. 7.

Salts and medium effects. The reactions of **1b** with tetrazole and alcohol were also studied in the presence of DIAT and a more soluble salt, *N*,*N*-diisopropylethylammonium tetrazolide (DIEAT). The salts alone neither resulted in the tetrazolysis of **1b** nor catalyzed its alcoholysis. When both DIAT or DIEAT and tetrazole were present, the reactions proceeded at a rate similar to that in the absence of salt. The rate-retarding effect of DIAT observed by Dahl *et al.* was not detected,[3a] probably because in our experiments excess of tetrazole was used and the solvent used was THF instead of acetonitrile, which solvates the salt more effectively. Accordingly, in contrast to the alcoholysis of **2b**, the reactions of **1b** are not kinetically affected by addition of tetrazolide salts at conditions used in the present work.

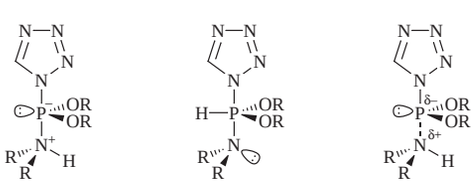
The sensitivity of alcoholysis of **2b** to medium effects was further investigated to elucidate whether the second-order dependence on tetrazole is truly of kinetic origin or just a first order relationship biased by the medium effect of added tetrazole. The kinetics of alcoholysis of **2b** were followed in the presence of 0.5 M of MeCN or pyrrole, neither of which had any effect on the reaction rate. Salts like DIAT, again, considerably enhance the reaction: DIEAT and $Bu_4N^+Br^-$ both showed even larger accelerating effects than the less soluble DIAT. DIEAT also affected the tetrazole-catalyzed alcoholysis of **1b** by diminishing the accumulation of **2b**.

Discussion

Mechanism of the aminolysis of 2b

The aminolysis of tetrazolylphosphite **2b** is first-order in the concentration of both reactants and hence the most obvious mechanistic explanation is a rate-limiting nucleophilic attack of the amine on phosphorus and subsequent (or concerted) departure of the tetrazolide anion. Since the attacking nucleophile undoubtedly is the neutral amine, a proton has to be removed from the amine nitrogen at some stage of the process. Evidently the proton is transferred to another molecule of amine, which is the strongest base in the system. Because the process is only of first-order in the concentration of amine, only one amine molecule is present in the transition state. This means that the proton is not transferred in a concerted process with the nucleophilic attack, but in some subsequent step.

Consequently, a pentacoordinated ylide-type transition state (**4a**) may be assumed. This structure has a prototopic tautomer, a neutral pentacovalent phosphorane-like structure (**4b**), the analogues of which have been postulated to be transition states in phosphoramidite alcoholyses[15] and even detected in reactions of some cyclic phosphites.[16] The existence of **4b** on the reaction path is, however, improbable in the present case: **4a** is in any case formed first and it is capable of giving the products without rearrangement. The negative charge on phosphorus is simply transferred to the tetrazolide group upon rupture of the P–N bond. Quantum chemical comparison between analogues of **4a** and **4b** also predicts the ylide structure to be the energetically favored species.[8a] The most probable transition state



4a **4b** **4c**

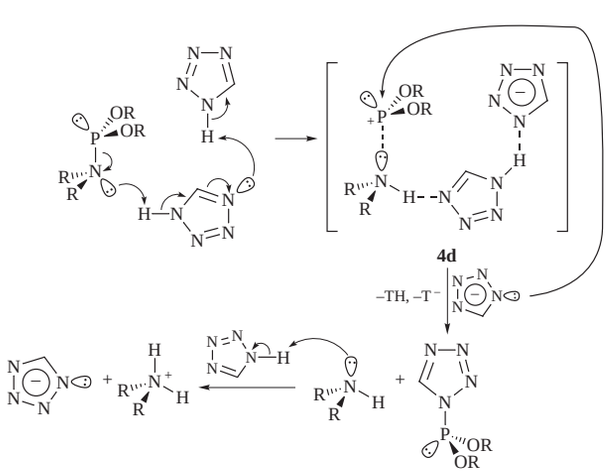
structure, receiving support from molecular modelling,[8] is a 'softened' ylide with a partial bond between the amine nitrogen and phosphorus both thus carrying only a partial charge (**4c**).

Mechanism of the tetrazolysis of 1b

The tetrazolysis of **1b** is essentially the reverse of the aminolysis of **2b**. However, the principle of microscopic reversibility cannot be applied here since the forward and reverse reactions take place under different conditions and no true equilibrium exists between **1b** and **2b**. To obtain **2b** from **1b**, the amidite nitrogen has to be protonated and tetrazole bonded to the amidite phosphorus. Tetrazole is the only proton donor present and thus evidently the protonating species. It is a relatively strong acid ($pK_a = 4.76$ in water), the protolysis of which is strongly on the side of the tetrazolide anion if only a suitable proton acceptor is provided, as noted in the Results section. A small amount of the anion is likely to exist in the solution even before the substitution has released DIA, which means that the species responsible for nucleophilic attack may be either neutral tetrazole or the tetrazolide anion which is likely to be more reactive.

During the substitution, tetrazolide concentration increases together with the protonation of released DIA until the medium soon comes saturated with the very slightly soluble salt and a constant tetrazolylphosphite concentration is achieved. If DIAT is added to the system before the reaction begins this low concentration exists already at the very first stages of the reaction. If more soluble DIEAT is used, the situation is analogous, only with considerably higher tetrazolide concentration. However, these changes in tetrazolylphosphite concentration show no effect on the rate of tetrazolysis of **1b**. This gives us two mechanistic alternatives. (1) Tetrazolide is not the attacking species. Tetrazole acts both as proton donor and nucleophile, which explains the second-order kinetics in tetrazole concentration. (2) Tetrazolide attacks after the rate limiting step, being thus kinetically invisible. The reaction is second order in tetrazole, because two tetrazole molecules participate in the protolytic activation step.

Alternative 1 would give a solid explanation for the observed second-order kinetics in tetrazole and lead to a transition state resembling the one established for the aminolysis of **2b**. Nevertheless, it has to be rejected since it is based on the assumption that neutral tetrazole would be as good a nucleophile as the corresponding anion. This leaves us alternative 2 even though for the time being we are unable to envisage the exact role of the two tetrazole molecules involved in the rate-limiting step. One alternative is presented in Scheme 3. At the intermediate **4d** the



Scheme 3

tetrazole molecules are still associated with the protonated amidite and the proton has been transferred to the amidite nitrogen. Quantum chemical calculations suggest that in such a species the electronic structure resembles that of phosphenium–amine-complex. The electrons of the former P–N bond are drawn to the nitrogen atom, the positive charge is localized on the phosphorus and only a weak interaction remains between P and N instead of a covalent bond. This, naturally, enhances the susceptibility of phosphorus towards nucleophilic attack.[8]

Mechanism of the alcoholysis of 2b

The alcoholysis of **2b** may take place either by an uncatalyzed or catalyzed pathway. The most straightforward mechanism for the uncatalyzed pathway that is first-order in concentration of both reactants, is the nucleophilic attack of alcohol followed by deprotonation and departure of tetrazole. Tetrazolylphosphite **2b** is clearly more reactive than amidite **1b** which is not capable of undergoing uncatalyzed alcoholysis.

The alcoholysis of **2b** is catalyzed by tetrazole and tetrazolide salts. Their influence cannot result from nucleophilic participation, since tetrazolide ion constitutes the leaving group of the reaction. What remains is the acid and base catalysis: tetrazole may assist by protonating the leaving group (two tetrazole molecules involved in the process as discussed above in the case of tetrazolysis of **1b**), tetrazolide anion by deprotonating the alcohol after nucleophilic attack. This would be in agreement with the greater effect of the anion: tetrazole is already a good leaving group, the protonation of which is not likely to assist the reaction as much as the deprotonation of the rather unfavorable oxonium cation yielded by the attack of the alcohol. The effect of the tetrabutylammonium bromide cannot really be compared with that of tetrazolides, since halogenide ions may act also as nucleophiles.[6]

Mechanism of alcoholysis of 1b

The key question concerning the mechanism of phosphoramidite alcoholysis is whether the reaction proceeds solely *via* intermediate **2b**, or could the reaction pathway branch before **2b**. Since the disappearance of **1b** is independent of the alcohol concentration, such a branched process would have to take place *via* a transition state that does not contain the nucleophile and could after the rate limiting step be attacked either by tetrazolide or alcohol yielding **2b** or **3b**, respectively. Discussion on tetrazolysis of **1b** has suggested transition state **4d** that meets with these requirements. The ratio of its reaction with tetrazole and its possible reaction with alcohol can only be deduced from the extent of accumulation of **2b** which is also affected by the rate of disappearance of **2b**. Consequently, any change in the concentration of either tetrazole, tetrazolide ion or alcohol has multiple effects to the reaction system and fails either to prove or reject the existence of the path from **4d** to **3b**. Nevertheless, the possible occurrence of such a process cannot be denied. The fact remains that **2b**, which is known to react with alcohol, is detected during tetrazole-catalyzed alcoholysis of **1b**. The reaction of **2b** with alcohol has to proceed *via* an intermediate other than **4d**, because the reaction is first-order in both reactants. Consequently, **2b** is not a dead-end species,[1] but at least part of the tetrazole-catalyzed alcoholysis of **1b** definitively proceeds *via* **2b**.

Simulation of the reaction system

To determine how well the theory of two irreversible consecutive reactions describes the system, the observed time-dependent concentration of the reaction components was compared to that obtained by a stochastic simulation. The partial reactions and their rate laws are shown in Table 3 together with the (separately) determined values of rate constants (see Results section) that were used in the simulation.

Fig. 7 shows the experimental data (points indicated) together with the simulated time-dependent concentrations (solid curves) given by the equations and rate constants of model 1 in Table 3. The experimental points systematically deviate from the simulated behavior in the following respects.

Table 3 Kinetic parameters for the simulated model for the reaction system

Reaction	Rate law	Rate constants, model 1 [a]	Rate constants, model 2 [a]
1b + TH ⟵ **2b** + DIA	$-\frac{d[\mathbf{1b}]}{dt} = k_1[\mathbf{1b}][TH]^2$	$k_1 = 0.31$	$k_1 = 0.185$
1b + Bu^{t}OH ⟵ **3b** + DIA	$-\frac{d[\mathbf{1b}]}{dt} = k_3[\mathbf{1b}][TH]^2$	$k_3 = 0$	$k_3 = 0.125$
2b + Bu^{t}OH ⟵ **3b** + TH	$-\frac{d[\mathbf{2b}]}{dt} = (k_{2u} + k_{2c}[TH]^2)[\mathbf{2b}][Bu^tOH]$	$k_{2u} = 0.022$, $k_{2c} = 1.27$	$k_{2u} = 0.022$, $k_{2c} = 1.27$
DIA + TH ⟵ DIAT	$-\frac{d[DIA]}{dt} = k_p[DIA][TH]$	$k_p > 1000$	$k_p > 1000$

[a] Units: k_1 and k_3, dm^6 mol^{-2} s^{-1}; k_{2u}, dm^3 mol^{-1} s^{-1}; k_{2c}, dm^9 mol^{-3} s^{-1}; k_p, dm^3 mol^{-1} s^{-1}.

(1) Too low and too late maximum concentration of **2b** during the alcoholysis. (2) Slightly too fast formation of **3b** at early stages of the reaction: **[3b]** is larger than **[2b]**. (3) Non-sigmoidal shape of **3b** formation. The discrepancy, though not large, is disturbing. In particular, the slow formation of **2b** at the beginning of the reaction indicates that the constructed model fails to fully describe the behavior of the system. We therefore tried model 2 (Table 3) that allows **4d** to yield both **3b** and **2b** assuming that the product ratio of these processes depends on the ratio of corresponding nucleophiles, *i.e.* alcohol and tetrazolide anion. An example of the good fit thus obtained is depicted in Fig. 7 (dotted lines). The deviations of model 1 were diminished in a similar manner for all runs.

Conclusions

We have presented evidence that the tetrazole-catalyzed alcoholysis of phosphoramidite **1b** proceeds at least mainly *via* tetrazolylphosphite **2b**. Tetrazole acts first as an acid catalyst to give intermediate **4d**, which then reacts with tetrazolide anion and yields **2b**. However, **4d** could also be able to react with alcohol: our results lend support to the existence of this competing reaction path that does not involve **2b** as an intermediate, though no definite proof for the theory is available.

Experimental

Syntheses

General. All reagents and solvents were dried and stored under N_2: PCl_3 and Bu^{t}OH were distilled. MeOH (anhydrous grade) was used as such. Pr^{i}OH was distilled and stored over 4 Å molecular sieves. $(Pr^i)_2NH$ and $(Pr^i)_2NEt$ were stirred with KOH pellets, distilled and stored over KOH. MeCN was distilled from CaH_2 and stored over it. Hexane, THF, [$^2H_8$]THF and CD_3CN were stirred with CaH_2 and stored over it. The NMR spectra were registered at 500 MHz (125 MHz for ^{13}C and 202 MHz for ^{31}P). Chemical shifts are given in ppm and coupling constants in Hz. For ^1H and ^{13}C NMR, TMS was used as an internal standard, for ^{31}P 70% H_3PO_4 was used as an external standard. $CDCl_3$ was used as NMR solvent in identification of spectra. Mass spectra were registered by electron impact at 70 eV. The reaction conditions differed to some extent from those published earlier,[17,18] and new purification methods were used along with the old ones.[19,6] Therefore the full descriptions of syntheses are given.

***N*,*N*-Diisopropylphosphoramidodichloridite $Cl_2PN(Pr^i)_2$ (5).** $(Pr^i)_2NH$ (39.3 cm^3, 280 mmol) was added dropwise to a solution of PCl_3 (13.1 cm^3, 150 mmol) in hexane (350 cm^3) under N_2 at $t < 0$ °C. The resulting white slurry was stirred at room temp. for 1 h, filtered and the precipitate $[(Pr^i)_2NH{\cdot}HCl]$ was washed with hexane (4 × 150 cm^3). Solvent was removed and the residue distilled under reduced pressure: **5** (23.2 g, 82%) as a colorless clear liquid, bp 75–77 °C/5 mmHg. δ_H 3.90 (br m, 2H), 1.25 (d, 12H, $^3J_{HH}$ 6.7). δ_C 48.13 (d), 23.42 (br s). δ_P 170.2 (br). *m*/*z* 201 (M^+).

Dimethyl *N*,*N*-diisopropylphosphoramidite, $(MeO)_2PN(Pr^i)_2$ (1a). A solution of MeOH (4.1 cm^3, 99 mmol) and $(Pr^i)_2NEt$ (17.0 cm^3, 99 mmol) in hexane (10 cm^3) was added dropwise to **5** (10.0 g, 49 mmol) in hexane (30 cm^3) under N_2 at $t < 0$ °C. The resulting slurry was stirred at room temp. for 2 h, filtered and the precipitate $[(Pr^i)_2NEt{\cdot}HCl]$ was washed with hexane (4 × 50 cm^3). The hexane fractions were washed with 5% $NaHCO_3$ (4 × 50 cm^3), saturated NaCl (2 × 50 cm^3) and dried with Na_2SO_4 (overnight) and CaH_2 (1 h). The solvent was removed, *n*-BuLi in hexane (2.5 M, 1.2 cm^3) was added and the mixture stirred for 1 h. Vacuum distillation over Na (0.15 g) gave **1a** (4.72 g, 49%) as a colorless clear liquid, bp = 50–52 °C/3 mmHg. δ_H 3.54 (d septet, 2H, $^3J_{HH}$ 6.8, $^3J_{HP}$ 9.7), 3.37 (d, 6H, $^3J_{HP}$ 13.1), 1.14 (d, 12H, $^3J_{HH}$ 6.8). δ_C 50.50 (d, $^2J_{CP}$ 18.1), 42.58 (d, $^2J_{CP}$ 12.4), 24.65 (d, $^3J_{CP}$ 7.1). δ_P 150.3 (br m). *m*/*z* 193 (M^+), *M* 193.123 84 ($C_8H_{20}NO_2P$ requires 193.123 17).

Diisopropyl *N*,*N*-diisopropylphosphoramidite $(Pr^iO)_2PN(Pr^i)_2$ (1b). Essentially the procedure described for **1a** was used. The distilled product (4.6 g, 53%) was further purified by column chromatography (silica gel 60, THF) followed by distillation in reduced pressure. **1b** (2.75 g, 32%) was obtained as a clear colorless liquid, bp = 75–80 °C/4.5 mmHg. δ_H 4.04 (d septet, 2H, $^3J_{HH}$ 6.1, $^3J_{HP}$ 10.3), 3.59 (d septet, 2H, $^3J_{HH}$ 6.8, $^3J_{HP}$ 9.9), 1.24 (d, 6H, $^3J_{HH}$ 6.1), 1.21 (d, 6H, $^3J_{HH}$ 6.1), 1.17 (d, 12H, $^3J_{HH}$ 6.9). δ_C 66.21 (d, $^2J_{CP}$ 19.1), 42.57 (d, $^2J_{CP}$ 12.4), 24.46 (d, $^3J_{CP}$ 7.2), 24.34 (d, $^3J_{CP}$ 6.7), 24.40 (d, $^3J_{CP}$ 6.2). δ_P 142.5 (br quintet). *m*/*z* 249 (M^+), *M* 249.185 73 ($C_{12}H_{28}NO_2P$ requires 249.185 77).

Di-*tert*-butyl *N*,*N*-diisopropylphosphoramidite, $(Bu^tO)_2PN(Pr^i)_2$ (1c). Essentially the procedure described for **1a** was used. After mixing of the reagents the solution was refluxed at 75 °C for 4 h. Vacuum distillation yielded **1c** (4.4 g, 59%) as a clear colorless liquid, bp = 71–77 °C/2.5 mmHg. δ_H 3.59 (d septet, 2H, $^3J_{HH}$ 6.7, $^3J_{HP}$ 10.4), 1.31 (d, 18H, $^4J_{HP}$ 0.8), 1.14 (d, 12H, $^3J_{HH}$ 6.7). δ_C 74.38 (d, $^2J_{CP}$ 10.1), 43.00 (d, $^2J_{CP}$ 12.8), 30.97 (d, $^3J_{CP}$ 8.3), 24.12 (d, $^3J_{CP}$ 8.3). δ_P 130.0 (t, $^3J_{PH}$ 10.1). *m*/*z* 277 (M^+).

Diisopropyl tetrazolylphosphite, $(Pr^iO)_2PN_4CH$ (2b). 1.0 g of **1b** was weighed into a two-leg Schlenk vessel and 18 cm^3 of commercial 0.47 M tetrazole in dry MeCN was added under Ar. The mixture was stirred for 15 min and MeCN was removed under reduced pressure. 20 cm^3 of pentane was added to the resulting slurry, the mixture was stirred for 15 min and filtered. The precipitate was washed with 10 cm^3 of pentane, and the solvent was removed under reduced pressure to give a slightly yellow clear liquid. The purity of the product determined by ^{31}P NMR was 67%, the main impurities being the hydrolysis product, $(Pr^iO)_2P(O)H$ (δ_P 6.4, 7%) and an unidentified side product (δ_P 129.0, 15%). δ_H 9.00 (1H, s), 4.52 (d septet, 2H, $^3J_{HH}$ 6.1, $^3J_{HP}$ 9.1), 1.28 (d, 6H, $^3J_{HH}$ 5.9), 1.14 (d, 6H, $^3J_{HH}$ 5.9). δ_C 142.5 (s), 70.6 (d, $^2J_{CP}$ 10.9), 22.78 (d, $^3J_{CP}$ 2.6), 22.46 (d, $^2J_{CP}$ 2.6). δ_P 126.1 (br).

Kinetic methods

Equilibrium studies. Solvent (CD_3CN) and reactants were introduced into a septum-sealed NMR tube with a gastight HPLC syringe to obtain 0.5 cm^3 of 0.25 mol dm^{-3} solution of

the starting material. The concentration distribution of phosphorus compounds was monitored by ^{31}P NMR (NNE irradiation mode, 8 scans, accumulation time 1.0 s, pulse delay 10 s).

Kinetic measurements. Solvent ([$^2H_8$]THF) and reactants were introduced into a septum-sealed NMR tube using a gastight HPLC syringe. Sample volume after addition of all components was 0.50–0.60 cm^3 and the phosphorus reactant concentration 90–110 mmol dm^{-3} depending on the reaction conditions. The clock was started as the initiating reagent was added and the tube was rapidly turned upside down to mix the solution before insertion into the magnet. The first spectrum (NNE irradiation mode, 6 scans, accumulation time 1.0 s, pulse delay 1.5 s) was in most cases detected within 60 s of the beginning of reaction.

Though dried solvents and reactants were used, about 30% of the starting material was hydrolyzed in reactions of **1b**. Hydrolysis and alcoholysis of **1b** only proceeds if tetrazole (or some other catalyst) is present and gives $(Pr^iO)_2P(O)H$ and DIA, which together with tetrazole yields the sparingly soluble DIAT as white flakes. In runs with **2b** $(Pr^iO)_2P(O)H$ is already present as the byproduct of the preceding step regardless of whether **2b** was generated *in situ* (method 3, DIAT present), or synthesized separately (method 1, DIAT absent). Additional hydrolysis may take place in the NMR sample, since **2b** reacts spontaneously with any water available yielding tetrazole and $(Pr^iO)_2P(O)H$. However, tetrazole and alcohol added to **2b** at the beginning of the run have only a small hydrolytic effect. Generally in all runs of **1b** and **2b** the actual concentration of the reactant after hydrolysis was 60–80 mmol dm^{-3}. The variation in the amount of hydrolysis between different runs was less than 5%. During a run, the concentration of the hydrolysis product remains constant within ±2 mmol dm^{-3}, which gives an indication of the accuracy of the method applied.

Calculations. Rapid processes, above all hydrolysis, were assumed to be completed before any substitution reaction took place. These processes affect the initial concentrations of the starting material, tetrazole, DIA and DIAT, which was taken into account in calculations. During the course of reaction the ratio of the concentrations of phosphorus compounds was assumed to be directly proportional to the ratio of their ^{31}P NMR signal integral values. The concentrations of tetrazole and alcohol were calculated from the observed concentrations of the phosphorus compounds on the basis of the stoichiometry of the reactions. The initial rates of the reactions were estimated by fitting an exponential curve to the observed data points of the starting material concentration. Good fit was achieved using eqn. (11). Parameters b, m and n of eqn. (11)

$$\frac{1}{[A]} = b + me^{t/n} \qquad (11)$$

were optimized (assuming that the dependence 1/[A] *vs.* $e^{t/n}$ is linear) for each run using a simple square-sum minimizing solver routine. The very last data points of a run were usually discarded to get a better fit at the beginning of the reaction.

Simulations. Simulations were run using Chemical Kinetics Simulator software by IBM.[20]

References

1 É. E. Nifant'ev and M. K. Grachev, *Russ. Chem. Rev.* (*Engl. Transl.*), 1994, **63**, 575; *Usp. Khim.*, 1994, **63**, 602.
2 S. L. Beaucage and R. P. Iyer, *Tetrahedron*, 1992, **48**, 2223.
3 (*a*) B. H. Dahl, J. Nielsen and O. Dahl, *Nucl. Acids Res.*, 1987, **15**, 1729; (*b*) O. Dahl, *Phosphorus Sulfur*, 1983, **18**, 201.
4 S. L. Beaucage, *Tetrahedron Lett.*, 1984, **25**, 375.
5 É. S. Batyeva, V. A. Al'fonsov, G. U. Zamaletdinova and A. N. Pudovik, *Russ. J. Gen. Chem.* (*Engl. Transl.*), 1976, **46**, 2120; *Zh. Obshch. Khim.*, 1976, **46**, 2204.
6 É. E. Nifant'ev, M. K. Gratchev, S. Yu. Burmistrov, L. K. Vasyanina, M. Yu. Antipin and Yu. T. Struchkov, *Tetrahedron*, 1991, **47**, 9839.
7 D. Gonbeau, G. Pfister-Guillouzo, M.-R. Mazières and M. Sanchez, *Can. J. Chem.*, 1985, **63**, 3242.
8 (*a*) A. A. Korkin and E. N. Tsvetkov, *Russ. J. Gen. Chem.* (*Engl. Transl.*), 1987, **57**, 1929; *Zh. Obshch. Khim.*, 1987, **57**, 2155; (*b*) A. A. Korkin, A. M. Mebel and E. N. Tsvetkov, *Russ. J. Gen. Chem.* (*Engl. Transl.*), 1988, **58**, 900; *Zh. Obshch. Khim.*, 1988, **58**, 1015; (*c*) A. A. Korkin and E. N. Tsvetkov, *Bull. Chem. Soc. Fr.*, 1988, 335; (*d*) A. A. Korkin and E. N. Tsvetkov, *Russ. J. Inorg. Chem.* (*Engl. Transl.*), 1989, **34**, 161; *Zh. Neorg. Khim.*, 1989, **34**, 295.
9 (*a*) S. Yu. Burmistrov, L. K. Vasyanina, M. K. Grachev and É. E. Nifant'ev, *Russ, J. Gen. Chem.* (*Engl. Transl.*), 1989, **59**, 2360; *Zh. Obshch. Khim.*, 1989, **59**, 2639; (*b*) É. E. Nifant'ev, M. K. Gratchev, S. Yu. Burmistrov, M. Yu. Antipin and Yu. T. Struchkov, *Phosphorus Sulfur*, 1992, **70**, 159.
10 (*a*) G. I. Koldobskii and V. A. Ostrovskii, *Russ. Chem. Rev.* (*Engl. Transl.*), 1994, **63**, 797; *Usp. Khim.*, 1994, **63**, 847; (*b*) S. J. Wittenberger, *Org. Prep. Proced. Int.*, 1994, **26**, 499.
11 (*a*) S. Berner, K. Mühlegger and H. Seliger, *Nucl. Acids Res.*, 1989, **17**, 853; (*b*) S. Berner, K. Mühlegger and H. Seliger, *Nucleosides, Nucleotides*, 1988, **7**, 763.
12 E. S. Batyeva, V. A. Al'fonsov and A. N. Pudovik, *Dokl. Chem.* (*Engl. Transl.*), 1988, **303**, 332; *Dokl. Akad. Nauk SSSR*, 1988, **303**, 632.
13 B. G. Cox, *Modern Liquid Phase Kinetics*, Oxford University, New York, 1994, p. 10.
14 The solubility of DIAT in THF is less than 10 mg dm^{-3}, and hence an extremely small amount of the salt is sufficient to give a saturated system without the accuracy-lowering drawbacks of excessive precipitation.
15 K. A. Petrov, É. E. Nifant'ev, T. N. Lysenko and V. P. Petrov, *Russ J. Gen. Chem.* (*Engl. Transl.*), 1961, **31**, 2214; *Zh. Obshch. Khim.*, 1961, **31**, 2377.
16 Y. Watanabe, S. Maehara and S. Ozaki, *J. Chem. Soc., Perkin Trans. 1*, 1992, 1879.
17 O. J. Scherer and N. Kuhn, *Chem. Ber.*, 1975, **108**, 2478.
18 J. W. Perich and R. B. Johns, *Synthesis*, 1988, 142.
19 É. E. Nifant'ev, M. K. Grachev, S. Yu. Burmistrov and L. K. Vasyanina, *Russ. J. Gen. Chem.* (*Engl. Transl.*), 1988, **58**, 895; *Zh. Obshch. Khim.*, 1988, **58**, 1011.
20 The software is available at http://www.almaden.ibm.com/st/msim/ordrform.html (19.11.1997).

Paper 8/01250D
Received 12*th February* 1998
Accepted 17*th April* 1998