Alcoholysis of dialkyl tetrazolylphosphonites

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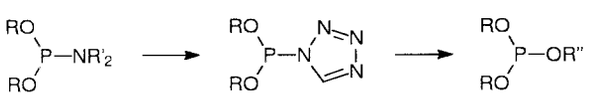
Kinetics of the reaction of diisopropyl tetrazolylphosphonite with *tert*-butyl alcohol in dry THF have been studied in the presence of various acids, bases and salts that catalyze the process. Ammonium azolide salts were found to be considerably more efficient catalysts than the corresponding azole acids or tertiary amine bases. For instance, the relative rates obtained with *N*,*N*-diisopropylethylammonium tetrazolide, *N*,*N*-diisopropylethylamine and tetrazole were 104, 28 and 1, respectively. The salts of strong protolytes turned out to be better catalysts than those of weak ones. The susceptibility of the reaction rate to the pK_{BH^+} of the base is fairly strong (Brønsted $\beta = 0.41$) compared to the sensitivity to the pK_a of azoles ($\beta = 0.17$). The mechanisms of catalysis are discussed.

Introduction

Modern automated synthesis of DNA utilizes the reactive phosphoramidites **1**, the dialkylamino group of which may be easily displaced by the entering sugar hydroxy function in the presence of an acidic activator.[1,2] Amine hydrohalides and azoles are known to catalyze the reaction and the most commonly applied catalyst is tetrazole[3] (TH), which is in principle capable of acting as both an acid and a nucleophile. Intermediary formation of tetrazolylphosphonites† (**2**) has been detected during tetrazole-promoted alcoholyses of **1** and they are usually considered to be intermediates of the reaction. One of the mechanistic key questions of this reaction is whether it proceeds solely *via* a tetrazolylphosphonite intermediate or is there possibly a competing route that bypasses involvement of tetrazole as a nucleophile in the reacion.[1,4,5] This problem was addressed in our previous study,[6] where some evidence for **2** lying on the pathway from **1** to **3** was presented (Scheme 1).



Scheme 1

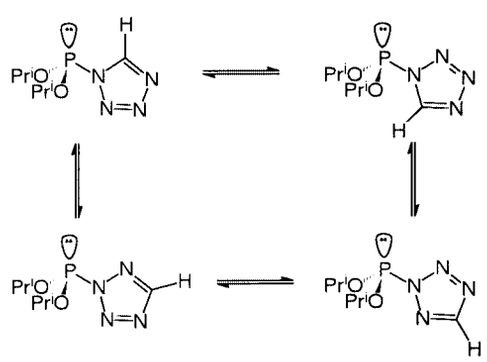
Tetrazolylphosphonites can be prepared from **1** and tetrazole, but they have seldom been isolated in pure form, because they are unstable compounds, being especially susceptible to hydrolysis by atmospheric moisture. Compounds **2** are known to react with alcohols to give **3** and with secondary amines to give **1**.[5,6] Nevertheless, the data on the reactivity of tetrazolylphosphonites and factors influencing it are scarce. A thorough understanding of the behaviour of **2** is, however, a prerequisite for solid conclusions concerning the mechanism of phosphoramidite alcoholysis. For this purpose, we now report the reaction of diisopropyl tetrazolylphosphonite (**2a**) with *tert*-butyl alcohol (Bu′OH), a reaction known to be first-order in the concentrations of both reactants. Second-order catalysis by tetrazole as well as a marked sensitivity towards added salts were detected in the previous study.[6] A more extensive study on catalysis of the reaction by various azole acids, amine bases and their salts has been carried out to learn how the efficiency of a given type of catalyst depends on its structure and protolytic strength.

† In a previous paper (E. J. Nurminen, J. K. Mattinen and H. Lönnberg, *J. Chem. Soc.*, *Perkin Trans. 2*, 1998, 1621) these species were incorrectly named by the editor as dialkyl tetrazolylphosphites.

Results

Structural properties of 2a

The ^{31}P NMR spectrum of **2a** shows that in dry THF this compound exists as several isomers: one major component (δ = 125.9 ppm, ~75%) and two or three (broadened overlapping signals) minor components (δ = 128–129 ppm, ~10%). According to saturation transfer experiments these isomers are in equilibrium with each other and cannot therefore be isolated. This is in agreement with the observed parallel disappearance of the signals of all isomers during the alcoholysis. The observed isomers are best explained by the fact that a tetrazole ring can be attached to phosphorus either *via* its 1- or 2-nitrogen and in both cases with two different rotational orientations (Scheme 2). Similar 1*H*–2*H* tautomerism has recently



Scheme 2

been observed for the tetrazole moiety of Irbesartan, a novel drug compound.[7] The interconversion of both the rotational and constitutional isomers is slow on the NMR timescale because rotation around the P–N bond is hindered by pπ–dπ interaction[8] and bulky isopropyl groups, and cleavage of the bond is required for the constitutional isomerization.

The equilibrium between the isomers of **2a** can be rationalized by a mechanism similar to that of racemization observed for optically active trivalent phosphorus compounds bearing an appropriate leaving group.[9–11] Racemization does not involve the energetically unfavourable inversion of the phosphorus center, but takes place *via* intermolecular exchange of labile groups at phosphorus.[9,10] A cyclic transition state involving two

(or more) molecules has been proposed[11] for the process that is known to be accelerated by traces of ammonium salts[9] and nucleophilic impurities.[10] As a result of this, in the presence of salt the ^{1}H NMR signals of the diastereotopic methyl protons of the isopropyl groups in **2a** are broadened to two lumps instead of clear doublets. The interconversion processes of isomers are even faster in acetonitrile, where both isopropyl groups give only one broad methyl signal, and the ^{31}P NMR signals of the isomers collapse to one averaged signal. In addition to the above mentioned isomers, there are some impurities visible in the ^{31}P NMR spectrum including the hydrolysis product, diisopropyl hydrogenphosphonate $(Pr^iO)_2P(O)H$ ($\delta = 6.4$ ppm), the concentration of which remained at the average level of 7% during the kinetic runs. The phosphorus impurities have not been found to affect the rate of the studied reaction.

Pure isolated **2a** that is practically free from protolytic impurities is surprisingly stable. One must bear in mind that both the hydrolysis and alcoholysis of tetrazolylphosphonite release tetrazole, known to be a moderate catalyst for these processes, and hence they are autocatalytic: once initiated, the reactions proceed with increasing rate until most of the starting material has been consumed. When protected from atmospheric moisture, purified **2a** can be stored practically unchanged for several weeks and its uncatalyzed reaction with 3 equiv. of Bu^{t}OH has a $t_{1/2}$ longer than 3 h. However, even traces of a suitable salt added to the reaction medium will speed up the process to completion within a few minutes.

The significant catalytic effect that even traces of protolytes produce gives rise to some practical considerations: 1) to obtain reliable kinetic results **2a** must be purified as well as possible from protolytic impurities present in the reaction mixture. 2) The purity of **2a** is best controlled by measuring the rate of its alcoholysis in the absence of added catalysts. Hence, the kinetic results obtained with different synthesized batches of **2a** are only comparable with each other if the rates of their uncatalyzed alcoholyses are equal. 3) The determination of the true rate constant of the uncatalyzed alcoholysis of **2a** is a complicated and elaborate task, since it would require either complete absence of all impurities or exact determination of their remaining trace concentrations. In the scope of the present work the problem is not very relevant, and hence the effort required was not considered worthwhile. Accordingly, it remains unclear whether the non-zero value observed results only from the presence of impurities or if it does really reflect the true ability of **2a** to react with Bu^{t}OH without any catalytic assistance.

Kinetics of alcoholysis of 2a

The reaction of **2a** with *tert*-butyl alcohol in THF in the presence of azole acids, tertiary amine bases or ammonium azolide salts was followed. The kinetic runs were performed at 20 °C using ^{31}P NMR spectroscopy for monitoring. Since the high reactivity of tetrazolylphosphonite prevents measurements under pseudo-first-order conditions, the method of initial rates was applied: for each catalyst, the initial rate of the appearance of the phosphite product **3a** at several catalyst concentrations was determined. In most cases, a good linear relationship ($r > 0.99$) between $v_0/\{[\mathbf{2a}][Bu^tOH]\}$ and catalyst concentration [cat] was obtained, as indicated by eqn. (1).

$$\lim_{t\to 0}\frac{d[\mathbf{3a}]}{dt} = v_0 = (k_u + k_c[cat]_0)[\mathbf{2a}]_0[Bu^tOH]_0 \qquad (1)$$

Some of the most weakly catalytic salts that were used at high concentrations, however, showed deviation from the linear dependence, suggesting higher than first-order dependence on the catalyst concentration (Fig. 1). This may refer to catalysis by ion triplets, quadrupoles *etc*. resulting from ion aggregation that typically takes place in solvents of low relative permittivity

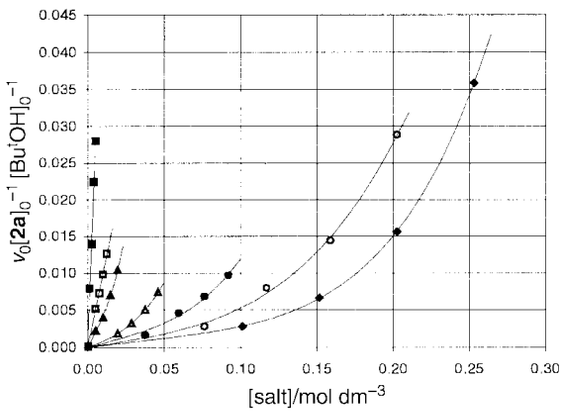


Fig. 1 The reaction of **2a** with Bu^{t}OH in the presence of various ammonium tetrazolides in THF at 20 °C: the dependence of $v_0/\{[\mathbf{2a}][Bu^tOH]\}$ on salt concentration. Notation: ■ = DBU tetrazolide, □ = diisopropylethylammonium tetrazolide, ▲ = tributylammonium tetrazolide, △ = dimethylbenzylammonium tetrazolide, ● = methylmorpholinium tetrazolide, ○ = triallylammonium tetrazolide, ◆ = diisopropylanilinium tetrazolide.

(ε(THF) = 7.4). This phenomenon is taken into account in eqn. (2) by inducing a $[cat]^n$ term ($n > 1$). In order to compare only the catalytic strengths of single ion-pairs and to avoid complications that arise in nonlinear cases, where several parameters are involved for each catalyst, we solved the parameters of eqn. (2) for these catalysts and used the first-order coefficients as a measure of catalyst efficiency. These values equal the slopes of the dependencies at [cat] = 0, and the results are thus being extrapolated to infinite dilution, where aggregation is minimal.

$$v_0 = (k_n + k_c[cat]_0 + k_c'[cat]_0^n)[\mathbf{2a}]_0[Bu^tOH]_0 \qquad (2)$$

The relative acidity constants of the catalysts were determined in dry THF at 20 °C by examining the protolytic equilibrium between two acids of comparable strength and extending the measurements to the whole set of catalysts in a stepwise manner. Accordingly, a strong base was added to an equimolar mixture of acids and the degree of deprotonation was determined on the basis of ^{13}C NMR shifts as described in the Experimental section. The pK_a value of tetrazole was assumed to be 4.9 and the pK_{BH^+} value of dimethylbenzylamine 8.9. The pK_a values of the other protolytes were calculated from these with the aid of the relative protolytic strengths obtained by the stepwise approach. The acidity constants and the catalytic constants are listed in Table 1.

Acid catalysis. Various azoles, such as 5-(4-nitrophenyl)-1*H*-tetrazole,[12] 5-(ethylthio)-1*H*-tetrazole[13] and 3-nitro-1,2,4-triazole, have previously been used as activators in oligonucleotide synthesis. The usage of these (we applied 5-(methylthio)-1*H*-tetrazole instead of the ethyl derivative) as catalysts in the studied reaction gave an interesting result: an azole introduced to the solution of **2a** very rapidly replaced tetrazole at phosphorus, and a mixture of the new azolylphosphonite and the original **2a** is obtained. The exchange reaction was completed in less than 20 seconds, which is the time required for registration of the first NMR spectrum. The concentration ratio of the azolylphosphonites depended on the amount of azole added, and it remained constant during the alcoholysis, indicating that the two species were rapidly equilibrated. Azoles being more acidic or less acidic than tetrazole behaved similarly in this respect. On using tetrazole as catalyst a similar exchange reaction undoubtedly takes place, although it cannot be observed as the reactant and product in this case are the same compound.

Table 1 The reaction of **2a** with Bu^{t}OH in presence of various catalysts in THF at 20 °C: third-order rate constants k_c (dm^6 mol^{-2} s^{-1}) and dissociation constants of protolytic additives

Catalyst	pK_a [a]	pK_{BH^+} [a]	k_c
3-Nitro-1,2,4-triazole	5.2	—	0.004
1*H*-Tetrazole	4.9	—	0.009
5-Methylthio-1*H*-tetrazole	4.2	—	0.011
5-(4-Nitrophenyl)-1*H*-tetrazole	3.7	—	0.21
Diisopropylethylamine	—	10.0	0.25
Tributylamine	—	9.7	0.05
1-Methylmorpholine	—	8.5	0.01
DIEA 3-nitro-1,2,4-triazolide	5.2	10.0	0.96
DIEA 5-methylthiotetrazolide	4.2	10.0	1.2
DIEA 5-(4-nitrophenyl)tetrazolide	3.7	10.0	1.7
DIEA perchlorate [b]	—	10.0	0.32
Tetrabutylammonium tetrazolide [b]	4.9	—	3.1
DBU tetrazolide	4.9	13.2	5.7
DIEA tetrazolide	4.9	10.0	0.94
Tributylammonium tetrazolide	4.9	9.7	0.40
N,*N*-Dimethylbenzylammonium tetrazolide	4.9	8.9	0.078
1-Methylmorpholinium tetrazolide	4.9	8.5	0.054
Triallylammonium tetrazolide	4.9	7.8	0.033
N,*N*-Diisopropylanilinium tetrazolide	4.9	6.8	0.024

[a] pK_a and pK_{BH^+} values in THF measured in current work. For details see Experimental section. [b] Measurements carried out using a different batch of **2a** than for other catalysts.

Because of the rapid transazolidation it was impossible to measure a rate constant referring to the catalytic effect of a single azole: the introduction of the catalyst yielded a mixture of two dialkyl azolylphosphonites and two azoles, and hence four different catalytic processes may occur simultaneously. Still, it is possible to measure the alcoholysis rate of this mixture at various initial concentrations of the added azole, and calculate the catalytic constants for the mixtures. These constants, although not having a well-defined physical significance, reflect both the nucleophilic and protolytic influence of the azoles, and they can therefore be regarded as the best available indicator of the overall catalytic efficiency. Stronger acids seem to be better catalysts than the weaker ones.

Base catalysis. Time-dependent product distributions of the base-catalyzed reactions of **2a** with Bu^{t}OH show a clear indication of autocatalysis: the reaction releases tetrazole, a relatively strong acid that protonates the amine used as base catalyst. The salt thus formed is a more efficient catalyst than the original amine, as discussed below in more detail, and the gradual conversion of the base to salt during the reaction hence results in the observed rate enhancement. Consequently, detailed quantitative study of the base catalysis becomes difficult, since the catalytic effect of the added base cannot be distinguished from that of the mixture of protolytes present in the solution already at early stages of the reaction. That is why the catalytic constants for only a few amines were determined: in each case a similar autocatalysis was observed. The strongest bases proved to be the best catalysts.

Catalysis by salts. This is the most effective type of catalysis for tetrazolylphosphonite alcoholysis. The catalytic constants determined for different ammonium azolide salts indicate that the salts derived from strong protolytes are better catalysts than those derived from weak ones. The pK_{BH^+} of the cation is clearly the most important factor affecting the catalytic efficiency: Plotting the log k_c values obtained with ammonium tetrazolides *vs.* pK_{BH^+} gives a Brønsted β value of 0.41 (± 0.05) with correlation coefficient $r = 0.92$ (Fig. 2). The considerable variation of amine structure, wide pK_{BH^+} range and different degrees of aggregation are likely to be responsible for the observed deviations. The pK_a of the azole has a less pronounced

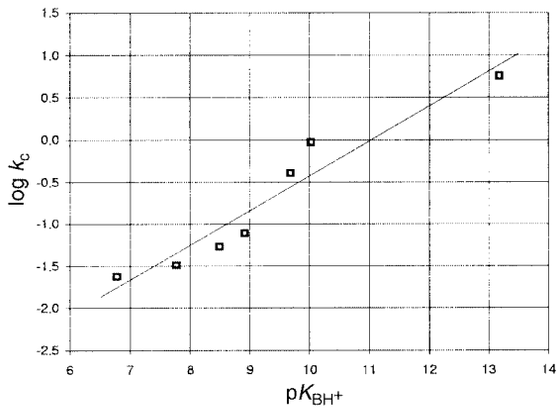


Fig. 2 The reaction of **2a** with Bu^{t}OH in the presence of various ammonium tetrazolides in THF at 20 °C: Brønsted dependence of log k_c on pK_{BH^+} of ammonium ions.

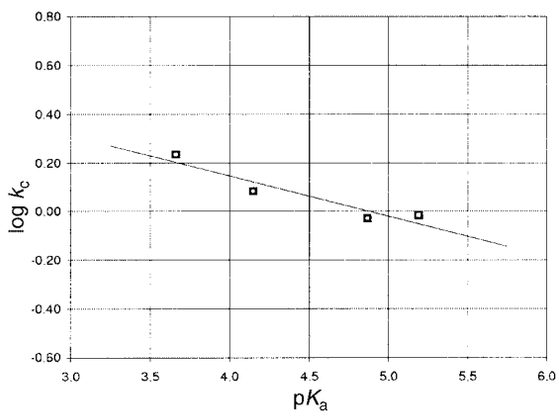


Fig. 3 The reaction of **2a** with Bu^{t}OH in the presence of various diisopropylethylammonium azolides in THF at 20 °C: Brønsted dependence of log k_c on pK_a of azolide ions.

effect on k_c, the β value being 0.17 (± 0.04) with $r = 0.89$ (Fig. 3). In spite of the limited accuracy of the calculated Brønsted β values, the trend favouring salts of weakly protolytic ions is clear, the emphasis being on the acidity of the ammonium ion. The catalytic constants of tetrabutylammonium tetrazolide and DIEA perchlorate cannot be included in the above mentioned trends, since these salts represent the extreme cases, where the salt cannot act as an acid or base, correspondingly. The observed non-zero values suggest that the capability to act as proton donor or acceptor is not a prerequisite for the catalytic activity of salts in the reaction studied. This is in agreement with the catalysis of tetrabutylammonium bromide observed previously.[6]

To gain information on the possible co-operativity of bases and their conjugate acids as catalysts the reaction was followed in the presence of both diisopropylethylammonium tetrazole (DIEAT) and tetrazole (TH) or DIEAT and diisopropylethylamine (DIEA). The experiments are analogous to conventional buffer catalysis measurements in aqueous solution. The k_c values for the mixtures were obtained as slopes of the plot v_0/{[**2a**][Bu^{t}OH]} *vs.* [DIEAT] (Fig. 4). When an additional protolyte, either an acid or base was present, higher k_c values resulted (Table 2). Additional base had a more marked rate-accelerating effect than additional acid.

The observed catalytic constants of the mixtures were then plotted *vs.* $[TH]_0$ and $[DIEA]_0$ and catalytic rate constants of TH and DIEA were obtained as the slopes and that of DIEAT as the intercept. These values were used as the initial values for an iteration that optimized the fit of calculated constants with the observed data points yielding k_c values 0.92, 0.34 and 1.02 for DIEAT, TH and DIEA, respectively. Fig. 4 shows how the result of the fitting (presented with solid lines) meets

Table 2 The reaction of **2a** with Bu^{t}OH in presence of mixtures of DIEAT and DIEA or TH in THF at 20 °C: third order rate constants k_c (dm^6 mol^{-2} s^{-1}) with respect to DIEAT concentration

[DIEA]:[DIEAT]:[TH]	k_c
0:1:2	1.66
0:1:1	1.22
0:1:0	0.92
1:1:0	1.99
2:1:0	3.06

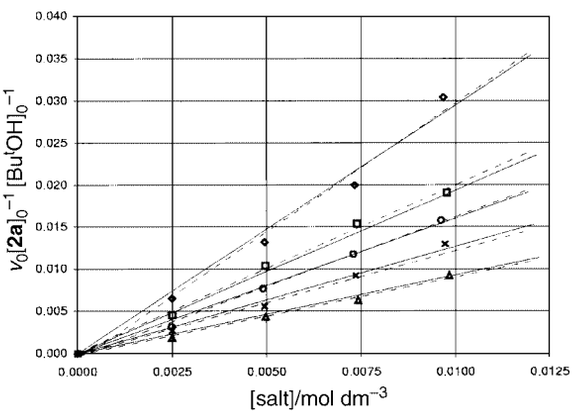


Fig. 4 The reaction of **2a** with Bu^{t}OH in the presence of mixtures of DIEAT and DIEA or TH in THF at 20 °C: the dependence of $v_0/\{[\mathbf{2a}][\mathrm{Bu^tOH}]\}$ on [DIEAT]. Notation: ◇ DIEA:DIEAT = 2:1, □ DIEA:DIEAT = 1:1, ○ DIEA:TH = 1:2, × = DIEA:TH = 1:1, △ DIEAT only. Dotted lines are calculated from data with linear regression (representing k_c values of Table 2) and solid lines are based on the optimized catalytic constants of DIEAT, DIEA and TH.

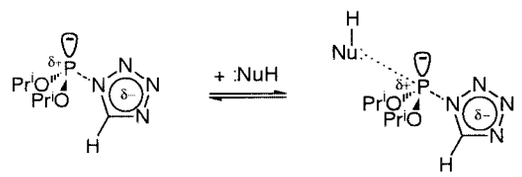
the observed data. It is worth noting that the catalytic constants of TH and DIEA are considerably higher in the presence than in the absence of the salt.

Discussion

The relative permittivity of THF ($\varepsilon = 7.4$) is close to that of ethyl acetate (6.0), diethyl ether (4.2) and chloroform (4.7), rather than acetone (20.7), acetonitrile (36.7) or DMSO (46.7).[14] Its protolytic contribution can be neglected and it has very limited capability to solvate ions: in such a medium reactions that involve proton transfer, a partially charged transition state, or charged primary products are likely to proceed reluctantly. At low relative permittivity charged particles are unfavoured species that require better stabilization than the solvent is able to offer. This makes the interactions between the polar solvate molecules more important as a means of lowering the energy of charged species and charge formation during reactions.[15] These properties provide a reasonable background to the two characteristic features of tetrazolylphosphonite alcoholysis in THF: the surprisingly slow uncatalyzed reaction and high sensitivity of rate to protolytic additives.

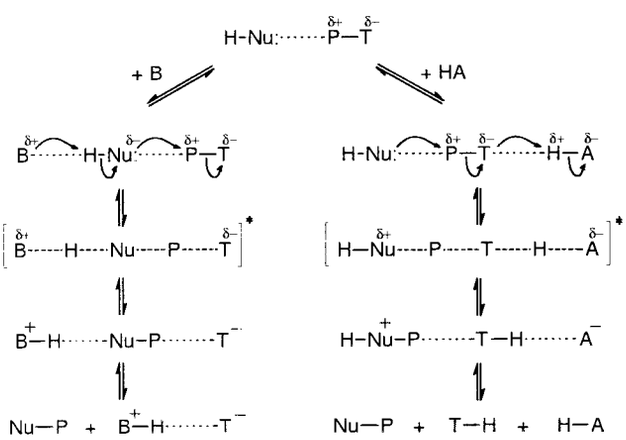
In solvents of low relative permittivity acids and bases may prefer dimeric forms[16] while the energetically most favoured alternative for ions is association as contact ion-pairs with cation and anion in the same solvent cage.[15] Especially at higher concentrations, salts may also form aggregates of several ion-pairs. Considerable association of protolytes leads to altered kinetic orders,[17] as seen in the cases of some ammonium salts in this work and tetrazole in our previous work. Catalysis may simultaneously take place by the first-order and higher-order pathways and therefore distinguishing between these alternatives is neither possible nor meaningful. From the mechanistic point of view, the order of catalysis is actually rather insignificant as it describes more the aggregation degree of the catalyst rather than the interaction between the catalyst and the substrate.

The characteristic property of tetrazolylphosphonite is the lability of the bond between the electron-withdrawing tetrazole group and trivalent phosphorus. The situation is similar to that proposed for N-protonated phosphoramidite:[18] the P–N bond is lengthened and polarized with partial negative charge on nitrogen and positive charge on phosphorus, the susceptibility of which to nucleophilic attack is thus enhanced. The dipolar starting material is easily associated with nucleophiles present in solution (Scheme 3). Without an added catalyst this



Scheme 3

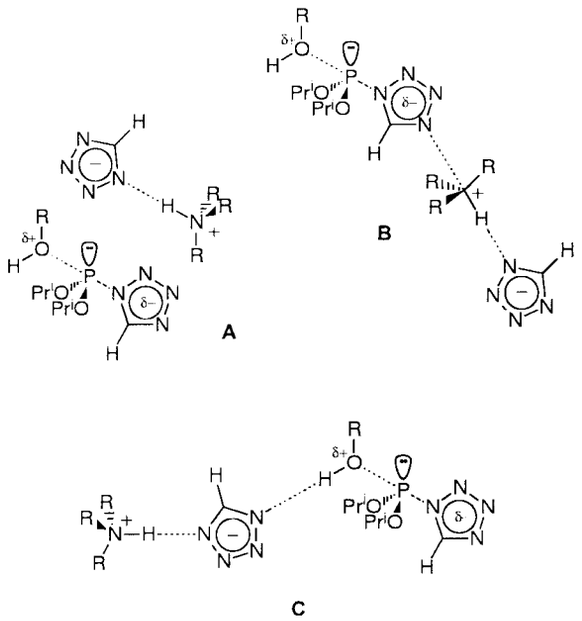
preassociated complex is, however, practically unable to cross the energy barrier involved in cleavage of the P–N bond and formation of the P–O bond. An acid catalyst can assist the cleavage of the P–N bond by protonation of the leaving group. An acidic azole, for example, can form a hydrogen bond to the departing tetrazolide. Base, in turn, can promote the formation of a covalent P–O bond by deprotonating the attacking nucleophile. Both catalysts trigger the rate-limiting substitution step of the reaction that is likely to take place in a more or less concerted manner. The full charges developed on the immediate products are stabilized by the opposite charge still present within the same solvate cage. The remaining protolytic rearrangements take place rapidly after this (Scheme 4).



Scheme 4

The catalysis by salts is a more complicated matter. The nucleophilic contribution of the azolide can be ruled out, since a) no transazolidation is observed in the presence of salts; the azole can only be changed if the attacking azole is introduced in acidic form, and b) nucleophilic catalysis would not assist the reaction in the case of the tetrazolide anion since the leaving group already is a tetrazolide ion. Neither can the salt catalysis be solely of protolytic origin, because a) salts have larger catalytic constants than stronger acids and bases, b) the reactions in the presence of salt catalysts lack the autocatalytic shape although strongly acidic tetrazole is liberated in the course of the process and c) salts of the most weakly acidic cation and the most weakly basic anion are the best catalysts.

Our results are best explained by ion-pair catalysis, a subtype of salt catalysis common in nonpolar solvents where salts exist as ion-pairs. The catalytic effect of the salt rises from its ability to polarize the medium[19] and provide stabilization to the



Scheme 5

partially charged and ionic species involved in the reaction.[15] In solvents such as THF, whose ability to solvate charged species is highly limited, salt effects of this type may be enormous[17] and salts are commonly more effective catalysts than acids or bases.[20,21] It is worth noting that the studied salts derived from a tertiary amine and an azole do not fit the conventional concept of salt effects because they can, and obviously do, participate in the reaction as protolytes. This is not the origin of the catalytic effect, as discussed above, and salts may well catalyze the reaction without being proton donors (tetrabutylammonium tetrazolide) or acceptors (DIEA perchlorate). Nevertheless, observed catalytic coefficients indicate that salts capable of acting both as acids and bases are superior catalysts due to their ampholytic nature.

Ion-pair catalysis is often attributed to intimate interactions between the ion-pairs and substrate molecules, such as those depicted in Scheme 5. These associations are thought to promote the ionization of substrate molecule (A)[22] or stabilize the charges of the transition state (B and C).[15,23] Alternatively, the effect of ion-pairs has been rationalised on a macromolecular level by an ion-pair atmosphere model that explains the rate enhancement by the salt-induced polarization of the medium rather than specific events taking place on molecular level.[19,22] The effect is thought to be analogous to substitution of the solvent with a more polar one, such as acetonitrile, that is known to be a better solvent for the studied reaction. Anyway, the result is a more marked polarization of tetrazolylphosphonite, which leads to the closer association of the attacking alcohol and the phosphorus center before the rate-limiting step. Since the pre-equilibrium thus yields a structure closer to the transition state, the activation energy is lowered and the reaction is able to proceed without protolytic assistance. It is worth noting that the added salt also lowers the energy level of the immediate products and the salt ions are able to act as protolytes promoting the formation of final products after the rate-determining step.

The dependence of reaction rate on the salt concentration is generally written as eqn. (3),[19,20,22–24] consistent with eqn. (1)

$$k_{obs} = k_0(1 + b[\text{salt}]) \qquad (3)$$

applied to our results. Winstein *et al.* have reported curvature that arises from association of the salt at high concentration and leads to catalysis by dimers or other aggregates.[17] Mathematical formulation of this phenomenon would require the insertion of a 1.5th or second order term in the equation as is the case in salts of weakly basic amines used in the present work.

Brønsted dependencies qualitatively similar to the one observed for ammonium ions in the present work have previously been reported by others.[20] The rationalization for this is that the catalytic effectiveness of an ion-pair depends on the charge density on its poles: in the case of a weakly acidic cation and a weakly basic anion the charge is at a maximum and the diminished interaction within the ion-pair enables larger interactions with external charged centers of the substrate.[15] The reason for the less pronounced dependence on the azolide ion basicity might be that the differences in their protolytic strength arise from delocalization of negative charge in the aromatic heterocycle. In this case pK_a is a poor measure of the charge density in the dipole, and the β value remains small.

The acid or base catalysis in the presence of salt has in several cases been found to result in a higher reaction rate than the one expected from additivity of the individual effects.[21,25] The unexpectedly high acceleration has been attributed to co-operative catalysis involving the protolyte and ion-pair in same transition state. The phenomenon has not been thoroughly investigated, but in cases where data allowed formulation of a rate equation, a term containing the concentration of both catalysts was included (eqn. (4)).[25] Our results are qualitatively

$$v_0 = (k_u + k_{c1}[\text{HA}]_0^2 + k_{c2}[\text{HA}]_0[\text{salt}]_0)[\mathbf{2a}]_0[\text{Bu}^t\text{OH}]_0 \qquad (4)$$

consistent with this, but we did not detect co-operative second-order catalysis as seen clearly from the linearity of dependencies in Fig. 4: the catalytic constant of the salt proved to be independent of the presence of acids or bases while the catalytic constants of the latter ones were higher in the presence of salt than in its absence, but were still not dependent on the salt concentration (eqn. (5)).

$$v_0 = (k_u + k_{c1}[\text{HA}]_0 + k_{c2}[\text{salt}]_0)[\mathbf{2a}]_0[\text{Bu}^t\text{OH}]_0 \qquad (5)$$

Ionization and dissociation of an organic molecule in a weakly dissociating medium occurs in a stepwise manner: heterolytic bond cleavage leads to a contact-ion-pair (CIP), which can dissociate partially to form a solvent-separated ion pair (SSIP) and completely to give two free ions (eqn (6)).

$$\text{A–B} \rightleftharpoons \text{A}^+\text{B}^- \rightleftharpoons \text{A}^+\|\text{B}^- \rightleftharpoons \text{A}^+ + \text{B}^- \qquad (6)$$

Reactions occurrng *via* free ions are subject to retardation of the reaction rate by a common ion mass effect first shown by Ingold *et al*. SSIPs, in turn, enable the so-called special salt effect proposed by Winstein *et al*.[26] Neither of these effects is observed in the present study, as expected in a nonpolar solvent such as THF, which means that the charge formation during the reaction takes place within one solvate cage and only CIPs are involved before the rate-limiting step. This explains why azolide anions were not capable of replacing the tetrazole ring of **2a**: transazolidation would require a SSIP with a full positive charge on phosphorus and since this is never formed, azolide anion is always more strongly bound to its counterpart in the ion-pair than any charged center outside of it. Hence, the mechanism of the alcoholysis can not be dissociative; fully charged ions can only develop after the attack of nucleophile on the phosphorus center.

Unlike the azolide anions, azoles resulted in transazolidation so rapidly that it had already reached equilibrium while alcoholysis had barely started. The reactivity difference has two alternative explanations: a) the azole may have a significantly higher affinity towards the trivalent phosphorus; competing successfully with the alcohol at the pre-association

stage, or b) the azole is much more acidic than the alcohol and hence the deprotonation involved in the substitution is faster for the azole. The latter explanation, however, is valid only if the deprotonation takes place during the rate-determining step, which is unlikely in an acidic medium. Therefore, it appears reasonable to conclude that azole is a better, kinetically favoured, nucleophile for tetrazolylphosphonites than alcohol, which gives the thermodynamically more stable product.

Experimental

Synthesis of **2a**, a description of the kinetic measurements and an analysis of the data have been published previously.[6] The amount of hydrolytic decomposition was kept to a minimum by purification of the phosphoramidite used as starting material, usage of only a very dry acetonitrile solution of tetrazole and careful filtration of the diisopropylammonium tetrazolide salt. Attempts to purify **2a** with distillation at reduced pressure (argon atmosphere) were not successful since at the pressure achieved by our vacuum pump (0.1 mbar) the boiling point of the product was too high and it was partially decomposed. Additional hydrolysis during kinetic measurements was kept to a minimum: sample solutions were dried with molecular sieves and stored in vials under airtight Teflon-coated butyl rubber septa, and NMR tubes were dried in an oven prior to use. NMR spectra were recorded at 500 MHz for ^{1}H, 202 MHz for ^{31}P and 125 MHz for ^{13}C.

The relative dissociation constants of acids were determined as follows: the ^{13}C NMR shifts were measured for each acid and the corresponding conjugate base, which was obtained by adding strong base (DIEA) in the solution. The strength of two acids were then compared with each other by introducing a small amount of a strong base (DIEA) into a mixture of the two acids. The concentrations of deprotonated species of the acids were calculated from the ^{13}C NMR chemical shift of the mixture using eqn. (7), and the ratio of the dissociation constants was then calculated by eqn. (8). The ratio

$$[A^-] = \frac{\delta_{HA} - \delta_{HA+A^-}}{\delta_{HA} - \delta_{A}}[HA]_0 \quad (7)$$

$$\frac{K_{A1}}{K_{A2}} = \frac{[A_1^-][HA_2]}{[HA_1][A_2^-]} \quad (8)$$

was determined at several concentrations of added base and the relative pK_a value of the acid was calculated using the average of these. Each acid was compared in this manner to its closest neighbours in the aqueous pK_a-value scale. Relative dissociation constants of bases were measured in a similar manner using strong acid (TFA) as the proton donor.

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