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The Extension of the Mechanistic Concept of the Nucleophilic Catalysis in the Silicon Chemistry to Some Reactions of the P(III) Center: Analogies between Silylation and Phosphorylation

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ABSTRACT

Many observations prove that a number of silylation reactions of a trialkylsilyl halide-uncharged base system occur with the transient formation of a 1:1 tetrahedral silicon ionic complex of the silyl halide with the base. Some catalytic processes of phosphorylation of protonic substrates with tricoordinate phosphorus halides in mixture with an uncharged base show similar features to these silylation reactions, implying that a similar mechanism may operate. It was demonstrated that Ph_2PCl phosphorylates t-BuOH faster under catalysis with 4-N,N-dimethylamino pyridine or N-methylimidazole than in the presence of Et_3N by a factor of 400 and 33, respectively. The catalytic phosphorylation process exhibits a very low activation energy and a high negative value of entropy of activation. The interaction of the uncharged bases with model tricoordinate phosphorus halides was demonstrated to lead to the formation of ionic 1:1 complexes without changing the coordination number of phosphorus, in full analogy to the silyl halide complex formation. Finally, the interaction of phosphorous tris(dimethylamide) with a silyl iodide and a phosphorous iodide results in both cases in the formation of the ionic 1:1 complex, which also leads to analogous reactions of exchange of the amide group with iodide. These close similarities imply that some phosphorylation reactions with tricoordinate phosphorus halides catalyzed with uncharged bases occur via a tricoordinate phosphorus cation intermediate.

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NUCLEOPHILIC CATALYSIS IN SILYLATION

Weak uncharged organic bases, including some nitrogen heterocycles and oxyphosphoryl compounds, are known to be very effective catalysts of the substitution reactions at the phosphorus and silicon centers [1–4]. This catalysis has been extensively studied by Corriu and coworkers, who found that the nucleophile-catalyzed silylation of protic substrates with triorganochlorosilanes is first order with respect to each of the substrates and also to the base [5–7]. These catalytic reactions also show a very low activation energy and a high negative entropy of activation. In contrast to commonly accepted rules of the stereochemistry of substitution reactions, the displacement of chlorine at silicon proceeds with retention of the configuration at the silicon center. There is general agreement concerning the nucleophilic nature of this catalysis. However, two different mechanistic pathways are proposed: 1) The mechanism involves the formation of a pentacoordinate silicon molecular complex of the silicon substrate with the catalyst, which can exchange the leaving group, for example, chlorine, with the nucleophilic substrate group via a six coordinate silicon transition state or intermediate [4–6] (Equation 1).

2) A double inversion pathway initially involves the fast, reversible formation of an ionic complex of tetracoordinate silicon as a result of the reaction of the silicon substrate with the nucleophile [1, 7]. This intermediate exchanges the departing group with the nucleophilic reagent according to an S_N2 process in the rate limiting step (Equation 2). Both

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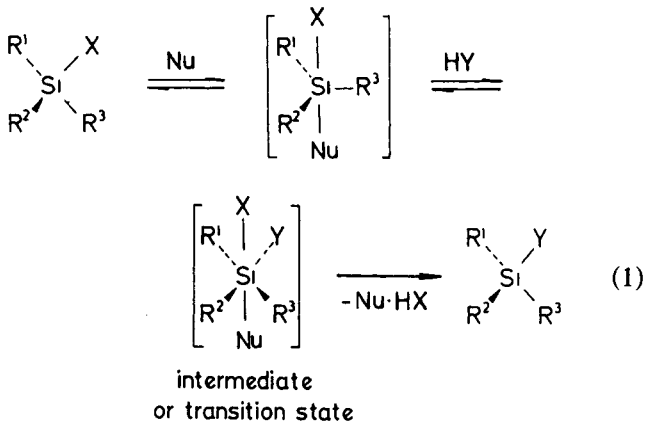
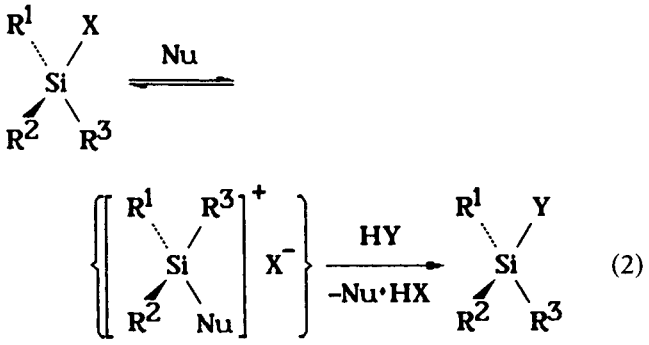


(1)

steps occur with inversion, which leads to retention of configuration at the silicon center in the overall displacement process.



(2)

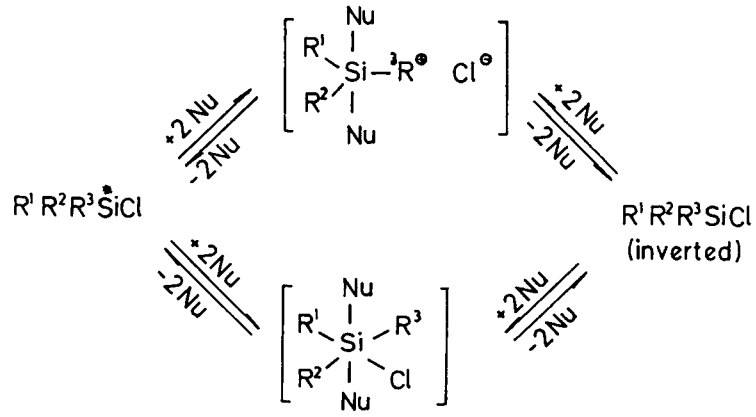
Although there are many arguments for the operation of the extracoordinate silicon mechanism for some groups of substrates, including silyl fluorides or compounds forming cyclic structures [8, 9], the double inversion pathway seems to be more common for the reactions of open chain trialkylsilyl chlorides, bromides, and iodides [3, 7, 10–12]. This mechanism does not invoke either the extracoordination of silicon or the departure from generally accepted rules of stereochemistry. It explains the activation of the silicon center in reactions with nucleophilic reagents, as silicon bears the partial negative charge and is loosely bound to the nucleophilic catalyst. Other arguments for this mechanism are as follows: 1) No 1:1 molecular extra coordinate silicon complex of the uncharged base with an open chain trialkylsilyl chloride, bromide or iodide has so far been isolated, although ionic tetrahedral silicon complexes of these species are common [3]. 2) The dynamic behavior of these ionic complexes fits well the scheme of Equation 2. In particular, the equilibrium of the complex formation is quickly established on the NMR time-scale in many cases [7, 11, 12]. The enthalpy and entropy of the complex formation usually have appreciably negative values, which explains the low activation energy and the highly negative entropy of activation values observed for the catalytic reaction [3].

Additional agruments for the tetrahedral silicon ionic intermediate arise from kinetics studies of the racemization at the silicon center of optically active silyl chlorides induced by the uncharged nucleophiles. This reaction was shown to be second order with respect to the nucleophile, and it also exhibits a very low activation enthalpy and a high negative value of activation entropy [13], which was explained by the reversible formation of an achiral intermediate complex of hexa- or penta-coordinate silicon incorporating two nucleophile molecules (Equation 3).

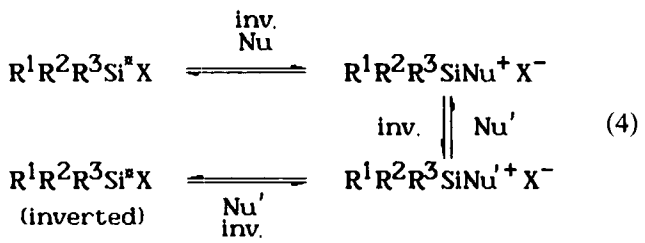
Although reversible formation of the achiral complexes must lead to racemization, all kinetic features of these reactions could also be well understood on the grounds of a pathway involving a 1:1 ionic complex of the silane with the nucleophile. The complex may exchange the nucleophilic ligand leading to racemization (Equation 4) [7].

Bassindale et al. [14] also observed a direct exchange of the anion between the ionic complex and the silyl halide; however, such a mechanism for the racemization of silyl chlorides may lead to a different kinetics law than that found [13].

In order to distinguish between pathways 3 and 4, kinetics studies were performed using (trimethylsilyl)diphenyl phosphate as the model catalyst [15]. In this case, according to Equation 2, the tetrahe-

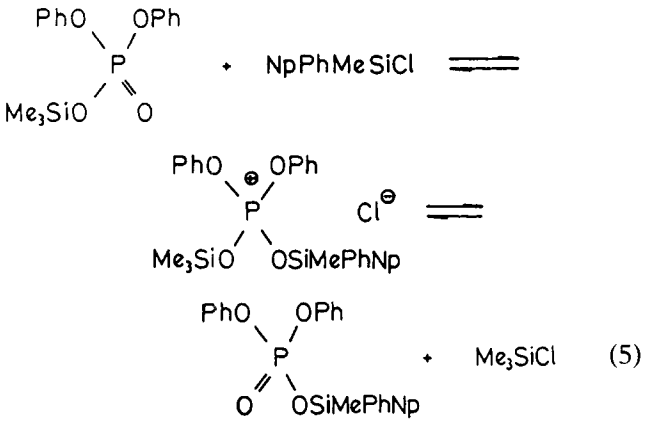


(3)



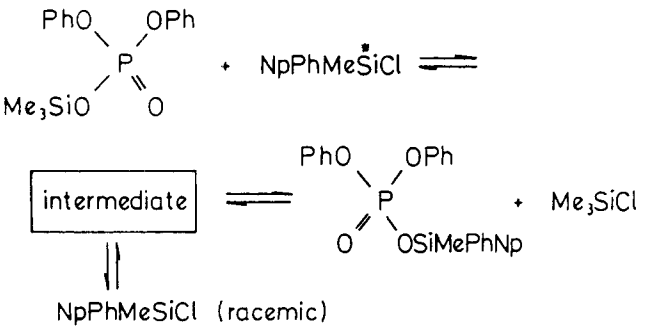
(4)

dral silicon complex has the character of a phosphonium salt in which the cation bears two silyl groups (Equation 5), which should lead to fast silyl group exchange.



(5)

Indeed, fast exchange (transesterification) has been observed as the competitive process to racemization. It was reasonable to assume that both these processes should proceed via the same intermediate according to a generalized scheme (Equation 6).



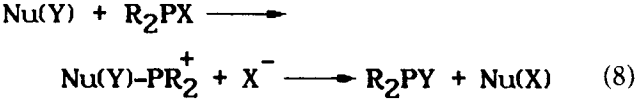
(6)

If the intermediate were one of the achiral species that appear in Equation 3, then every act of the intermediate formation would be the act of racemization. Therefore, the racemization could not proceed more slowly than the transesterification. However, it was shown that, not only is the exchange of the silyl group faster, but it also leads to the transient formation of the optically active ester [15]. Thus, this result favors the pathway of Equation 4. The transesterification reaction was also demonstrated to exhibit some similar features to the racemization process, that is, low activation enthalpy and highly negative activation entropy values were observed, which strengthens the assumption of a common intermediate for both competitive processes.

FEATURES AND MECHANISMS OF SOME REACTIONS OF P(III) HALIDES INVOLVING UNCHARGED BASES: NUCLEOPHILIC CATALYSIS IN PHOSPHORYLATION

The concept of the extracoordinate silicon intermediate pathway of the substitution at silicon catalyzed by uncharged bases has been transferred to catalytic reactions at a tetracoordinate phosphorus center [16]. Thus, the question arises whether it is possible to extend to phosphorus chemistry the double inversion pathway. Particularly interesting is the application of this concept to reactions of tricoordinate phosphorus substrates since the nucleophilic catalysis also seems to play an important role in P(III)chemistry. It is used to accelerate some processes of nucleoside phosphorylation and reactions leading to generation of the internucleotide bond [17, 18]. Thus, the mechanism considered here involves the attack of an uncharged nucleophile on a tricoordinate phosphorus center, causing the ionization of a phosphorus–halide bond (without increasing the coordination number of the phosphorus atom) and activating the phosphorus center to further reactions according to general schemes presented by Equations 7 and 8.

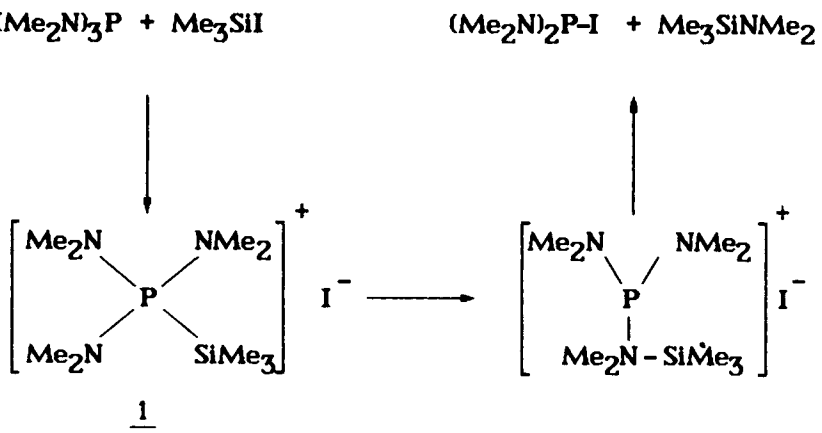
(7)



(8)

It should be mentioned that the analogous reaction to that of Equation 8 was demonstrated to occur for the silicon center as a result of its reaction with a P(III) nucleophile. Trimethylsilyl iodide was shown to react with the hexamethyltriamide of phosphorous acid in a very selective way, substituting only one dimethylamide group by iodine (Equation 9). The reaction occurs very fast at room temperature and leads to an almost theoretical yield of the bis(dimethylamide) of iodophosphorous acid [19].

The reaction involves the transient formation of the 1:1 ionic complex of the silyl iodide with the phosphorous triamide nucleophile **1**, the complex being detected in the CH_2Cl_2 solution at −50°C both by conductometric titration as well as by ^{31}P NMR



(9)

1

spectroscopy. The phosphorus resonance of the amide nucleophile in the methylene chloride solution is shifted as a result of the complex formation from δ = 120 to 64. The same ^{31}P NMR signal of the complex appears when trimethylsilyl bromide is mixed with the phosphorus triamide in CH_2Cl_2 at $-50°C$, which confirms the structure of **1**. A large additional shielding of the phosphorus on complex formation is due to the back donation of the charge from the lone electron pairs of nitrogen to phosphorus. This is a common feature of all similar complexes that will be discussed later. The ^{31}P NMR signal of the complex shows satellites due to the ^{31}P–^{29}Si spin–spin coupling, J_{P-Si} = 115 Hz. Correspondingly, the ^{29}Si NMR spectrum shows a doublet separated by 115 Hz. The intermediate **1** may react towards the displacement products by 1,2 shifts of the silyl group to nitrogen followed by the cleavage of the Si—N bond, as depicted in Equation 9.

The conductometric titration of the phosphorus triamide with Me_3SiI at ambient temperature also revealed the formation of an ionic species that is not the complex **1** or any other complex of trimethylsilyl iodide. The displacement reaction, Equation 9, occurs under these conditions so fast and in such a clean way that only the product $(Me_2N)_2PI$, unreacted substrate $(Me_2N)_3P$, and (trimethylsilyl)dimethylamine are present in the system when Me_3SiI is introduced to an excess of $(Me_2N)_3P$. The maximum of the conductance is observed when about half of the stoichiometric amount of the silyl iodide is introduced, that is, when the phosphorus substrate and the phosphorus product are in the molar ratio 1:1, which implies the formation of a 1:1 ionic complex according to Equation 10. Analogous complexes were obtained in reactions of phosphenium ions with phosphines [20].

$$(Me_2N)_3P + (Me_2N)_2PI \rightleftharpoons [(Me_2N)_3P\text{-}P(NMe_2)_2]^+ I^- \quad (10)$$

2

The structure of the complex **2** was fully confirmed by an NMR spectroscopic study. The system that should contain equimolar amounts of $(Me_2N)_3P$ and $(Me_2N)_2PI$ (0.5 equivalent of the Me_3SiI introduced) shows only two ^{31}P NMR signals, one for $(Me_2N)_3P$ and one for $(Me_2N)_2PI$, both broadened and shifted markedly to higher field (Figure 1). These observations point to the interaction between these two species. Lowering the temperature to $-30°C$ results in the further shift and further broadening. Eventually, on lowering to $-60°C$ two sharp doublets appear assigned to the complex **2**. Thermodynamic parameters of the complex formation were found to be the following: $\Delta H = -10.7$ Kcal mol^{-1}; $\Delta S = -33.8$ cal mol^{-1} deg^{-1}.

This is the type of complex corresponding to the structure of the intermediates of the generalized Equations 7 and 8, formed by the ionization of the phosphorus–iodine bond as a result of the nucleophilic attack of $(Me_2N)_3P$ at the phosphorus center. There is accordingly a full analogy to the formation of the phosphorus–silicon complex **1** of Equation 9. One might speculate that the formation of this complex could give rise to the exchange of substituents between two phosphorus atoms of the complex in analogy to the reaction of Equation 9. Since this is a degenerate exchange it cannot be directly observed. That is why another model was adopted making use of iododiphenyl phosphite in place of the iodophosphorous diamide. Low temperature ^{31}P NMR studies proved that an analogous complex to that of the iodophosphorous diamide was formed (see Figure 2). It was further demonstrated that the formation of this complex activates the phosphorus center to further reactions. At room temperature a fast and clean exchange of the amide group for iodine takes place, which could be rationalized on the ground of an analogous mechanism to that of the substituent exchange between phosphorus and silicon (see Equation 11).

This reaction fits very well to the generalized Equation 8 and is an example proving that, in some reactions, substituent exchanges between two P(III) compounds, which are very common processes, may

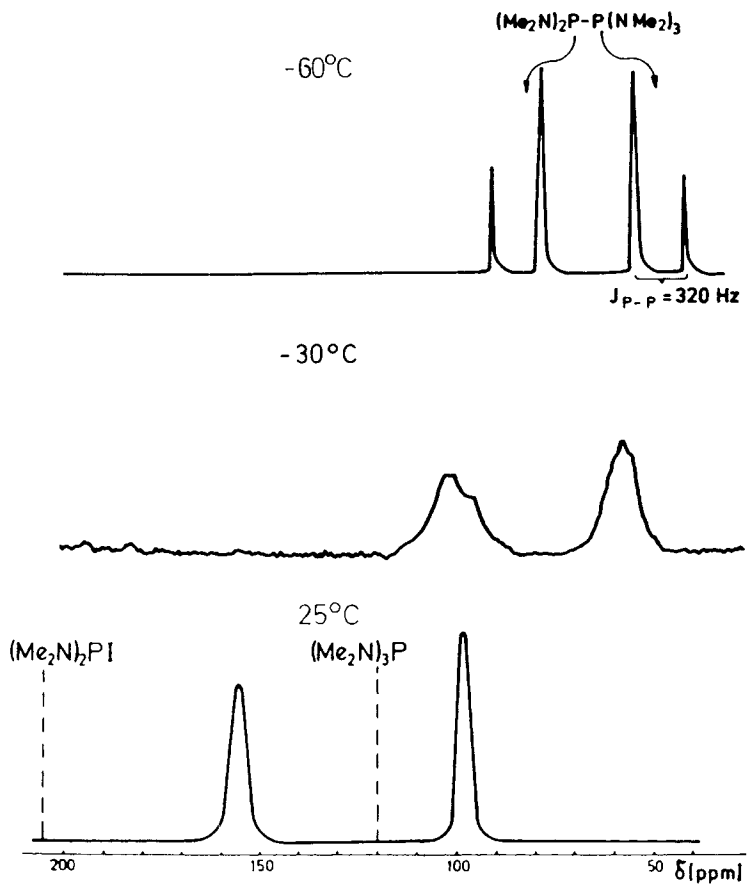


FIGURE 1 {^{1}H} ^{31}P NMR spectra of $(Me_2N)_3P$ + $(Me_2N)_2PI$ 1:1 in CH_2Cl_2 at various temperatures.

$$(Me_2N)_3P + (PhO)_2PI \longrightarrow \left[Me_2N-P(OPh)-P(OPh)-NMe_2\right]^{\oplus} I^{\ominus} \longrightarrow (Me_2N)_2PI + Me_2NP(OPh)_2 \quad (11)$$

3

proceed via a tricoordinate phosphorus ionic complex.

The question remains whether the tricoordinate phosphorus center may also be activated in this way to nucleophilic substitution reactions according to the generalized Equation 7. In order to approach this problem, the reactions of phosphorous hexamethyltriamide with some classical uncharged nucleophilic catalysts, *N*-methylimidazole (NMI) and 4-*N*,*N*-dimethylaminopyridine (DMAP), have been studied. The conductometric titration curves of iodophosphorous diamide with NMI and DMAP in methylene chloride at −30°C adopt a shape characteristic of that for the formation of a 1:1 ionic complex (see Figure 3). The equilibrium of the complex formation lies well to the side of the complex.

The results of the conductometric studies were fully confirmed by ^{31}P NMR spectroscopic studies. On mixing equimolar amounts of iodophosphorous tetramethyldiamide with NMI in methylene chloride at −60°C the signal of the phosphorus nucleus of the amide at δ 214 almost disappears, while a new signal at δ 113 arises. This signal was assigned to the ionic complex **4**. At this temperature the equilibrium is established slowly with respect to the NMR time scale. Thus, this complex, Equation 12, shows similar features to those obtained with P(III) nucleophiles.

$$(Me_2N)_2PI + MeN\langle\rangle N \rightleftharpoons \left[(Me_2N)_2P\text{-}N\langle\rangle NMe\right]^{\oplus} I^{\ominus} \quad (12)$$

4

An analogous complex is formed as a result of the reaction of iodophosphorous amide with DMAP, this complex showing at −60°C in CH_2Cl_2 the phosphorus resonance at δ = +126.

In analogy to complexes of uncharged bases with silyl halides, chlorophosphorous anhydrides also are expected to form similar 1:1 ionic complexes, although the equilibrium of their formation must lie strongly to the side of uncomplexed species. However, even small stationary concentrations of these complexes could be kinetically significant in nucleophile-catalyzed substitution at the P(III) center. Thus, complexes of halogen-anhydrides of tricoor-

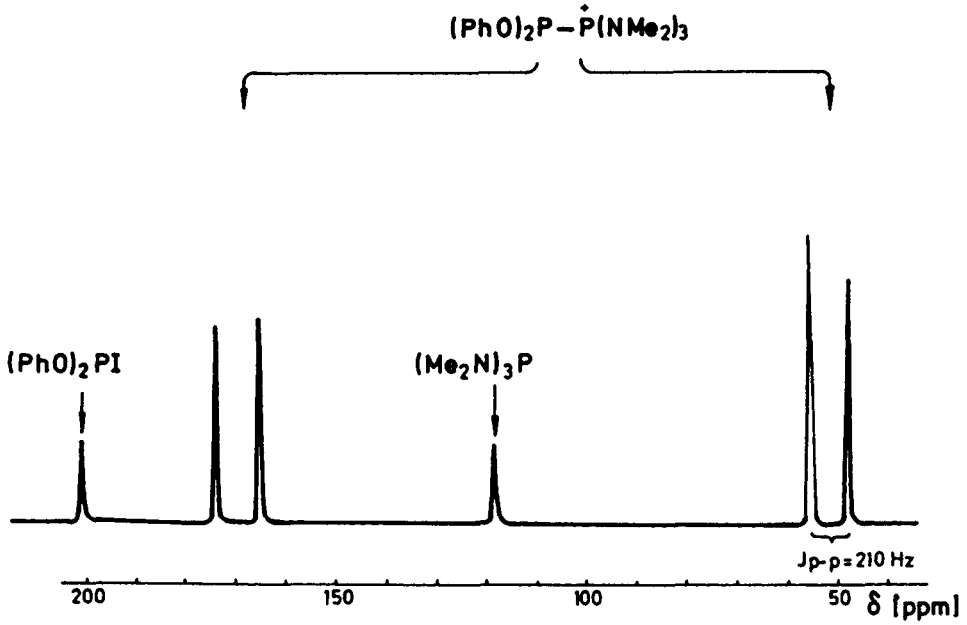
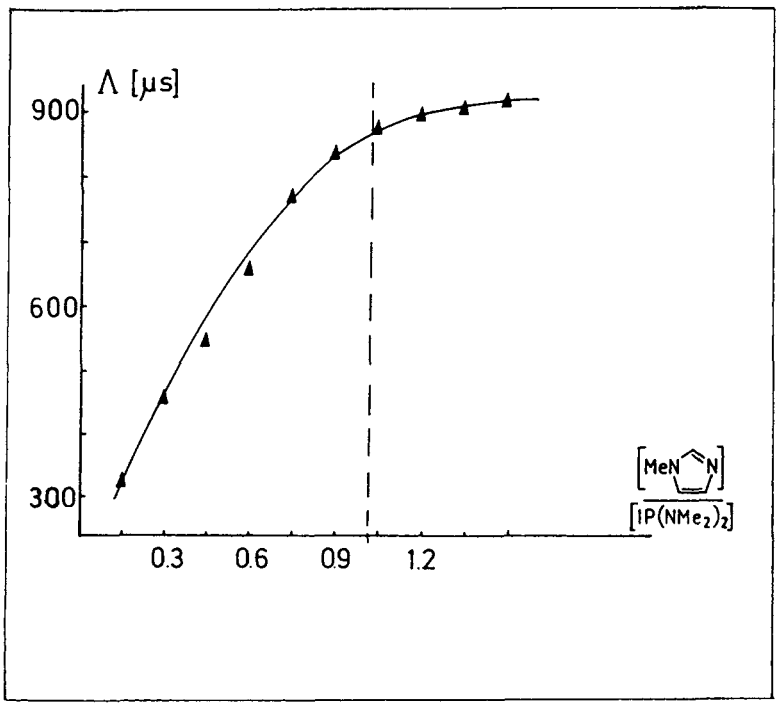


FIGURE 2 $\{^1H\}$ ^{31}P NMR spectrum of $(Me_2N)_3P$ + $(PhO)_2PI$ 1:1 in CH_2Cl_2 at −60°C.

dinate phosphorus with uncharged bases DMAP or *N*-methylimidazole may appear as intermediates in these types of processes. In order to learn about kinetic features of such reactions and to demonstrate the catalytic activity of the *N*-methylimidazole and DMAP, the kinetics of the reaction of *t*-butanol with chlorodiphenylphosphine has been studied. The reaction was carried out in CH_2Cl_2 in the presence of a stoichiometric amount of triethylamine as the HCl-acceptor. The reaction leads to substitution of the chlorine atom by the *t*-butoxy group. Triethylamine presumably also plays the role of a weak catalyst, as the *t*-butanolysis also goes smoothly without addition of NMI or DMAP. However, the presence of small amounts of these bases causes a strong catalytic effect (see Fig. 4 and Table 1). The rate of this phosphorylation reaction of a protic substrate with a phosphinous chloridate,

FIGURE 3 The conductometric titration of $(Me_2N)_2PI$ 0.2 mol dm^{-3} in CH_2Cl_2 with NMI at −30°C.



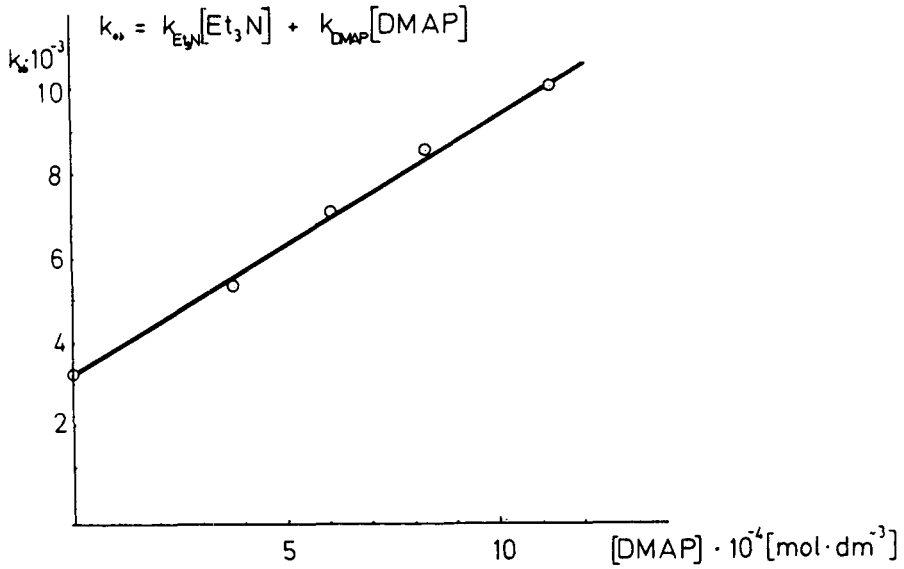
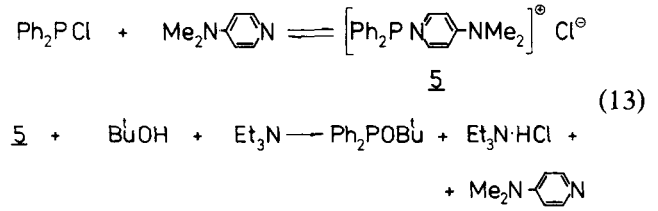


FIGURE 4 The dependence of the rate constant observed $k_{obs} = k_{Et_3N}[Et_3N] + k_{DMAP}[DMAP]$ for the reaction of *t*-BuOH and Ph_2PCl in methylene chloride at 25°C in the presence of Et_3N and DMAP on the DMAP concentration $[t\text{-BuOH}]_0 = [Ph_2PCl]_0 = [Et_3N]_0 = 0.2$ mol dm^{-3}.

promoted with various nitrogen bases, shows a similar pattern to the rate of a silylation reaction with a silyl chloride catalyzed with the same bases (Table 1), although the catalysis is more effective for the silylation process. The phosphorylation reaction catalyzed with DMAP shows a very low activation energy and a highly negative entropy of activation, which also were features of the nucleophile catalyzed substitution reactions at the silicon center [5].

Thus, it is reasonable to postulate that the catalytic phosphorylation reactions studied here involve the transient formation of a 1:1 ionic complex of tricoordinate phosphorus according to Equation 13.



(13)

Many substitution reactions of phosphorous anhydrides in the presence of uncharged bases may follow the double inversion pathway analogous to that accepted for some nucleophile-catalyzed substitution reactions at silicon.

EXPERIMENTAL SECTION

Materials

N-methylimidazole, 4-*N*,*N*-dimethylpyridine, *t*-butanol, methylene chloride, diphenylchlorophosphine, phosphorous tris-dimethylamide, and triethylamine were all reagent grade commercial products. They were purified by distillation shortly before the pertinent application. Iodophosphorous bis-dimethylamide was obtained by the reaction of phosphorous tris-dimethylamide with trimethylsilyl iodide according to the method described in [19].

NMR studies were performed with a Bruker NSL 300, or a Jeol JNM FX-60 FT spectrophotometer,

TABLE 1 Kinetic Parameters for the Nucleophile-Catalyzed Phosphorylation of *t*-BuOH with Ph_2PCl in CH_2Cl_2

Catalyst	*Catalytic Constant* mol^{-2} dm^6 deg^{-1}	*Relative Rate*	$\Delta H^{\ddagger}$ *Kcal mol*$^{-1}$	$\Delta S^{\ddagger}$ *cal mol*$^{-1}$ *deg*$^{-1}$	*Relative Rate for a Silylation Reaction*[a]
Et_3N	$1.5\ 10^{-2}$	1			1
NMI[b]	0.5	33			930
DMAP[c]	67	400	−0.3[d]	−57	3200

[a] For the reaction of (trimethylsilyloxy)isopropylmethylsilyl chloride with pentamethyldisiloxanol in methylene chloride [21].
[b] *N*-methylimidazole.
[c] 4-*N*,*N*′-dimethylaminopyridine.
[d] Assumed to be about 0.0.

taken in methylene chloride solution with a CD_2Cl_2 lock. Chemical shifts are reported relative to external 85% H_3PO_4.

Kinetics Studies

The phosphorylation reaction of *t*-butanol with diphenyl chlorophosphite in the presence of Et_3N and NMI or DMAP in CH_2Cl_2 solution at 25°C and 0°C was followed by measuring the electrolytic conductance of the reaction system with a Radelkis conductometer equipped with a special conductivity cell equipped with a stirrer. Conductometric titrations were performed using a Radelkis conductometer.

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