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Nucleophilic Displacements on Phosphorus

Reaction of Hydroxyl Ion and *Iso*nitroso Acetone with Organofluorophosphorus Compounds

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The reactions of hydroxyl ion and of *iso*nitroso acetone with three organofluorophosphorus compounds have been studied. The three compounds are dimethoxyphosphoryl fluoride, methoxyethylphosphoryl fluoride and diethylphosphoryl fluoride. The thermodynamic functions, activation energy and activation entropy have been calculated and discussed in relation to physical and chemical behaviour of substrates and nucleophilic reagents. This study together with observations made by other workers indicate that nucleophilic displacements on phosphorus depend on an intimate cooperation between the polarity and polarisability of the phosphorus compounds and the basicity and polarisability of the nucleophilic reagent.

Many organofluorophosphorus compounds are known to be highly toxic to insect and animal life [1,2]. The main reason for their toxicity is their ability to inhibit the cholinesterase enzymes. The inhibition of the enzymes by these compounds cannot be reversed by dilution or dialysis. Aldridge [3] and later Tammelin [4] have shown that the process of inhibition is due to phosphorylation of the enzyme. It has been observed that several nucleophilic reagents as hydroxylamine and some of its derivatives, in particular hydroxamic acids and oximes, react quickly with the phosphorylated enzyme and in this way restore its original activity [5,6]. Due to their ability to restore the enzyme activity, these groups of compounds have been named reactivators. In the last years it has been found that the reactivators also very quickly react with organofluorophosphorus compounds in nearly neutral water solution [7–9]. In the present work we have been interested in correlating the alkaline hydrolysis of some organofluorophosphorus compounds with the nucleophilic reaction between a reactivator and the same phosphorus compounds. The investigations have been performed by an electrometric titration method. The instrumental set up in very similar to that developed by Larsson and Hansen [10].

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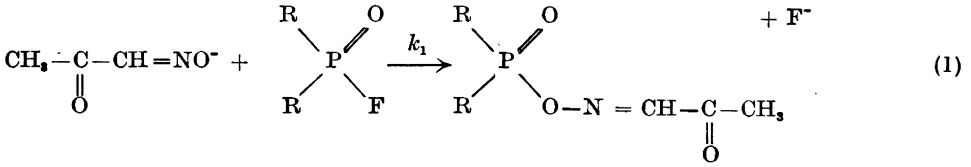
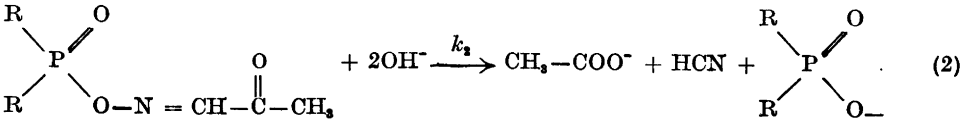
KINETICS OF THE REACTION BETWEEN ORGANOFLUOROPHOSPHATES AND *iso*NITROSO ACETONE

The kinetics of the reaction between several organofluorophosphates and different oximes were studied by Green and Saville [8]. When a great excess of oximes was used they found that the decomposition of the organofluorophosphates followed a first order law. The rate was proportional to the ionized form of the oximes. The rate was followed by titration of the total amount of acids formed. For every mole of organofluorophosphate decomposed 3 moles of acid were neutralized. They postulated a two steps reaction mechanism:



(1)



(2)

In the pH region of pH 7.5 Green and Saville [8] found that step (1) was rate determining. The total amount of acid produced as function of time obeyed a first order law. They concluded therefore that the second step in the reaction was immeasurably rapid.

The three organofluorophosphates studied in this paper were very reactive and it was found preferable to study the reaction between the oxime *iso*nitroso acetone and the organofluorophosphates in the pH-interval 6.00—6.70. In this region it was observed that the production of acid during the course of reaction did not follow a first order law. In Fig. 1 is plotted the acid production of the reaction as function of time. The curve shows an inflection in the first minutes of hydrolysis. An analysis of the experimental values showed that the rate of the second step in the above reaction was slow enough to influence on the kinetic of the decomposition reaction.

In the two-step reaction between organofluorophosphates and *iso*nitroso acetone (eqns. (1) and (2)) one mole of hydroxyl ions is consumed in the first step and two moles in the second step. The reaction is studied at so low pH that the dissociation of hydrocyanic acid is negligible. When great excess of *iso*nitroso acetone is used (*i.e.* the concentration of *iso*nitroso acetone remains approx. constant during the reaction) we get for the decomposition of organofluorophosphate:

$$-\frac{dC_N}{dt} = k_1 \cdot C_N \qquad (3)$$

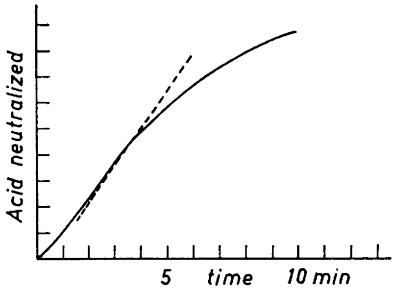


Fig. 1. Acid production in the hydrolysis of methoxyethylphosphoryl fluoride with *iso*nitroso acetone as function of time.

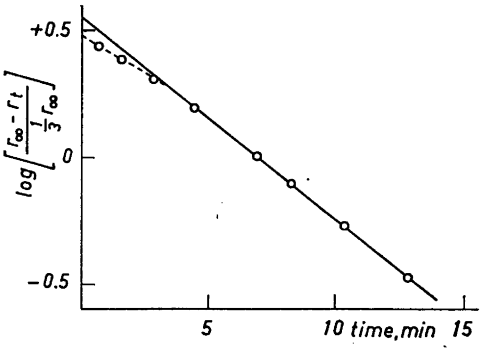


Fig. 2. Determination of the rate constant for the reaction between methoxyethylphosphoryl fluoride and *iso*nitroso acetone at pH = 6.00 according to eqn. (13).

where k_1 = pseudo first order rate constant of the first step. C_N = concentration of organofluorophosphate. The rate of formation and disappearance of the phosphorylated *iso*nitroso acetone is governed by the following equation:

$$\frac{dC_{NR}}{dt} = k_1 \cdot C_N - k_2 \cdot C_{NR} \quad (4)$$

C_{NR} = concentration of the phosphorylated *iso*nitroso acetone,
k_2 = pseudo first order rate constant of the second step.

The amount of hydroxyl ions used during the first step as function of time is:

$$C_{OH^-(1)} = C_{N_0} - C_N \quad (5)$$

where, by integration of eqn. (3)

$$C_N = C_{N_0} \cdot e^{-k_1 t} \quad (6)$$

C_{N_0} = the initial concentration of organofluorophosphate.

Integration of eqn. (4) after inserting the value of C_N from eqn. (6) gives:

$$C_{NR} = \frac{k_1 C_{N_0}}{k_2 - k_1} (e^{-k_1 t} - e^{-k_2 t}) \quad (7)$$

The material balance gives for the amount of hydroxyl ions used during the second step:

$$\tfrac{1}{2} C_{OH^-(2)} = C_{N_0} - C_N - C_{NR} \quad (8)$$

The total amount of hydroxyl ions consumed as function of time is thus:

$$C_{OH^-(total)} = C_{OH^-(1)} + C_{OH^-(2)} = 3(C_{N_0} - C_N) - 2\ C_{NR} \quad (9)$$

which by insertion of eqns. (6) and (7) gives:

$$C_{OH^-(total)} = C_{N_0}\left[3 + \frac{k_1 - k_2}{k_2 - k_1} e^{-k_1 t} + \frac{2k_1}{k_2 - k_1} e^{-k_2 t}\right] \quad (10)$$

An exact solution of k_1 and k_2 from eqn. (10) cannot be found. In this work we have used a graphical extrapolation method. The experimental values showed that $k_2 \gg k_1$, and thus, at high values of t the second exponential term of eqn. (10) goes rapidly towards

zero. Therefore, if we only use the experimental values of $C_{OH^-(total)}$ at relatively high t-values we get a good approximation for k_1 by taking only the first exponential term of eqn. (10):

$$C_{OH^-(total)} = 3\,C_{N_0} + C_{N_0} \cdot \frac{k_1 - 3\,k_2}{k_2 - k_1} \cdot e^{-k_1 t} \tag{11}$$

or in logarithmic form:

$$\log\left(\frac{3\,C_{N_0} - C_{OH^-(total)}}{C_{N_0}}\right) = -\log\left(\frac{k_1 - 3\,k_2}{k_2 - k_1}\right) - \frac{k_1 t}{2.303} \tag{12}$$

We therefore find k_1 by plotting $\log\left(\frac{3\,C_{N_0} - C_{OH^-(total)}}{C_{N_0}}\right)$

as function of t. If the method can be used we shall get a straight line with tangens $-\frac{k_1}{2.303}$. The intercept which the line cuts of the ordinate-axis is $-\log\frac{k_1 - 3\,k_2}{k_2 - k_1}$. Inserting k_1 in the latter equation gives k_2. The automatic recording instrument which is connected with the titrator, plots the number of turns of the micrometer screw as measure of concentration. Eqn. (12) is then transformed to:

$$\log\frac{r_\infty - r_t}{1/3\,r_\infty} = -\log\frac{k_1 - 3\,k_2}{k_2 - k_1} - \frac{k_1}{2.303} \cdot t \tag{13}$$

where r_∞ = number of turns of the micrometer screw when all the organofluorophosphate is transformed to end products (3 moles OH^- are consumed per mole organofluorophosphate). r_t = number of turns at the time t.

Fig. 2 shows the plot of the experimental values for the reaction between methoxyethylphosphoryl fluoride and *iso*nitroso acetone according to eqn. (13).

The second order rate constants, k_{R^-} recorded in Table 1 are found from the formula:

$$k_{R^-} = \frac{k_1}{C_{A^-}} \tag{14}$$

where C_{A^-} is the concentration of the anion of the *iso*nitroso acetone at the pH used. C_{A^-} is calculated from the following equation:

$$C_{A^-} = a_0 \frac{\text{antilog}\,(\text{pH} - \text{p}K - \log\gamma)}{1 + \text{antilog}\,(\text{pH} - \text{p}K - \log\gamma)} \tag{15}$$

where a_0 is the total concentration of *iso*nitroso acetone and γ is the activity coefficient of the hydrogen ions.

The rate constants of the reaction with hydroxyl ion were calculated according to the following equation [11]:

$$k_1 = k_{OH^-} \cdot C_{OH^-} = k_{OH^-} \cdot \frac{a_{OH^-}}{f_{OH^-}} \tag{16}$$

k_1 is the first order rate constant at a fixed pH determined by the extrapolation method of Guggenheim [12]. k_{OH^-} is the second order rate constant for the reaction with hydroxyl ion. a_{OH^-} and f_{OH^-} are the activity and activity coefficients, respectively, of the hydroxyl ions.

Values of the Arrhenius activation energy E_A were obtained in the usual fashion from the gradients of plots of $\log k$ *vs.* $\frac{1}{T}$.

The entropy of activation was calculated according to the formulae of Eyring [13] for reaction in solution:

$$k_r = e \cdot \frac{k\,T}{h} \cdot e^{-E_A/RT} \cdot e^{\Delta S^{\neq}/R} \tag{17}$$

EXPERIMENTAL

Materials. Dimethoxyphosphoryl fluoride, methoxyethylphosphoryl fluoride and diethylphosphoryl fluoride were synthesized in this institute [14]. The compounds were redistilled immediately before use and their equivalent weights were determined by hydrolysis of the compounds with excess of 0.1 N $Ba(OH)_2$ followed by back-titration with 0.1 N HCl.

Dimethoxyphosphoryl fluoride, b.p. 54°/20, equiv. wt, found: 63.9, calc. 64.0. Methoxyethylphosphoryl fluoride, b.p. 58°/20, equiv. wt, found 63.3, calc. 63.0. Diethylphosphoryl fluoride, b.p. 72°/9, equiv. wt, found 61.7, calc. 62.0. *Iso*nitroso acetone was synthesized according to description in the literature [15].

Kinetic measurements. The rates of the hydrolysis were studied by means of an automatic recording titrator. The instrument used was a Radiometer Titrator, type TTTI. The principle of the instrumental set up is that the acid products formed during the hydrolysis of the organofluorophosphates are neutralized by automatic addition of alkali at such a rate that the pH of the reaction solution is maintained constant. The alkali is delivered from a 5 ml syrette driven by a micrometer screw connected with a motor. The motor is started and stopped automatically by the titrator when the pH of the solution drifts below or above the required value. A Radiometer glass electrode, type G 202 A was employed and a saturated calomel electrode type K 300 was used as reference electrode. The fluctuation during the reaction was approximately ± 0.02 pH-units. A constant temperature circulating water bath maintained the jacketed reaction vessel at ± 0.05°C. The capacity of the reaction vessel was 50 ml. An automatic recording device connected with the micrometer screw records the number of turns of the micrometer screw as function of time. The number of turns are used as relative measure of the amount of alkali added. The pH-meter in the titrator was standardized against a known buffer before each run. The procedure for the titration was the following:

The phosphorus compound was immediately before use weighed out and diluted with 50 ml 0.1 N KCl to a concentration of approximately 2×10^{-4} M. When the reaction with hydroxyl ion was studied, the titrator was standardized against a known buffer, the instrument set at the required pH and the automatic titration started. This reaction was studied in the pH-range 7.70—9.00. When the rate of the reaction between *iso*nitroso acetone and the organofluorophosphate was determined the 0.1 N potassium chloride solution contained a hundred fold excess of *iso*nitroso acetone. The drop in concentration of *iso*nitroso acetone during the reaction could therefore be neglected. The reaction was studied in the pH-range 6.00—6.70. The concentration of sodium hydroxide added from the syrette was 0.05 N. The slight dilution of the reaction solution during the hydrolysis due to the added alkali was neglected in the calculation of the rate constants.

The second order rate constants k_{OH^-} and k_{R^-} were calculate according to eqns. (13), (14) and (16). The pK values of *iso*nitroso acetone were determined by potentiometric titration and found to be 8.30 and 8.15 at 25°C and 35°C, respectively. The activity coefficients of hydrogen ions in 0.1 N KCl are 0.782 and 0.778 at 25°C and 35°C [16]. The activity coefficients of the hydroxyl ions in 0.1 N KCl (0.776 and 0.762) at 25°C and 35°C were taken from the paper of Larsson [11]. In Table 1 are recorded the data from the present study. The estimated errors in the rate constants are approximately ± 3 %. This corresponds to the accuracy of the rate constants found by Larsson and Hansen [10], determined by a similar instrumental set up.

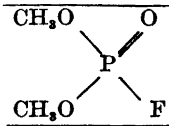
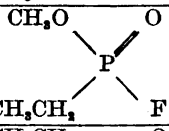
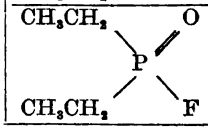
DISCUSSION

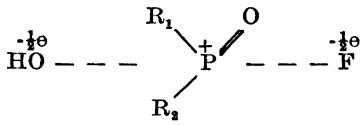
The reactions between organic chloro- or fluorophosphorus compounds and nucleophilic reagents are generally believed to belong to A-2 mechanisms [11,18]. From theoretical reasons one must assume that during formation of the transition state the collision complex adapts a bipyramidal (sp^3d hybridised) transition state with the reacting groups and the phosphorus atom collinear:

Table 1. Rate constants and thermodynamic functions for nucleophilic reactions of dimethoxy-, methoxyethyl- and diethylphosphoryl fluoride.

Compound	Reaction with hydroxyl ion			
	k_{OH}- l mole^{-1} sec^{-1}		Activation energy kcal/mole	Activation entropy E.U.
	25.1°C	35.1°C		
Dimethoxy phosphoryl fluoride	18.2	34.3	11.6	−16
Methoxyethyl phosphoryl fluoride	49.1	85.3	10.1	−19
Diethyl phosphoryl fluoride	726	1140	8.3	−20
	Reaction with anion of *iso*nitrosoacetone			
	k_R- l mole^{-1} sec^{-1}		Activation energy kcal/mole	Activation entropy E.U.
	25.1°C	35.1°C		
Dimethoxy phosphoryl fluoride	4.01	8.82	14.3	−10
Methoxyethyl phosphoryl fluoride	4.58	9.32	12.9	−14
Diethyl phosphoryl fluoride	3.40	6.35	11.5	−20

Table 2. Stretching frequencies of the P=O and P−F bands of phosphorus compounds and their association constants with phenol in CCl_4[14].

Compound	Stretching frequencies cm^{-1}		Association constants 20°C
	P=O	P−F	
	1 308	864	26.3
	1 295	858	82.5
	1 278	845	129.9



(I)

Displacement reactions of optically active phosphorus compounds give strong evidence for this interpretation [19]. The activation energy necessary to form the transition complex according to (I) should be expected to decrease with increasing residual positive charge on the phosphorus atom. This increase will render the P-atom more susceptible to attack from the nucleophile. The activation energy for the nucleophilic reaction between hydroxyl ion or the anion of *iso*nitroso acetone with the three different fluorophosphorus compounds studied in this paper (Table 1), decreases successively when methoxy groups are replaced by alkyl substituents. This observation is attributed to the mesomeric effect ($+M$) of alkoxy groups. Such an effect will reduce the positive charge on the phosphorus atom and in this way counteract the attack from nucleophilic agents. The observed results are in accordance with the general electronic picture of the phosphorus compounds discussed in the previous paper [14]. In Table 2 are recorded the stretching frequencies of the P=O and P—F bonds of the three fluorophosphorus compounds studied. In the same table are also included the association constants of the dimeric hydrogen bond complexes between phenol and the same compounds in carbon tetrachloride. The increase of the polarity of the P=O and P—F bonds from the dimethoxyphosphoryl fluoride to diethylphosphoryl fluoride is consistent with the above conclusions. The same conclusion can also be drawn from the activation energy of the reaction with hydroxyl ion of the three last phosphorus compounds recorded in Table 3.

Table 3. Thermodynamic function of nucleophilic substitutions on phosphorus.

Substrate	Reagent	Activation energy kcal/mole	Activation entropy E.U.
Diethoxyphosphoryl *p*-nitrophenoxyde ○	OH^-	7.4	−45
	OOH^-	8.3	−33
Methyl *iso*propoxy phosphoryl fluoride	OH^- □	9.1	−24
	OOH^- □	7.7 ± 1.6	−20 ± 5
	OCl^- ■	11.4	−18
Trimethyl phosphate ●	OH^-	16.3	−32
Dimethyl ethylphosphonate ●	OH^-	14.0	−34
Methyl diethylphosphonate ●	OH^-	10.6	−40

● Values calculated from the paper of Hudson and Harper [18].
○ Values calculated from the paper of Epstein, Demek and Rosenblatt [24].
□ Values taken from the papers of Larsson [11,25].
■ Values calculated from the papers of Epstein *et al.*[26].

It has been observed that the reactions between organophosphorus compounds and substituted hydroxamic acids obey a linear relation between the logarithms of the rate constants and the logarithms of the dissociation constants of the corresponding hydroxamic acids [9,17]:

$$\log k = \log G + \beta(\mathrm{p}K\text{—}14) \qquad (16)$$

where G and β are constants. The proportionality factor β decreases when alkyl groups in the phosphorus compounds are substituted with alkoxy groups[9]. The importance of the basicity of the nucleophilic reagent in substitution reactions with the phosphorus compounds must therefore decrease from the alkyl to the alkoxy substituted compounds. According to Hammet [20] we must assume that the thermodynamic reason for the above mentioned linear relationship is that the entropy of reaction remains approximately constant for the reactions between the particular phosphorus compound and the different hydroxamic acids. This assumption is based on the similarity between the above linear relation and the expression of the rate constant according to the transition state theory (eqn. (17)) [20]. It seems therefore reasonable to assume that the importance of the basicity of the nucleophilic reagent in substitution reactions with phosphorus compounds should be reflected largely in the activation energy term. We arrive also to the conclusion that the activation energies of nucleophilic reactions with alkoxy substituted phosphorus compounds as compared with alkyl substituted compounds, should be less susceptible to changes of the basicity of the attacking reagents. The last assumption is supported by the activation energy data in Table 1.

The general tendency of the calculated entropy of activation for the nucleophilic displacement on phosphorus is to oppose the effect of the activation energy (Tables 1 and 3). A favourable activation energy is compensated by an unfavourable activation entropy and *vice versa*. We assume that this effect is connected with the differences in the polarisability of the reacting molecules. In a previous paper [14] where the hydrogen bond formation between phenol and organophosphorus compounds was studied, a similar compensating action between the enthalpy and entropy of the equilibrium reaction was observed. It was postulated that the polarity of the hydrogen bond successively increased with increasing strength of the hydrogen bond. Due to the polarity or the polarisability of the solvent molecules an increase in the polarity of the hydrogen bond will contribute to a stronger orientation of solvent molecules and a corresponding decrease in entropy. At the beginning of this discussion was mentioned that there is strong evidence for the view that the nucleophilic reaction of fluorophosphorus compounds belong to an A-2 mechanism. It appears to be well established that bimolecular reactions of type A-2 are always accompanied by a large negative activation entropy due to the partial valence bonds which are formed in the transition state [21,22]. A considerable part of the reaction entropy is attributed to the difference in the orientation of solvent molecules in the transition state and the reacting molecules [21,22]. If the electronic effects in the reacting molecules are of such character that they are able to decrease the charge concentration in the transition state we should expect an increase in the activation entropy. During the formation

Table 4. The rate constants for the reaction between tetraethylpyrophosphate and different anions.

Anion	k_R l mole^{-1} min^{-1} ●	pK of corresponding acids
OH^-	21	14
$AcC(CH_3) = NO^-$	16	9.3
$(Ac)_2C=NO^-$	35	7.4
$AcCH=NO^-$	59	8.3
$BzNHO^-$	160	8.8
OOH^-	2 180	11.8
ONO^-	high	—
$S_2O_3^{--}$	unmeasurably small	—

● Values taken from the work of Green *et al.*[9]

of the transition state in the reactions between the nucleophiles and the phosphorus compounds recorded in Table 1, the electronic effect of the methoxy groups will be expected to contribute to a delocalization of the charge in the collision complex. We therefore attribute the observed favourable entropies of the reactions of the methoxy substituted compounds to this delocalization effect which correspondingly will decrease the solvent constriction in the transition state.

The strong influence of substituents in phosphorus compounds upon delocalization of the charge in nucleophilic substitution may be attributed to the fact that the available *d*-orbitals of phosphorus are involved in π-bonding and that these orbitals during the formation of the transition state also can enter the σ-bond structure of the activated complex. The character of the partial valence bonds of the activated complex will thus approach the character of true chemical bonds rather than a special orientation of reacting molecules with correspondingly great charge separation.

From Table 1 it is observed that the reactions of *iso*nitroso acetone with the phosphorus compounds proceed with much higher entropies of reaction than the corresponding reactions of the hydroxyl ion. We suggest that in this case the transition state has the possibility to delocalize the charge due to the partial valence bonds by mutual electromeric cooperation between the phosphorus compound and the attacking reagent.

A favourable entropy of reaction seems to be a common feature for all the reagents of low basicity which show abnormally high rate of reaction with the organophosphorus compounds, the reactivators included. In Table 4 are collected some results from the literature [11,23–26]. It is observed that all of the reactive nucleophiles are strongly polarisable molecules. It seems therefore possible that the explanation put forward for the *iso*nitroso acetone will apply to all of the different nucleophilic reagents studied.

Studies of nucleophiles with very high reactivity with phosphorus compounds reveal that it is an oxygen atom in the reagents which participates in

the displacement reaction (Table 4)[9]. The preference of the oxygen atom to participate in the displacement reaction with phosphorus compounds is most likely due to its high negativity and its small size. These qualities will make the oxygen atom favourable for π-bond formation with the *d*-orbitals of phosphorus. Linear polarisable groups as HOO^-, ClO^-, $O=N-O^-$, $-NHO^-$, $-C=N-O^-$ appear to be a common feature of the highly reactive nucleophiles (Table 4). Substitution in the atom adjacent to the reacting oxygen atom with greater groups than hydrogen (*e.g.* methyl) always reduce the reactivity of the nucleophiles with the phosphorus compounds. It seems reasonable to attribute this effect to steric retardation.

Nucleophilic reactions with the phosphorus compounds seems to be strongly dependent on two main factors of the nucleophilic reagent: its basicity and its polarisability[9,27,28]. The above mentioned observations indicate that the basicity effect is chiefly reflected in the activation energy term and the polarisability effect especially in the entropy term. Nucleophilic displacements on phosphorus depend also on the polarity and the polarisability of the phosphorus compounds[9]. The basicity effect of the nucleophilic reagent is most pronounced in reactions with phosphorus compounds of the highest polarity, and the polarisability effect of the reagent is most effective in reactions with the strongest polarisable substrate.

The kinetic studies in this paper together with the previous hydrogen bond studies of phosphorus compounds[14] point to the conclusion that the significance of the mutual polarisability of reactants is much greater in the reactions of phosphorus compounds than in the reactions of carbon compounds. It seems possible that just this property of phosphorus may play an important role in the wide-spread transphosphorylation processes which occur in all living tissues. A kinetic study of the biochemical reaction between cholinesterase and the three organofluorophosphorus compounds which have been studied in this paper (Table 1) has shown that the relative rates of reaction between cholinesterase and the phosphorus compounds correspond to the relative rates between *iso*nitroso acetone and the same phosphorus compounds. In both cases methoxyethylphosphoryl fluoride was found to react most rapidly with cholinesterase resp. *iso*nitroso acetone. This observation points to the conclusion that the rate determining factors in the phosphorylation of cholinesterase and *iso*nitroso acetone appear to be governed by the same fundamental properties of the reactants. In our opinion the relationship in reaction properties of cholinesterase and *iso*nitroso acetone gives reasonable explanation of the effectiveness of the reactivators to regenerate phosphorylated cholinesterase.

The kinetic study of the phosphorylation of cholinesterase will be published elsewhere.

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