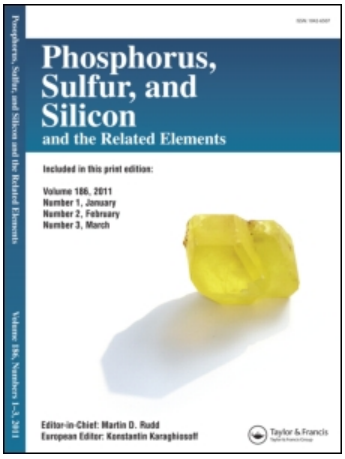

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New Aspects of the Staudinger React

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NEW ASPECTS OF THE STAUDINGER REACTION

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Abstract The unique inductive control of the first step of the Staudinger reaction is used for determination of the inductive characteristics of various radicals.The data are used for elaboration of a new direction in a purposeful synthesis of phosphorus pesticides which are more safe for people and surroundings.

The rate constants of the initial association of the reagents (Scheme 1) k_1 are independent of mesomeric or steric interaction of the substituents at phosphorus and are defined completely by the inductive influence on P(III) atom[1].

$$R^1R^2R^3P + PhN_3 \xrightarrow{k_1} R^1R^2R^3PN_3Ph \xrightarrow[-N_2]{k_2} R^1R^2R^3P{=}NPh \quad (1)$$

Although the size and the ability of R to conjugate with P(III) reactive site vary in the series, the log k_1 values are linearly related only to the $\Sigma\sigma_I$ of the substituents[2]:

$$\log k_1 = 2.274 - 5.65\,\Sigma\sigma_I \quad r = 0.996\,,\ s = 0.08 \quad (2)$$

The unique inductive control of the first step of the Staudinger reaction is used for determination of the inductive characteristics of radicals X according to eq.(3) derived from the Hammett correlation eq.(2).

$$\Sigma \sigma_I \pm 0.01 = 0.405 - 0.176 \log k_1 \qquad (3)$$

The radical X is introduced into the model compound $(EtO)_2P\text{-}X$ and the imination (PhN_3) rate constant k_1 is determined. In[3] typical examples are presented.The data on the inductive characteristics of the radicals are used for elaboration of a new direction in a purposeful synthesis of phosphorus pesticides.

EXAMPLE

The introduction of C=C bond into the α-position of the alkoxy group leads to substantial increase of its electron-withdrawing potency. The subsequent variations in vinyloxy moiety are not accompanied by any change in its electron-withdrawing potency.[3] At the same time vinyl phosphates differ in anticholinesterase activity which is dependent on the substituents in the leaving group. Thus the reason of this biochemical effect must be sought not in the phosphorylating potency of a P-inhibitor (due to the electrophilicity of P-atom) but in the stereoelectronic interaction of the inhibitor molecule with the enzyme active site on the stage of the active complex formation. This is confirmed experimentally (cf.[4]). Kinetic analysis of acetylcholinesterase (AChE) inhibition by a series of biologically active phosphates is perfor-

med according to scheme (4).

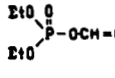
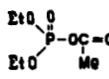
$$E + I\text{-}X \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} (E \cdot I\text{-}X) \xrightarrow{k_p} E\text{-}I + X^- \quad (4)$$

E - enzyme, I-X - inhibitor, $K_D = k_{-1}/k_1$ - dissociation constant of enzyme-inhibitor complex, k_p - phosphorylation rate constant, $k_i = k_p/K_D$ - effective bimolecular rate constant.

The kinetic experiments are carried out by the known method in vitro[4,5]. Table 1 illustrates the kinetics of inhibition of human AChE by vinyl phosphates.

Table 1

∝-Effect in Inhibition of Human Erythrocyte AChE by Vinyl Phosphates

Inhibitor	$K_D \cdot 10^6$, M	k_p, min^{-1}	$k_i \cdot 10^{-5}$, $M^{-1}min^{-1}$	LC_{50}, % housefly	LD_{50}, mg/kg white mice
	4.5	0.94	1.63	0.0012	6.4
	670.0	0.90	0.01	0.0075	435
∝-Effect	150	0.95	160	6.2	68

Introduction of the ∝-methyl substituent leads to a 160-fold decrease in inhibitory potency. The main reason for this is a considerable decrease in affinity (as reflected in increase of K_D values) brought about by steric crowding at phosphorus. The analogous effects are observed for other P-pesticides[6]. This conception based on the dominant factor - affinity of inhibitor and enzyme - opens wide prospects in search for active P-pesticides beyond the framework of the Schrader's

formula with a single leaving group.We believe it's possible to obtain effective P-pesticides with two or three leaving groups. The data in Table 2 demonstrate one of the examples of realization of this idea. Compounds 2 and 3 are effective insecticides being low toxic to mice.

Table 2

Inhibition of Human Erythrocyte AChE by Mono-, Bis- and Trisvinyl Phosphates and Some Toxicological Data

Inhibitor	$K_D \cdot 10^5$ M	k_p, min^{-1}	$k_i \cdot 10^{-4}$ $M^{-1}min^{-1}$	LD_{50}, mg/kg, white mice	LC_{50} % grain aphides
$Cl_2C{=}CHO{-}P(O)(OEt)(OEt)$	0.45	0.74	16.3	6.4	0.016
$Cl_2C{=}CHO{-}P(O)(OC(Me){=}CHCl)(OEt)$	3.3	0.83	3.7	320	0.003
$Cl_2C{=}CHO{-}P(O)(OC(Me){=}CHCl)(OC(Me){=}CHCl)$	1.8	0.40	2.1	580	0.008

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