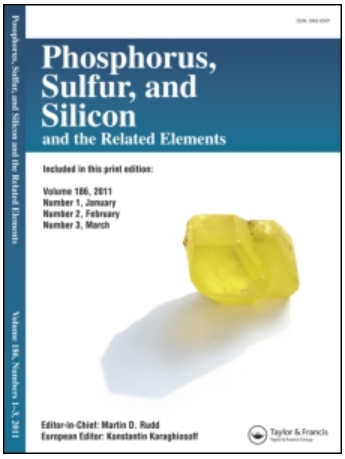

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QSAR in Reactions of Organophosphorus Inhibitors with Acetylcholinesterase

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QSAR IN REACTIONS OF ORGANOPHOSPHORUS INHIBITORS WITH ACETYLCHOLINESTERASE

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Abstract Structure-activity relationships in inhibition of acetylcholinesterase by organophosphorus compounds (YO)(Z)P(O)SX have been analyzed using the equation $\log k_i = C + \rho\sigma + \varphi\Pi$ with Taft σ^* for substituent electronegativity and Hansch Π for hydrophobicity. The obtained relationships have been used for optimizing the structures of organophosphorus inhibitors for their maximum anticholinesterase activity.

The highly specific reaction of organophosphorus inhibitors (YO)(Z)P(O)SX with the serine hydroxyl group in the active site of acetylcholinesterase is a good example of an enzyme affinity labelling by low-molecular compounds. In this communication we show how the information from the analysis of quantitative structure-activity relationships (QSAR) in terms of Hammet-Taft equations can be used to predict the inhibitors of maximum anticholinesterase activity.

The correlations have been analyzed in accordance with the equation

$$\log k_i = C + \rho^*\sigma^* + \varphi\Pi, \qquad (1)$$

where σ^* is the Taft constant for substituent electronegativity and Π is the Hansch constant for its hydrophobicity, k_i is the second-order rate constant of the enzyme active site phosphorylation. The most remarkable feature in the reactions of acetylcholinesterase with the inhibitors (YO)(Z)P(O)SX is an extremely high sensitivity of k_i to the electron-accepting substituents in the leaving group -SX. It has been shown that the dependence of $\log k_i$ upon σ^* in the reaction of cobra venom acetylcholinesterase with $(C_2H_5O)_2P(O)SX$ has a ρ^*-value as high as 4 compared with 2 for alkaline hydrolysis of these compounds.[1] For the

reaction of $(C_2H_5O)(CH_3)P(O)SX$ with bovine erythrocyte acetylcholinesterase (data from ref.2), $\rho^* = 4.3$.

There are no systematic studies for the estimation of σ^* for the influence of the phosphoryl part of the inhibitors on their anticholinesterase activity but it appears to be about 2, as in alkaline hydrolysis. This conclusion comes from the comparison of k_i for the inhibitors $[CH_3O(CH_2)_nO](CH_3)P(O)SC_4H_9$-*n* with n=2-5 in the reaction with erythrocyte acetylcholinesterase[3].

In contrast, by the influence of substituents' hydrophobicity, the phosphoryl part of the inhibitors surpasses the leaving group about twofold. In designing active inhibitors one must, however, consider different "length tolerances" of the binding areas for the phosphoryl part and the leaving group of the inhibitors in the active site of acetylcholinesterase.[4] In Figure 1 the dependence of log k_i^R upon Π_R for the reaction of $(RO)(CH_3)P(O)SC_4H_9$ with erythrocyte acetylcholinesterase is shown. The relationship splits into two straight lines with a point of intersection at $\Pi = 2$ (n-butyl radical with n=4 in $R=-C_nH_{2n+1}$). For the breaking point the length of the substituent but not its hydrophobicity is critical as the log k_i for the compounds with branched substituents, which have the Π-values considerably greater than 2 but are not longer than n-butyl, fall on the initial straight line. Thus the substituents in the phosphoryl part of good inhibitors may be bulky their length should not exceed that of n-butyl radical. For the leaving group the length of a substituent is not so critical - in $(C_2H_5O)(CH_3)P(O)SC_nH_{2n+1}$ the straight line in the plot of log k_i versus Π holds up to n=7, which enables considerable contribution into the hydrophobic term in equation (1) to

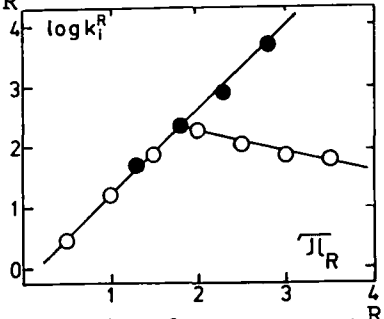

FIGURE 1. Plot of log k_i^R against Π_R for acetylcholinesterase phosphorylation by $(RO)(CH_3)P(O)SC_4H_9$, $R = C_nH_{2n+1}$. o, normal, and ●, branched, hydrocarbon radicals.

be originated from the leaving group.

It is interesting that in acetylcholinesterase reactions the presence of positive charge in a substituent does not interfere with its hydrophobic interaction with the enzyme active site. The influence of X = $-(CH_2)_nS^+(CH_3)C_2H_5$ with n=2-6 on the reactivity of $(C_2H_5O)_2P(O)SX$ against acetylcholinesterase in terms of log k_i - $\rho^*\sigma^*$ from equation (1) can be described by $|\pi|$ without counting the effect of the substituent positive charge in conventional π-constants[5]. This has been explained by a compensating effect[5] of a special anionic point in the enzyme active site. Recent results from our laboratory, however, suggest that the basis for such "charge tolerance" may be overall negative charge density on the surface of the enzyme (as a globular polyelectrolyte) molecule.[6,7]

Considering these peculiarities of the interaction of acetylcholinesterases with their organophosphorus inhibitors, and based on QSAR in the reaction of $(C_2H_5O)(CH_3)P(O)SX$ with erythrocyte acetylcholinesterase[2] for which equation (1) can be written as $\log k_i^X = 1.45 + 4.3\sigma_X^* + 0.8\pi_X$, we suggest a new series of highly active inhibitors for acetylcholinesterases: $[(CH_3)_nA^+-(CH_2)_2O](CH_3)P(O)SX$, where X is chosen on the principle of giving maximal value of $\rho^*\sigma^* + \varphi\pi$ within the limits of the "length tolerance" in the inhibitor leaving group binding area on the enzyme active surface; A^+ is an onium atom ($\geqslant N^+$ - or $\geq S^+$- with n=3 or 2, respectively) which, supposedly[4], interacts with the substrate leaving group binding area in the active site of the enzyme. The proposed series is in principle different from "phosphocholine" inhibitors described by Tammelin[8] as the choline-like onium group here is located in the non-leaving phosphoryl part of the inhibitor which enables better use of both the leaving group "hydrophobic potential" and the specific interaction of $(CH_3)_nA^+-(CH_2)_2O-$ with the enzyme active site.

TABLE I Rate constants for the reaction of acetylcholinesterase with $[(CH_3)_3\overset{+}{N}CH_2CH_2O](CH_3)P(O)SX$ calculated in accordance with equation (1)

X	σ*	Π	$\rho^*\sigma^*+\varphi\Pi$ [a]	$k_i \cdot 10^{-9}$, $M^{-1}s^{-1}$
$-C\equiv C-C_6H_{11}$-cyclo	1.3	2.99	6.9	191
$-CH_2-CN$	1.75	-0.34	6.8	35.6
$-CH_2-Br$	1.4	1.1	6.2	15.9

[a] ρ* and φ from equation (1) for $(C_2H_5O)(CH_3)P(O)SX$ (see text); Δ log k_i = 3.63 for going from $-OC_2H_5$ to $-OCH_2CH_2\overset{+}{N}(CH_3)_3$, using ρ*=2 and φ=1.5; for $-(CH_2)_2\overset{+}{N}(CH_3)_3$, σ*=0.76 and $|\Pi|$=2.5.

In Table I the procedure of the activity-calculations by equation (1) is illustrated. As can be seen from the table, the calculated k_i-values for the active members of the proposed series of inhibitors exceed the rate constant of the diffusion-controlled second-order reactions[9] - $10^9 M^{-1}s^{-1}$. Therefore the expected second-order rate constants for the inhibitors in Table I should have the same values for all three compounds expressing the diffusion limit in acetylcholinesterase interaction with low-molecular affinity ligands.

REFERENCES

1. J.L.Järv, A.A.Aaviksaar, N.N.Godovikov, and D.I Lobanov, Bioorganic Chemistry (USSR), 2, 978 (1976).
2. M.I.Kabachnik, A.P.Brestkin, N.N.Godovikov, M.J.Michelson, E.V.Rozengart, and V.I.Rozengart, Pharmacol. Rev., 22, 355 (1970).
3. A.A.Abduvakhabov, Dr. Sci. Dissertation, Moscow, 1979.
4. J.Järv, A.Aaviksaar, N.Godovikov, and D.Lobanov, Biochem. J., 167, 823 (1977).
5. J.L.Järv, A.A.Aaviksaar, N.N.Godovikov, and D.I.Lobanov, Bioorganic Chemistry (USSR), 3, 268 (1977).
6. V.Tõugu, A.Pedak, T.Kesvatera, and A.Aaviksaar, FEBS Letters, 225, 77 (1987).
7. T.Kesvatera, J.Järv, and A.Aaviksaar, Phosphorus, Sulfur and Silicon, PSS 51/52, 878 (1990).
8. L.-E.Tammelin, Kem. tidskr., 70, 158 (1958).
9. A.Fersht, Enzyme Structure and Mechanism (W.H.Freeman and Company, New York, 1985), p. 148.