Correlations of the rate constants of phosphorylation reactions with the empirical parameters of the solvent polarity

V. E. Bel'skii

A. E. Arbuzov Institute of Organic and Physical Chemistry,
Kazan' Research Center of the Russian Academy of Sciences,
8 ul. Akad. Arbuzova, 420083 Kazan', Russian Federation.
Fax: +7 (843 2) 75 2253

Regression analysis of the solvent effects on the rate constants of nucleophilic substitution at the phosphoryl group was performed with the use of the empirical parameters of solvent polarity which characterize the ability of the solvents to electrophilic and nucleophilic solvation. The nucleophilic solvation of reagents by solvents, as a rule, favors the phosphorylation reactions. In the phosphorylation reactions of anionic nucleophiles, the electrophilic solvation of anions influences negatively the reactions rates. The phosphorylation of amines by chlorides of phosphorus acids is facilitated by the electrophilic solvation of a separated anion.

Key words: phosphorylation reactions, solvent effects, rate constants, regression analysis.

The kinetics of phosphorylation of anionic[1—6] and neutral nucleophiles[7—10] have been studied in various solvents for reactions proceeding with scission of the P—F,[1] P—Cl,[4,7,8] P—O,[2,6,9,10] and P—S[3,5] bonds. In these studies,[1,4—10] main attention was paid to reactions in aprotic (hydroxyl-free) solvents, where the phosphorylation reactions commonly proceed faster than in proton-donor solvents. The rate constants for phosphorylation of anionic nucleophiles vary in a wide range, when solvents are changed, sometimes by a factor of up to 10^6.[5] Considerable effects of the medium have also been observed for reactions with participation of neutral nucleophiles, alcohols, and amines, for which a change in a solvent can accelerate (or decelerate) a reaction by a factor greater than 100.[7—10]

In this work, a systematic regression analysis of the available kinetic data [1—10] was performed for reactions of nucleophilic substitution at the phosphoryl group to establish dependences between the reaction rate constants and the empirical parameters (descriptors) of solvents which characterize the ability of the solvents to solvate the reagents and transition complexes. Such dependences serve as a basis for prediction of the effect of the medium on the reaction rates[11] and can be useful for the search for an optimum solvent for a reaction.

Many types of descriptors are known which reflect various mechanisms of the solvation of dissolved substances; however, some of them correlate with each other because of the similarity in the model processes used for their determination.[11] It is reasonable to use the descriptors which are widely employed and determined for the most number of solvents. The normalized parameters of the solvent polarity according to Reichardt, E_T^N (see Ref. 11), as well as the averaged solvatochromic parameters, π^*, according to Kamlet—Taft,[12] were chosen in this work as a measure of the electrophilic solvating ability of solvents. The nucleophilic solvating ability of the solvents is evaluated on the basis of the normalized β_2^H scale (see Ref. 13) which is in agreement with the ealier β scale of Kamlet—Taft.[12] The solvents and descriptors used for the analysis are presented in Table 1.

Calculation Procedure

To examine the solvent effects for various reactions, the one-, two-, and multi-parameter models are used.[11—13] However, the multi-parameter models are seldom used because they require a great body of data for statistical calculations. In this work, the regression analysis was performed on the basis of two-parameter equations of the following type:

$$\log k = a_1 \cdot E_T^N + b \cdot \beta_2^H + \log k_0, \quad (1)$$

$$\log k = a_2 \cdot \pi^* + b \cdot \beta_2^H + \log k_0, \quad (2)$$

where k/L mol^{-1} s^{-1} is the rate constant of the reaction in the corresponding solvent, and a_1, a_2, b, and $\log k_0$ are the coefficients of the regression equations. The standard errors of coefficients, multiple correlation coefficients R corrected with respect to the number of degrees of freedom, and selected standard deviations s were estimated. The calculations were

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Table 1. Empirical parameters of solvent polarity

Solvent	E_T^N	π^*	β_2^H
n-Heptane (**1**)	0.012	−0.08	0
Tributylamine (**2**)	0.043	0.16	0.597
Benzene (**3**)	0.111	0.59	0.146
Dioxane (**4**)	0.164	0.55	0.453
Tetrahydrofuran (**5**)	0.207	0.58	0.510
Pyridine (**6**)	0.302	0.87	0.625
Hexamethylphosphoramide (**7**)	0.315	0.87	1.000
Nitrobenzene (**8**)	0.324	1.01	0.341
Benzonitrile (**9**)	0.333	0.90	0.423
Acetone (**10**)	0.355	0.71	0.497
N-Methylpyrrolidone-2 (**11**)	0.355	0.92	0.765
Dimethylacetamide (**12**)	0.401	0.88	0.730
Dimethylformamide (**13**)	0.404	0.88	0.663
Tetramethylenesulfone (**14**)	0.410	0.98	0.523
Dimethylsulfoxide (**15**)	0.444	1.00	0.775
Acetonitrile (**16**)	0.460	0.75	0.439
Nitromethane (**17**)	0.481	0.85	0.23
Propene carbonate (**18**)	0.491	0.83	0.42
Formamide (**19**)	0.799	0.97	0.58
tert-Butyl alcohol (**20**)	0.389	0.41	0.49
Isopropyl alcohol (**21**)	0.546	0.48	0.47
n-Butanol (**22**)	0.602	0.47	0.46
n-Propanol (**23**)	0.617	0.52	0.45
Ethanol (**24**)	0.654	0.54	0.44
Methanol (**25**)	0.762	0.60	0.41

Note. The E_T^N values were calculated from the literature data[11]; π^* from the literature data[12], and β_2^H from the literature data[13].

processed on a PC AT-486DX2 computer by the least squares method with the use of the program packet STATGRAPHICS.

Results and Discussion

Table 2 presents the reactions for which the *k* values in a series of solvents are known and the regression equations obtained from them. These data show the applicability of Eqs. (1) and (2) to the processes considered. The positive values of the *b* coefficients in the equations of (1) and (2) types show that the rates of the corresponding reactions increase with increasing nucleophilic solvating ability of solvents. The solvents with the enhanced β_2^H values can also serve as the general base catalysts for the reactions with amines.[9] The solvents most likely play a similar role in the reaction with the participation of the alcohol group of ethanolamine.

As seen in Table 2, the signs of coefficients a_1 and a_2 are different for various reactions. The positive values of the a_1 and a_2 coefficients (in Eqs. (1) and (2)) for the reactions between acid chlorides and amines can be rationalized as follows: the enhancement of the electrophilic solvation of Cl^- anion (an increase in the E_T^N and π^* values of solvents, see Table 1) that is abstracted from an intermediate[14] favors the reaction.

The a_1 and a_2 values for the phosphorylation reaction of the uncharged nucleophiles by *p*-nitrophenyl esters of the phosphorus acids are negative except for the a_2 value for the phosphorylation reaction of the alcohol group of ethanolamine, which is statistically insignificant as well as the a_1 value for this reaction. In these case, the a_1 and a_2 coefficients most likely reflect the positive role of the decrease in the electrophilic solvation of nucleophiles, interacting with the solvents according to the mechanism of general base catalysis.[9]

Table 2. Regression equations (1) and (2) for the rate constants (k/L mol^{-1} s^{-1}, 25 °C) of phosphorylation reactions in various solvents

Reaction (solvents)[a]	log*k*	*R*	*s*	*n*	Reference
$(Pr^iO)_2P(O)Cl + Bu_2NH$	$(3.93\pm0.81)\cdot E_T^N + (2.75\pm0.79)\cdot\beta_2^H - (3.87\pm0.23)$	0.966	0.29	7	7
(**1**, **3**, **4**, **8**, **10**, **16**, **17**)	$(1.65\pm0.79)\cdot\pi^* + (3.06\pm1.49)\cdot\beta_2^H - (3.93\pm0.45)$	0.882	0.52	7	
$Me(EtO)P(O)Cl + Bu^tNH_2$	$(4.08\pm2.20)\cdot E_T^N + (2.37\pm2.25)\cdot\beta_2^H - (3.29\pm0.72)^b$	0.832	0.50	5	8
(**3**, **4**, **8**, **10**, **17**)	$(3.72\pm1.28)\cdot\pi^* + (3.42\pm1.65)\cdot\beta_2^H - (5.14\pm1.16)^b$	0.843	0.49	5	
$Bu_2P(O)OC_6H_4NO_2$-*p* + $BuNH_2$	$(-0.68\pm0.50)\cdot E_T^N + (4.13\pm0.45)\cdot\beta_2^H - (4.25\pm0.34)$	0.969	0.19	7	9
(**2**, **5**, **6**, **13**, **15—17**)	$(-0.48\pm0.24)\cdot\pi^* + (4.34\pm0.38)\cdot\beta_2^H - (4.24\pm0.26)$	0.978	0.16	7	
$ClCH_2(PhO)P(O)OC_6H_4NO_2$-*p* +	$(-0.81\pm0.75)\cdot E_T^N + (3.95\pm1.10)\cdot\beta_2^H - (4.21\pm0.80)^c$	0.852	0.28	6	
+ $HOCH_2CH_2NH_2$	$(-2.55\pm1.27)\cdot\pi^* + (5.32\pm1.04)\cdot\beta_2^H - (3.10\pm0.94)^c$	0.915	0.22	6	10
(**6**, **13—16**, **19**)	$(-0.21\pm0.83)\cdot E_T^N + (3.75\pm1.22)\cdot\beta_2^H - (4.30\pm0.89)^d$	0.783	0.31	6	
	$(0.54\pm1.82)\cdot\pi^* + (3.54\pm1.48)\cdot\beta_2^H - (4.76\pm1.35)^d$	0.785	0.31	6	
$(EtO)_2P(O)OC_6H_4NO_2$-*p* + PhO^-	$(-5.58\pm3.33)\cdot E_T^N + (1.73\pm0.90)\cdot\beta_2^H + (1.38\pm1.72)$	0.869	0.34	5	6
(**7**, **10**, **13**, **15**, **16**)	$(-2.42\pm2.27)\cdot\pi^* + (3.37\pm1.31)\cdot\beta_2^H + (0.10\pm1.71)$	0.766	0.44	5	
$(PhO)_2P(O)Cl + {}^{36}Cl^-$	$(-3.06\pm0.81)\cdot E_T^N + (0.82\pm0.25)\cdot\beta_2^H - (0.98\pm0.40)$	0.952	0.13	6	4
(**7—9**, **16—18**)	$(2.78\pm0.40)\cdot\pi^* + (1.38\pm0.13)\cdot\beta_2^H - (4.88\pm0.36)$	0.984	0.08	6	
$(PhO)_2P(S)Cl + {}^{36}Cl^-$	$(-2.49\pm1.59)\cdot E_T^N + (1.09\pm0.50)\cdot\beta_2^H - (2.37\pm0.80)$	0.843	0.26	6	4
(**7—9**, **16—18**)	$(2.65\pm1.01)\cdot\pi^* + (1.55\pm0.32)\cdot\beta_2^H - (5.88\pm0.91)$	0.916	0.19	6	
$Me(Pr^iO)P(O)F + PhC(O)NHO^-$	$(4.75\pm2.39)\cdot E_T^N + (1.06\pm0.57)\cdot\beta_2^H - (3.94\pm1.17)$	0.842	0.22	5	1
(**10**, **13**, **15—17**)	$(2.38\pm1.17)\cdot\pi^* + (2.19\pm0.63)\cdot\beta_2^H - (3.27\pm0.84)$	0.845	0.22	5	
$Me(EtO)P(O)SEt + F^-$	$(-17.2\pm5.5)\cdot E_T^N + (1.67\pm1.62)\cdot\beta_2^H + (5.45\pm3.13)$	0.907	0.44	7	5
(**11—16**, **18**)	$(-4.62\pm4.23)\cdot\pi^* + (6.77\pm2.38)\cdot\beta_2^H + (0.13\pm3.11)$	0.729	0.71	7	

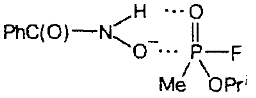
[a] Numbering of solvents is presented in Table 1. [b] The rate constants calculated at 11 °C. [c] For phosphorylation of amino group. [d] For phosphorylation of alcohol group.

A special feature of the phosphorylation of ethanolamine (see Table 2) is that the hydrogen bond between the OH group of ethanolamine and the phosphoryl group of the substrate forms along with the electrophilic solvation of the substrate by a solvent. The rate constants of phosphorylation of the alcohol group of ethanolamine are described by the following regression equation because of the small values of a_1 and a_2 in Eqs. (1) and (2):

$$\log k = (3.80\pm1.06)\beta_2{}^{H} - (4.42\pm0.65)$$
$$r = 0.873,\ s = 0.27,\ n = 6.$$

Phosphorylation of anionic nucleophiles is characterized, as a rule, by the positive values of the b coefficients and negative values of a_1 and a_2 (see Table 2). The latters show that a decrease in the electrophilic solvation of anionic nucleophiles by solvents (a decrease in the $E_T{}^N$ and π^* descriptors) favors the reactions.[11]

Phosphorylation of the anion of benzhydroxamic acid, for which the negative value of b and positive values of a_1 and a_2 are observed, is an exception. The change in the signs of coefficients for this reaction is likely due to the participation in the nucleophilic attack of the anion exhibiting bifunctional properties. The nucleophilic solvation of the NH groups of the latter hampers its bifunctional reaction with a substrate that involves the nucleophilic attack of the phosphorus atom by the O atom and the nucleophilic catalysis by the NH group.



The a_1 and a_2 coefficients with the opposite signs are obtained for the reactions of diphenylchlorophosphate and diphenylchlorothionphosphate (see Table 2); this fact was unexpected because of the similarity in the $E_T{}^N$ and π^* descriptors. Since the values of the $E_T{}^N$ descriptor are more exact, the a_2 values are incorrect. Note that a random correlation with the negative angular coefficient is observed between the $E_T{}^N$ and π^* descriptors for the series of solvents used,[4] although in a wide series of solvents, these descriptors change in parallel to each other.

For the reaction of *S,O*-diethylmethylphosphonate with F^- anion (see Table 2) in bipolar solvents (**11—16**, **18**, see Table 1), the coefficient b in the equation of the (1) type is statistically insignificant; hence, the following one-parameter regression is fulfilled in fact:

$$\log k = (-21.0\pm3.0)\cdot E_T{}^N + (9.26\pm1.30)$$
$$r = 0.953,\ s = 0.34,\ n = 7.$$

For this reaction in alcohol media (**20—25**, see Table 1), a similar equation is fulfilled:

$$\log k = (-5.32\pm0.45)\cdot E_T{}^N - (0.66\pm0.27)$$
$$r = 0.986,\ s = 0.13,\ n = 6.$$

The absolute value of the regression coefficient in alcohols is 4 times smaller as compared to bipolar solvents; hence, the alcohols exhibit a leveling effect on the reaction rates. The rate constant in water is not described by the latter equation and is not involved in calculation.

The leveling effect of ethanol has been observed previously for the phosphorylation of Na ethylate by *p*-nitrophenyldiethylphosphate, whose kinetics have been studied in the systems contained benzene, ethanol, and various bipolar solvents.[2] The effect of bipolar solvents on this reaction has been described in terms of the catalytic rate constants k_N/L^2 mol^{-2} s^{-1} at 25 °C for which the following regression equation has been obtained[2]:

$$\log k_N = 0.520\cdot \mathrm{p}K_{HB} - 0.623$$
$$r = 0.953,\ s = 0.23,\ n = 13.$$

A decrease in the slope of the latter dependence and in the k_N values with increasing ethanol content in the systems has been shown.[2] The pK_{HB} descriptors are similar to the $\beta_2{}^H$ descriptors and are determined from the constants for the complex formation of *p*-fluorophenol with bipolar compounds in a medium of CCl_4.[15] The polar molecules of solvents which form hydrogen-bond complexes with ethanol decrease its participation in the solvation of ethylate anion, making it the more reactive.[2]

It is interesting to note the interrelated change in either the coefficients a_1 and b or a_2 and b for the reaction with nucleophiles of the same type. In particular, for the reactions with the neutral nucleophiles, the following correlation is known:

$$a_1 = (-3.16\pm0.36)\cdot b + (12.0\pm1.2)$$
$$r = 0.981,\ s = 0.56,\ n = 5.$$

A similar correlation with a close angular coefficient is known for the reactions with anionic nucleophiles except for fluoride anion:

$$a_1 = (-3.66\pm0.38)\cdot b + (0.77\pm0.46)$$
$$r = 0.990,\ s = 0.78,\ n = 4.$$

Such correlations of the a_2 and b values are characterized by the lowered values of r (r = 0.862 for the reactions with neutral nucleophiles). For the reactions with anionic nucleophiles, the correlation between the a_2 and b values has r = 0.624 which is most likely due to the incorrect a_2 values for the reactions of diphenylchlorophosphate and diphenylchlorothionphosphate discussed above. The existence of these correlations show that in the cases mentioned, the intermolecular interaction of the reagents with solvents occurs via two interrelated mechanisms.

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