

## MECHANISM OF ALKALI-CATALYZED HYDROLYSIS OF DIPHENYL AMIDOPHOSPHATES

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Received July 7th, 1975

*Dedicated to Professor S. Škramovský on the occasion of his 75th birthday.*

The mechanism of alkali-catalyzed hydrolysis of N-substituted derivatives of diphenyl amidophosphates has been discussed on the basis of the found pH profile of logarithm of the rate constant, dependence of the rate constant on medium, and on the basis of the found values of the activation entropies. The suggested mechanism has been confronted with the found values of parameters of the Taft and the Hammett equations.

In literature<sup>1</sup> considerable attention has been paid to the acid-catalyzed hydrolysis of amidophosphoric acid and its derivatives, but the available data about the base-catalyzed hydrolysis of amidophosphoric acid are only fragmentary. S<sub>N</sub>2 mechanism is ascribed to the base-catalyzed hydrolysis of fluorides of substituted amidophosphoric acids<sup>2,3</sup> and to the base-catalyzed hydrolysis of esters and halogenides of diamidophosphoric acids<sup>4-7</sup>, whereas E1cB mechanism is ascribed to the base-catalyzed hydrolysis of substituted phenyl esters of phosphoric acid dianilides<sup>8,9</sup>. The experimental data summarized in the present paper allow to draw conclusions about mechanism of the hydrolytic reaction of N-mono- and N,N-dialkyl derivatives of amidophosphoric acid.

### EXPERIMENTAL

*Reagents.* Diphenyl esters of amidophosphoric acid were prepared by aminolysis of the respective chlorides of phosphoric acid diphenyl esters according to the literature: diphenyl amidophosphate<sup>10</sup> (I), diphenyl N-methylamidophosphate<sup>11</sup> (II), diphenyl N-cyclohexylamidophosphate<sup>11</sup> (III), diphenyl N-benzylamidophosphate<sup>12</sup> (IV), diphenyl N-phenylamidophosphate<sup>11</sup> (V), diphenyl N-(*p*-tolyl)amidophosphate<sup>13</sup> (VI), diphenyl N-(*p*-anisidyl)amidophosphate<sup>13</sup> (VII), diphenyl N-(*m*-chlorophenyl)amidophosphate<sup>13</sup> (VIII), diphenyl N-(*p*-bromophenyl)amidophosphate<sup>13</sup> (IX), diphenyl N-(*m*-nitrophenyl)amidophosphate<sup>13</sup> (X), diphenyl morpholidophosphate<sup>11</sup> (XI). Purity of the substances prepared was checked by their melting points determination and by elemental analysis (C, H, N). New derivative XII — diphenyl N-(*p*-dimethylaminophenyl)amidophosphate melted at 124–126°C (ethanol); for C<sub>20</sub>H<sub>21</sub>N<sub>2</sub>O<sub>3</sub>P (368.4) calculated: 65.21% C, 5.75% H, 7.60% N; found: 65.25% C, 5.92% H, 7.50% N.

From the obtained N-alkyl and N-aryl derivatives  $8 \cdot 10^{-5}$  and  $3 \cdot 10^{-5}$  M solutions, respectively, were prepared in borate and glycinate buffers in 50% (by wt.) ethanol. Diphenyl amido-, N-methylamido- and morpholidophosphates were dissolved ( $8 \cdot 10^{-5}$  M) in glycinate buffer in 10% (by wt.) ethanol. The described method<sup>14</sup> was used for pH determination of the solutions prepared.

pK Values of the N-aryl derivatives were measured spectrophotometrically with a Spektromom 202 apparatus, (MOM, Budapest) using the equation

$$E = (a_{H^+}/K)(E_A - E) + E_B, \quad (1)$$

where  $K$  is the dissociation constant and  $E$ ,  $E_A$  and  $E_B$  stand for the absorbances of the compound at the given proton activity, that of the undissociated form and that of anion, respectively.

The reaction kinetics was followed spectrophotometrically with the same apparatus with 1 cm quartz cells. When studying the kinetics up to 45°C, the solutions in calibrated flasks were immersed in a thermostat pre-heated at the required temperature  $\pm 0.1^\circ\text{C}$ . At higher temperatures ampoule technique was used. Optimum wavelength 236.5 nm for kinetic experiments, corresponding to the absorption maximum of phenolate ion was determined from the spectra. In the cases of N-(*m*-chlorophenyl) and N-(*p*-bromophenyl) derivatives the wavelength 255 nm was used, corresponding to the absorption maximum of diphenyl N-(*m*-chlorophenyl)- and N-(*p*-bromophenyl)amidophosphates.

The rate constant was computed from the equation

$$\log(E_\infty - E) = -kt/2.303 + \text{const.} \quad (2)$$

For linear dependence of  $\log(E_\infty - E)$  vs time in the whole time range the constant of Eq. (2) was equal to  $\log(E_\infty - E_0)$ , and the rate constant was calculated by the least squares method. Eq. (2) conforms to the condition of quasi-steady concentration of the intermediate. At lower pH values the concentration of the intermediate cannot be neglected, and the reacting system can be described formally by the following scheme of consecutive competitive reactions of the first order:



where A, B and C are the starting substance, the intermediate, and the product of the hydrolytical reaction, respectively. For the measured absorbances  $E_0$  and  $E_\infty$  at the time  $t = 0$  and  $t = \infty$ , respectively, it can be written:

$$E_0 = R + \alpha A_0, \quad (3)$$

$$E_\infty = R + \gamma C_\infty = R + \gamma A_0, \quad (4)$$

where  $R$  is the contribution of solvent,  $A_0$  is initial concentration of the starting substance,  $C_\infty$  is final concentration of the product, and  $\alpha$  and  $\gamma$  are molar decadic absorption coefficients of the starting substance and the product, respectively. From the definition scheme it follows:  $A_0 = C_\infty$ . At any time  $t$  ( $0 < t < \infty$ ), the absorbance  $E$  of the reacting system is given by the rela-

tion

$$E = R + \alpha A + \beta B + \gamma C, \quad (5)$$

where  $A, B, C$  are concentrations of the starting substance, the intermediate and the product at the time  $t$ , respectively. Eq. (5) is converted into Eq. (6) by introducing the known expressions for  $A, B, C$  and using Eqs (3) and (4) for  $\alpha$  and  $\gamma$ .

$$(E - E_{\infty}) = (E_0 - E_{\infty}) \exp(-k_1 t) + (\beta A_0 + R - E_{\infty}) [k_1 / (k_2 - k_1)] [\exp(-k_1 t) - \exp(-k_2 t)]. \quad (6)$$

Generally this equation cannot be solved, because the value  $\beta$  is not known, but if

$$k_1 \gg k_2 \quad (7)$$

or

$$k_1 \ll k_2, \quad (8)$$

then the terms containing  $\exp(-k_1 t)$  resp.  $\exp(-k_2 t)$  approach rapidly zero with increasing time, and Eq. (6) can easily be solved. If the condition (7) is fulfilled, Eq. (6) changes into (9) after a certain time.

$$(E - E_{\infty}) = W \exp(-k_2 t), \\ W = -(\beta A_0 + R - E_{\infty}) k_1 / (k_2 - k_1). \quad (9)$$

Logarithmic form of Eq. (9) is formally identical with Eq. (2). If condition (8) is fulfilled, Eq. (6) changes into Eq. (10) after a certain time<sup>15</sup>.

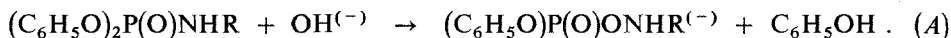
$$(E - E_{\infty}) = Z \exp(-k_1 t), \\ Z = E_0 - E_{\infty} + (\beta A_0 + R - E_{\infty}) k_1 / (k_2 - k_1). \quad (10)$$

Again logarithmic form of Eq. (10) is formally identical with Eq. (2). Comparison of Eqs. (9) and (10) indicates that analysis of formal kinetic relations cannot decide whether the reacting system obeys Eq. (9) (condition (7)) or Eq. (10) (condition (8)). The given problem can be solved unambiguously by stopping the reaction at about the half point and isolation of the individual compounds from the reacting system. In our case only the starting reagents and the reaction products were found both by chromatography and isolation. Therefrom it follows that the condition (8) and Eq. (10) hold for the reactions studied. In the case of validity of Eq. (10) the rate constant was determined graphically. The error in determination of the rate constants values was less than 5 per cent.

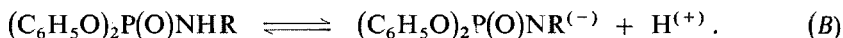
*Activation parameters of the hydrolytic reaction* were calculated from the values of rate constants obtained at four temperatures. Diphenyl amidophosphate was measured at 20, 25, 30, and 35°C, diphenyl N-(*m*-nitrophenyl)amidophosphate was measured at 50, 60, 70, and 75°C, diphenyl morpholidophosphate was measured at 75, 80, 90, and 95°C, and the other substances were measured at 35, 40, 45, and 50°C. All the compounds investigated conformed the Arrhenius diagram.

## RESULTS AND DISCUSSION

In alkaline medium the hydrolysis of diphenyl amidophosphates takes the following course<sup>16,17</sup>:



Only in the case of  $-\text{NH}_2$  derivative<sup>16,18</sup> the second phenoxy group can be split off in strongly alkaline medium. The compounds prepared are acidic and dissociate as it follows:



The measurable  $\text{p}K$  values are given in Table I. The values found fit the Hammett equation, the  $\rho$  constant being 2.94.

Investigation of the pH dependence of the hydrolysis rate constant of diphenyl N-methylamidophosphate showed that, at higher pH values, the kinetic curves could be expressed by equation of an isolated first order reaction. At lower pH values a delay was observed at the beginning of the reaction corresponding to the existence of an intermediate the stability of which increases with decreasing pH. Fig. 1 gives examples of the conversion curves. Similar effects were found also with other aliphatic derivatives. The dependence of logarithms of the rate constants on pH of medium was linear, its slope being 0.84 to 0.34 for individual derivatives. Table II gives the found rate constant values for various pH values. The rate constants values of N-alkyl derivatives at pH 12.30 at 45°C fit the Taft equation<sup>19</sup>, the found parameters being  $\rho^* = 0.89$ ,  $\delta = 0.024$  (small steric effect).  $\text{p}Q$  Values of all the compounds were above 14. The hydrolytic reaction takes place with N-disubstituted derivative, too (compound XI, Table II); therefrom it can be inferred

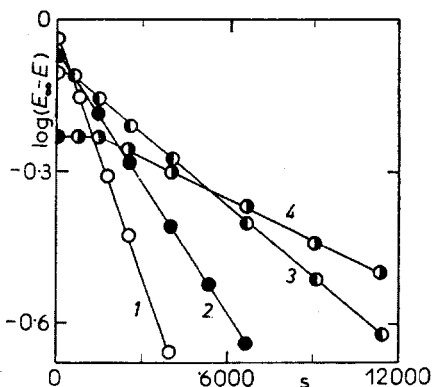


Fig. 1  
Conversion Curves of Diphenyl N-Methylamidophosphate at the Temperature 45°C in 50% (by wt.) Ethanol at Various pH  
Curve 1 pH 12.41; 2 pH 12.04; 3 pH 11.61; 4 pH 11.42.

that the hydrolysis of N-monoalkyl derivatives goes through the non-ionized form of the compound.

Dependence of logarithm of the hydrolytic reaction rate constant of diphenyl N-phenylamidophosphate on pH of the solution was linear, too, its slope being about unity, but all the kinetic curves fitted the scheme of isolated first order reactions. Similar agreement was observed also with the other N-aryl derivatives in the whole time range measured. Effect of ring substituent in arylamido group was followed at 46°C at pH 12.86. The found  $k_{\text{exp}}$  values are given in Table I. The used pH value when compared with the pK values in Table I leads to the conclusion that the hydrolytic reaction proceeds in the region of measurable dissociation of some of the compounds. From the analogy with diphenyl N-alkylamidophosphates it is likely that also the N-aryl derivatives undergo hydrolysis in the non-dissociated form. In this case Eq. (11) gives the reaction rate  $v$  in a medium of given  $\text{OH}^-$  ion activity.

$$v = k'a(\text{HA}). \quad (11)$$

The rate constant  $k'$  depends linearly on the  $\text{OH}^-$  ion activity ( $k' = k^0a(\text{OH}^-)$ ), and  $a(\text{HA})$  stands for the activity of the non-dissociated molecules which can be expressed by dissociation constants (Table I). If we neglect the difference between activity and concentration, and if we denote

$$c_T = [\text{A}^-] + [\text{HA}], \quad (12)$$

where  $c_T$  is the total concentration of the compound, and  $[\text{A}^-]$  stands for concentration of the anion, then Eq. (11) is changed into Eq. (13), where  $K$  is the dissociation constant

$$v = k'a(\text{H}^+) c_T / (K + a(\text{H}^+)). \quad (13)$$

TABLE I

pK Values of Diphenyl Aminophosphates at Room Temperature (found at the given wavelength) and Rate Constant Values of Hydrolysis at 46°C at pH 12.86

Compound	V	VI	VII	VIII	IX	X	XII
$\lambda$ , nm	249.6	249.6	243.5	256	256	256	—
pK	13.5	13.8	14.06	12.39	12.72	11.15	—
$k_{\text{exp}} \cdot 10^4, \text{s}^{-1}$	2.51	3.36	5.59	1.04	1.55	0.26	3.83
$k' \cdot 10^4, \text{s}^{-1}$	3.08	3.72	5.91	4.15	3.67	13.51	—

From Eq. (13) it follows for experimental rate constant:

$$k_{\text{exp}} = k' a(\text{H}^+) / (K + a(\text{H}^+)). \quad (14)$$

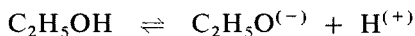
The values of  $k'$  computed from Eq. (14) are given in Table I. Their comparison indicates that ring substituents at the arylamido group affect but little the rate of the reaction studied. This conclusion agrees with the values of Table II where the substitution of a methyl group by phenyl group (the compounds *II* and *V*) results in an only small change of the rate constant.

TABLE II

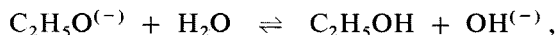
Hydrolysis Rate Constant Values of Diphenyl Amidophosphates at Various pH and Temperatures Measured in 50% (by wt.) Ethanol at 236.5 nm

pH	$k_{\text{exp}} \cdot 10^4, \text{s}^{-1}$	pH	$k_{\text{exp}} \cdot 10^4, \text{s}^{-1}$
compound <i>I</i> , 20°C		compound <i>V</i> , 45°C	
12.30	8.31	12.55	2.17
12.14	5.83	12.27	1.17
11.94	2.76	11.94	0.61
11.79	1.70	11.79	0.44
compound <i>II</i> , 45°C		compound <i>V</i> , 90°C	
12.41	3.31	11.78	4.46
12.30	2.40	11.28	1.46
12.04	2.19	11.17	1.26
11.77	1.10	10.82	0.81
11.61	0.94	10.62	0.32
11.42	0.63		
compound <i>III</i> , 45°C		compound <i>XI</i> , 95°C	
12.55	2.75	12.86	1.93
12.30	1.75	12.68	1.22
11.79	0.83	12.46	0.38
11.55	0.68	12.14	0.10
compound <i>IV</i> , 45°C			
12.55	4.99		
12.30	3.75		
11.77	2.07		
11.37	1.37		

Effect of medium was followed in hydrolyses of diphenyl amidophosphate, N-methylamidophosphate, and morpholidophosphate, 50% (by wt.) and 10% (by wt.) ethanol being used at the same temperature. Table III gives the results, wherefrom it can be seen that the increasing water concentration increases the value of rate constant. The change in  $\text{OH}^-$  ion activity due to the change of medium can be estimated from the equilibria:



and



characterized by the equilibrium constants  $K_A$  and  $K$ , respectively. Combination of the both equilibria leads to Eq. (15).

$$K_A K [\text{H}_2\text{O}] / [\text{OH}^-] = [\text{H}^+]. \quad (15)$$

TABLE III  
Hydrolysis Rate Constant Values of Diphenyl Amidophosphates at Various pH and Temperatures

Ethanol % (by wt.)	pH	$k_{\text{exp}} \cdot 10^4, \text{s}^{-1}$	Ethanol % (by wt.)	pH	$k_{\text{exp}} \cdot 10^4, \text{s}^{-1}$
compound I, 45°C					
50	11.92	7.85	10	11.44	74.55
	11.73	7.64		11.02	27.71
	11.36	3.62		10.83	18.66
compound II, 45°C					
50	12.86	9.30	10	12.21	15.94
	12.53	4.72		12.01	7.51
	12.30	1.88		11.77	3.10
	11.92	0.93		11.52	1.44
	11.73	0.68			
compound IX, 95°C					
50	12.86	1.93	10	12.34	2.02
	12.68	1.22		12.27	1.94
	12.46	0.38		12.17	1.20
	12.14	0.10		12.04	0.74

From Eq. (15) it follows that in various water-ethanol mixtures having constant  $H^+$  ion activity the  $OH^-$  ion activity increases with increasing water activity. Water concentration is 25.4 and 49 mol  $dm^{-3}$  for 50% (by wt.) and 10% (by wt.) ethanol, respectively. Thus at a given pH the change of medium from 50 to 10% (by wt.) ethanol results in doubling (approximately)  $OH^-$  ion activity, however, the experimental rate constant (Table III) increases about ten times. This experimental fact can be explained by formation of hydrogen bonds between the substrate and solvent, which facilitates the splitting off of phenolate ion. This explanation is supported also by the observed decrease of the rate constant value connected with the substitution of hydrogen atoms of  $-NH_2$  group by alkyl or aryl groups.

Table IV summarizes the activation parameters of the studied reaction. With N-alkyl derivatives the values characteristic for bimolecular mechanism of the rate-determining step were found<sup>20</sup>. The activation entropy value of diphenyl morpholidophosphate suggests fixation of a further water molecule in the activated complex<sup>21,22</sup>. The activation entropy value of the  $-NH_2$  derivative leads to a presumption of monomolecular mechanism of the rate-determining step. From the viewpoint of the activation entropy values, the alkali-catalyzed hydrolysis of the  $-NH_2$  derivative takes a course different from those of the studied series. In this respect it can be mentioned that only this substance changes both its phenoxy groups for hydroxy groups by boiling with alkali hydroxide<sup>16,18</sup>, whereas in the other cases only one phenoxy group can be substituted; lastly, also the dependence found in this work between pH and logarithm of the hydrolysis rate constant differs markedly in its slope when comparing the  $-NH_2$  derivative with the rest of the series studied. The activation entropy value of diphenyl N-phenylamidophosphate lies at the boundary of the values of monomolecular and bimolecular reactions, thus being unable to differentiate between the both mechanism. The activation entropy value of diphenyl N-(*m*-nitrophenyl)amidophosphate agrees with bimolecular mechanism.

On the basis of the given experimental data it can be concluded that the studied

TABLE IV

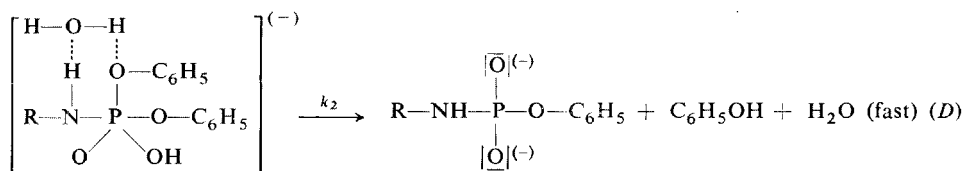
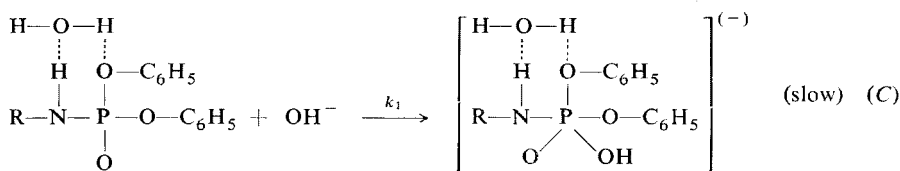
Activation Parameters of Alkali-Catalyzed Hydrolysis of Diphenyl Amidophosphates in 50% (by wt.) Ethanol at 308.15 K at pH 11.79

Compound	<i>I</i>	<i>II</i>	<i>III</i>	<i>IV</i>	<i>V</i>	<i>X</i>	<i>XI</i>
$\Delta H^\ddagger$ , kJ mol <sup>-1</sup>	100.2	63.5	55.8	70.5	93.0	60.9	55.3
$\Delta S^\ddagger$ , J mol <sup>-1</sup> deg <sup>-1</sup>	+24.8	-118.4	-150.5	-141.7	-36.0	-140.8 <sup>a</sup>	-168.5

<sup>a</sup> The value obtained at pH 12.86.

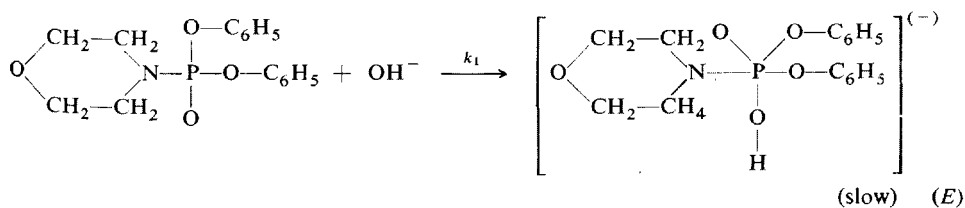


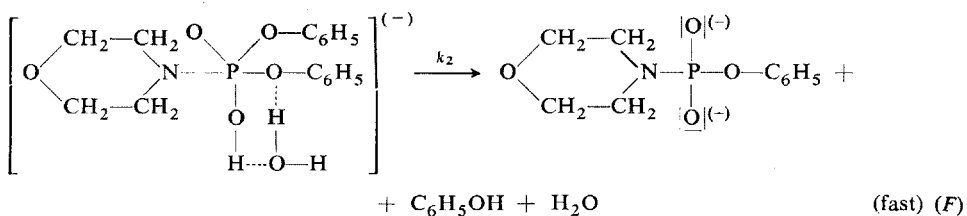
reaction of N-mono- and N-dialkyl derivatives has bimolecular rate-determining step. Comparison of the found activation entropy values (Table IV) with literature<sup>20</sup>, the found  $\rho^*$  value of the Taft equation, and the existence of relatively stable intermediate (from literature it is known that compounds of pentacovalent phosphorus are usual, whereas those of tricovalent phosphorus with  $p_\pi-p_\pi$  bonds add immediately water or polymerize<sup>23</sup>) point to the above conclusion. The found dependence of the rate constant on medium and comparison of the rate constants of N-monoalkyl- and N-dialkylderivatives lead to the idea of a marked influence of hydrogen bond with solvent on the reaction rate. Hence it can be written for N-monoalkyl derivatives



With respect to that both the synthetic experiments and chromatographic analysis of the reacting system failed to trap the intermediate<sup>17</sup>, the relation (8) holds for these derivatives, and the measured rate constant is identical with  $k_1$ ; see Eq. (10). The rate constant  $k_1$  belongs to bimolecular nucleophilic addition (Eq. (C)).

Similarly, nucleophilic addition is the first step of hydrolysis of the N-dialkyl derivatives, too (Eq. (E)). The intermediate formed binds water by hydrogen bond to give the ion I (this follows from the activation entropy values and from the dependence of the rate constant on medium). In accord with the found dependence of the rate constant on the composition of solvent it can be concluded that the added water molecule forms an intramolecular hydrogen bridge, thus facilitating the splitting off of phenoxide ion (Eq. (F)). In this case again  $k_1 \ll k_2$ , and nucleophilic addition is the slowest process in accord with the found value of activation entropy.





The hydrolysis of diphenyl N-arylamidophosphates was carried out on the synthetical scale in solutions containing high ethanol concentrations (up to 80%), and in the reaction mixtures only the corresponding phenyl N-arylamidophosphates were found both by chromatography and isolation. This fact prefers the idea of  $S_N2$  mechanism as in Eqs (C) to (F), because  $\text{E}1cB$  mechanism should produce a mixture of the corresponding monophenyl and phenyl-ethyl N-arylamidophosphates as it was the case with the acid-catalyzed hydrolysis<sup>1</sup>. The addition mechanism is supported also by the found values of activation entropies (Table IV). Therefore, it can be concluded that the mechanism of the alkali-catalyzed hydrolysis of the N-aryl derivatives is identical with that of N-alkyl derivatives, and that it can be formulated by equations analogous to the Eqs (C) to (F).

The reaction mechanism expressed in Eqs (C) to (F) agrees with that postulated for hydrolysis of other organo derivatives of phosphoric acid<sup>2-7</sup>, it also agrees with the synthetical experience concerning stability of pentavalent and trivalent phosphorus derivatives, and lastly, it fits the experimental material given in this paper.

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Translated by J. Panchartek.