REACTIVITY OF *p*-SUBSTITUTED BENZALDOXIMES IN THE CLEAVAGE OF *p*-NITROPHENYL ACETATE: KINETICS AND MECHANISM

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Received July 2, 2003
Accepted November 9, 2003

Eleven *p*-substituted benzaldoximes (*p*-XC_6H_4CH=NOH, where X = H, CH_3, CF_3, F, Cl, Br, OCH_3, $N(CH_3)_2$, $COOCH_3$, CN, NO_2) have been synthesized and their dissociation constants determined in 10% (v/v) aqueous dioxane at 35 °C. Under the same conditions, the pseudo-first order rate constants k_{obs} of their reactions with *p*-nitrophenyl acetate (PNPA) were measured at pH values from 7.8 to 10.8 and at concentrations c_{oxime} ranging from 0 to 4.00 × 10^{-3} mol l^{-1}. The kinetic model and mechanism of the said reaction was proposed by means of mathematical statistical modelling of the dependences of k_{obs} on pH and c_{oxime}. The mechanism involves a pre-equilibrium (k_{-1}/k_1) in which PNPA forms a tetrahedral intermediate (THI) with the deprotonated form of oxime. In the given medium, THI is in equilibrium with the non-reactive conjugated acid THIH (dissociation constant $K_{a,THIH}$) which is stabilized by intramolecular hydrogen bond. Depending on pH, the rate-limiting step consists either in formation of THI from educts (pH < p$K_{a,oxime}$) or in its spontaneous (k_2) and oxime-catalyzed (k_3, general acid catalysis) decomposition to products (pH > p$K_{a,oxime}$). Evaluation of substituent effects on dissociation constants ($K_{a,oxime}$) of the oximes showed that there is no direct conjugation between the substituent and the reaction centre (the found reaction constant $\rho(K_{a,oxime})$ = 0.91). The transmission coefficient of the transfer of these effects through C=N–O grouping corresponds approximately to one bond. The reaction constants in the Hammett equation obtained from the regression model are: $\rho(k_{-1}K_{a,THIH}/k_1)$ = 1.29, $\rho(k_2K_{a,THIH})$ = 0.20 and $\rho(k_3K_{a,THIH})$ = 0.67. These reaction constants have been discussed with the regard to the reaction mechanism suggested.

Keywords: Esters; Hydrolysis; Kinetic model; Oximes; Substituent effects; Acidity; Catalysis; Dissociation constants.

The anion resulting from the deprotonation of the hydroxyimino group in aldoximes and ketoximes represents due to so-called α-effect[1] a powerful

nucleophile which is able to cleave readily esters of carboxylic, phosphoric and alkylphosphonic acids. This fact has been utilized for reactivation of phosphorylated (phosphonylated) acetylcholinesterase (AChE). Various quaternary pyridinium aldoximes[1a,2] as 2-[(hydroxyimino)methyl]-1-methylpyridinium iodide (2-PAM), 1-{[(4-carbamoylpyridinium-1-yl)-methoxy]methyl}-2-[(hydroxyimino)methyl]pyridinium dichloride (HI-6), 4,4′-bis[(hydroxyimino)methyl]-1,1′-(oxydimethylene)dipyridinium dichloride (toxogonine) and others have been introduced as antidotes for treatment of intoxication by organophosphorus compounds. Amphiphilic quaternary pyridinium aldoximes[3] and ketoximes[4] in micellar solutions have been investigated as potential catalysts of hydrolysis of various esters of phosphoric acid (models of toxic organophosphorus warfare agents and pesticides). Kinetic benefit of micellar catalysis[5] represents a significant contribution to the observed rate of hydrolysis in this case.

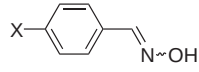
What is the source of the observed reactivity of heteroarenium oximes? The electron-withdrawing effect of the quaternary nitrogen in pyridinium oximes increases the acidity of the hydroxyimino group which is relatively low in non-substituted aromatic or aliphatic oximes[6] ($pK_a \approx 12–13$). The increased acidity of pyridinium aldoximes[1a,3] and ketoximes[4] ($pK_a \approx 8–10$) provides sufficient concentration of the nucleophilic oximate anion even in neutral solutions. Thus, the above-mentioned pyridinium oximes are considerably reactive towards organophosphates under mild conditions. Alternatively, in the case of chelate-forming heteroaromatic oximes, the increase in the acidity of the hydroxyimino group can be achieved by coordination to metal ions[7]. These complexes represent one of numerous examples of hydrolytic metalloenzyme models[8]. On the other hand, the nucleophilicity of the oximate anion formed is decreased by the same effect, *i.e.* by the electron withdrawal[1a]. Thus, the observed reactivity of any aryl or hetaryl oxime possessing an electron-withdrawing moiety towards esters (alkanoates, phosphates) is a result of two contradictory consequences of the electron withdrawal.

Terrier and coworkers[1a,1d] published a Brønsted plot for the *p*-nitrophenyl acetate (PNPA) cleavage by various oximate anions including those formed from pyridinium aldoximes used as AChE reactivators. This dependence of the logarithms of the bimolecular rate constants k_2 of the PNPA cleavage on pK_a values of the corresponding oximes falls into two different parts. The first one covering the interval of pK_a values from 7.1 to 8.0 is linear with the slope corresponding to β_{nuc} value of *ca* 0.7. The second one for less acidic oximes ($pK_a > 8.0$) is levelling off merging into a plateau at $pK_a \approx 9.0$.

Similar dependences were observed in the case of oximate reaction with phosphorus and sulfuric acid esters[9].

The cited studies[1a,1d,9] dealing with the cleavage of esters by oximes are in particular oriented to interpretation of the α-effect in connection with application of the Brønsted relationship. The kinetic model applied is usually very simple. It is presumed that the catalytic particle is the ionized or also non-ionized form of the oxime producing a tetrahedral intermediate in the rate-limiting step. This presumption is based on the linear dependence of the observed rate constant k_{obs} on actual concentration of oximate and/or oxime under suitable experimental conditions, especially at low analytical concentrations of oxime and low pH values. Deviations from the linear course were observed in the case of amphiphilic oximes above their critical micelle concentration[3d,4a] as a consequence of the local increase in the reactant concentration in the aggregates. In our opinion, the kinetic model of the PNPA reaction with oximes has not been given due attention: in particular, there exists no systematic study mapping and interpreting the course of this reaction within larger intervals of pH and oxime concentration.

The present paper is focused on a proposal of kinetic model of the PNPA cleavage by the oximes, a study of the substituent effects on the reactivity of oxime group in a series of *p*-substituted benzaldoximes in this reaction, and the corresponding reaction mechanism.



X	**a**	**b**	**c**	**d**	**e**	**f**	**g**	**h**	**i**	**j**	**k**
1	H	CH_3	CF_3	F	Cl	Br	OCH_3	$N(CH_3)_2$	$COOCH_3$	CN	NO_2

EXPERIMENTAL

The temperature data were not corrected. The TLC analyses were carried out on Kieselgel 60 F_{254} (Merck Laboratory Chemicals). The column chromatography was performed on Kieselgel 60 H (Merck Laboratory Chemicals). ^1H, ^{13}C, and ^{19}F NMR spectra were recorded on a Varian Gemini 300 at 300.08, 75.46, and 282.3 MHz, respectively. Chemical shifts (δ-scale) are reported in ppm relative to tetramethylsilane (^1H and ^{13}C NMR) or trichlorofluoromethane (^{19}F NMR) as an internal standard, coupling constants (*J*) are given in Hz. The reactions were followed on a spectrophotometer HP 8452A (diode array, Hewlett–Packard) equipped with a thermostated multicell transport cell holder HP 89075C.

Chemicals

4-(2-Hydroxyethyl)piperazin-1-ethanesulfonic acid) (HEPES), 4-(2-hydroxyethyl)piperazine-1-propanesulfonic acid) (HEPPS), 2-(cyclohexylamino)ethane-1-sulfonic acid (CHES),

3-(cyclohexylamino)propane-1-sulfonic acid (CAPS) and *p*-nitrophenyl acetate were obtained from Sigma. *p*-Nitrobenzaldehyde, *p*-cyanobenzaldehyde, *p*-acetoxybenzaldehyde, *p*-(trifluoromethyl)benzaldehyde, *p*-chlorobenzaldehyde, *p*-bromobenzaldehyde, *p*-fluorobenzaldehyde, *p*-(dimethylamino)benzaldehyde, *p*-methoxybenzaldehyde, *p*-methylbenzaldehyde and benzaldehyde were obtained from Aldrich.

Preparation of *p*-Substituted Benzaldoximes (**1a**–**1k**). General Procedure

Saturated aqueous solutions of hydroxylamine hydrochloride and potassium carbonate were added to a solution of *p*-substituted benzaldehyde in methanol. The reaction mixture was heated until 100% conversion of the benzaldehyde (TLC monitoring) was reached. The solvents were evaporated and the crude product was purified by column chromatography and crystallization. Compound **1a** was extracted from the reaction mixture with toluene and purified by distillation under reduced pressure. Identity of all the prepared compounds was confirmed by ^{1}H NMR spectra and melting points which were in all cases in accord with the published data. ^{13}C NMR spectra were recorded if they have not been published yet.

Benzaldoxime (**1a**): Yield 59%, b.p. 88 °C/0.8 × 10^2 Pa–92 °C/2.7 × 10^2 Pa (ref.[10] gives 92.5 °C/1.7 × 10^2 Pa). ^{1}H NMR ($CDCl_3$): 7.43 m, 3 H (H-3,4,5); 7.61 m, 2 H (H-2,6); 8.21 s, 1 H (CH=N) (ref.[11]).

p-Methylbenzaldoxime (**1b**): Yield 52%, m.p. 75–78 °C (chlorofom, petroleum ether) (ref.[12] gives 76–78 °C). ^{1}H NMR (DMSO-d_6): 2.49 s, 3 H (CH_3); 7.19 d, 2 H, J(3,2) = J(5,6) = 7.7 (H-3,5); 7.47 d, 2 H, J(2,3) = J(6,5) = 8.2 (H-2,6); 8.08 s, 1 H (CH=N); 11.12 s, 1 H (NOH) (ref.[13]).

p-(Trifluoromethyl)benzaldoxime (**1c**): Yield 58%, m.p. 98–101 °C (toluene, petroleum ether) (ref.[14] gives 101–102 °C). ^{1}H NMR (DMSO-d_6): 7.75 d, 2 H, J(3,2) = J(5,6) = 8.3 (H-3,5); 7.81 d, 2 H, J(2,3) = J(6,5) = 8.2 (H-2,6); 8.25 s, 1 H (CH=N); 11.64 s, 1 H (NOH) (ref.[15]). ^{13}C NMR (DMSO-d_6): 123.7 q, $^1J_{CF}$ = 272.6 (CF_3); 125.6 q, $^3J_{CF}$ = 3.8 (C-3,5); 127.1 s (C-2,6); 129.1 q, $^2J_{CF}$ = 32.5 (C-4); 137.2 s, (C-1); 147.2 s, (CH=N). ^{19}F NMR (DMSO-d_6): –61.1 (CF_3).

p-Fluorobenzaldoxime (**1d**): Yield 55%, m.p. 85–87 °C (water, ethanol) (ref.[16] gives 86–88 °C). ^{1}H NMR (DMSO-d_6): 7.23 m, 2 H (H-3,5); 7.63 m, 2 H (H-2,6); 8.14 s, 1 H (CH=N) (ref.[15]); 11.24 s, 1 H (NOH). ^{13}C NMR (DMSO-d_6): 115.6 d, $^2J_{CF}$ = 21.8 (C-3,5); 128.4 d, $^3J_{CF}$ = 8.4 (C-2,6); 129.6 s (C-1); 146.9 s (CH=N); 162.5 d, $^1J_{CF}$ = 246.2 (C-4). ^{19}F NMR (DMSO-d_6): –111.3 (F-4).

p-Chlorobenzaldoxime (**1e**): Yield 61%, m.p. 109–112 °C (chloroform, petroleum ether) (ref.[12] gives 108–109 °C). ^{1}H NMR (DMSO-d_6): 7.46 d, 2 H J(3,2) = J(5,6) = 8.3 (H-3,5); 7.60 d, 2 H, J(2,3) = J(6,5) = 8.2 (H-2,6); 8.14 s, 1 H (CH=N); 11.36 s, 1 H (NOH) (ref.[15]).

p-Bromobenzaldoxime (**1f**): Yield 66%, m.p. 106 °C (petroleum ether, ethanol) (ref.[17] gives 108 °C). ^{1}H NMR (DMSO-d_6): 7.53 d, 2 H, J(3,2) = J(5,6) = 8.2 (H-3,5); 7.58 d, 2 H, J(2,3) = J(6,5) = 8.8 (H-2,6); 8.13 s, 1 H (CH=N); 11.39 s, 1 H (NOH) (ref.[18]). ^{13}C NMR(DMSO-d_6): 122.4 (C-4); 128.3 (C-2,6); 131.7 (C-3,5); 132.3 (C-1); 147.2 (CH=N).

p-Methoxybenzaldoxime (**1g**): Yield 55%, m.p. 129–132 °C (petroleum ether, toluene) (ref.[19] gives 133 °C). ^{1}H NMR (DMSO-d_6): 3.77 s, 3 H (OCH_3); 6.95 d, 2 H, J(3,2) = J(5,6) = 8.2 (H-3,5); 7.52 d, 2 H, J(2,3) = J(6,5) = 8.3 (H-2,6); 8.07 s, 1 H (CH=N); 11.60 s, 1 H (NOH) (ref.[20]).

p-(Dimethylamino)benzaldoxime (**1h**). Yield 65%, m.p. 143–144 °C (water, ethanol) (ref.[21] gives 144 °C). ^{1}H NMR (DMSO-d_6): 2.92 s, 6 H ($N(CH_3)_2$); 6.69 d, 2 H, J(3,2) = J(5,6) = 9.3

(H-3,5); 7.39 d, 2 H, *J*(2,3) = *J*(6,5) = 8.8 (H-2,6); 7.96 s, 1 H (CH=N); 11.60 s, 1 H (NOH) (ref.[22]).

p-(Carboxymethyl)benzaldoxime (**1i**). Yield 58%, m.p. 119–122 °C (petroleum ether, toluene) (ref.[23] gives 120–121 °C). ^{1}H NMR (DMSO-d_6): 3.85 s, 3 H ($COOCH_3$); 7.73 d, 2 H, *J*(3,2) = *J*(5,6) = 7.7 (H-3,5); 7.97 d, 2 H, *J*(2,3) = *J*(6,5) = 8.2 (H-2,6); 8.23 s, 1 H (CH=N); 11.60 s, 1 H (NOH) (ref.[24]).

p-Cyanobenzaldoxime (**1j**). Yield 52%, m.p. 175–177 °C (water, ethanol) (ref.[25] gives 174–176 °C). ^{1}H NMR (DMSO-d_6): 7.76 d, 2 H, *J*(3,2) = *J*(5,6) = 8.2 (H-3,5); 7.83 d, 2 H, *J*(2,3) = *J*(6,5) = 8.2 (H-2,6); 8.22 s, 1 H (CH=N); 11.77 s, 1 H (NOH) (ref.[25]). ^{13}C NMR (DMSO-d_6): 111.5 (C-4); 118.8 (CN); 127.1 (C-2,6); 132.7 (C-3,5); 137.7 (C-1); 147.2 (CH=N).

p-Nitrobenzaldoxime (**1k**). Yield 59%, m.p. 128–130 °C (water, ethanol) (ref.[26] gives 129–134 °C). ^{1}H NMR (DMSO-d_6): 7.85 d, 2 H, *J*(2,3) = *J*(6,5) = 8.3 (H-2,6); 8.24 d, 2 H, *J*(3,2) = *J*(5,6) = 8.8 (H-3,5); 8.29 s, 1 H (CH=N); 11.86 s, 1 H (NOH) (ref.[27]).

In all cases, only one set of signals was observed in ^{1}H NMR spectra thus giving evidence of the isomeric uniformity of the prepared oximes.

Determination of p$K_{a,oxime}$

The p$K_{a,oxime}$ values of benzaldoximes **1a**–**1k** were determined spectrophotometrically using the standard procedure[28]. The benzaldoximes were titrated with sodium hydroxide at 35 °C in 10% (v/v) aqueous dioxane. The p$K_{a,oxime}$ values were calculated from Eq. (*1*)

$$A = \frac{A_{AH} K_{a,oxime} + A_{A^-} 10^{-pH}}{K_{a,oxime} + 10^{-pH}} \qquad (1)$$

using the absorbance *A*–pH dependences at two wavelengths (at the maxima of =N–OH and =N–O$^{(-)}$ forms) by non-linear regression. In Eq. (*1*), A_{AH} and A_{A^-} stand for absorbance of the non-dissociated and completely dissociated oxime solution, respectively.

Kinetic Measurements

Buffered solutions of oximes **1a**–**1k** in 10% (v/v) aqueous dioxane were prepared directly in the spectrophotometric cell. The concentration of biological buffers (HEPES (pH 7.8), HEPPS (pH 8.3), CHES (pH 9.3), CAPS (pH 10.3 and 10.8)) in the cell was 0.05 mol l^{-1}. No changes in pH were observed throughout the kinetic runs. The reactions were performed at constant temperature of 35 ± 0.1 °C. The reactions were initiated by injecting 2.0 × 10^{-3} mol l^{-1} solution of the PNPA substrate in acetonitrile into the spectrophotometric cell containing 2 ml of buffered solution of the catalyst (20 µl in all the cases; the resulting concentration of the substrate was 2.0 × 10^{-5} mol 1^{-1}).

For each of the benzaldoximes, the measurement of the observed rate constant k_{obs} was carried out in the above-mentioned buffers in the concentration range of added benzaldoxime, c_{oxime}, from 0 to 4.00 × 10^{-3} mol l^{-1}. The observed pseudo-first order rate constants were obtained by non-linear regression from the time dependences of absorbance at 400 nm (maximum of the *p*-nitrophenoxide anion absorption) using Origin 6.1 software[29].

The following values of the rate constant k_{buffer} of the PNPA cleavage (in s^{-1}) were obtained in buffered solutions in the absence of benzaldoximes: pH 7.8 (HEPES), k_{buffer} = (6.55 ± 0.17) × 10^{-5}, pH 8.3 (HEPPS), k_{buffer} = (8.27 ± 0.01) × 10^{-5}, pH 9.3 (CHES), k_{buffer} = (3.85 ±

0.01) × 10^{-4}, pH 10.3 (CAPS), k_{buffer} = (2.82 ± 0.03) × 10^{-3}, and pH 10.8 (CAPS), k_{buffer} = (7.55 ± 0.18) × 10^{-3}.

Mathematical-Statistical Treatment of the Experimental Data

For the mathematical-statistical modelling of the observed rate constant, k_{obs}, dependence on analytical concentration of the corresponding benzaldoxime, c_{oxime}, pH, and the buffer used, the weighted non-linear regression with the weights $1/k_{obs}$ was adopted. This procedure was chosen because the k_{obs} values changed with pH by up to 4 orders of magnitude, whereas the addition of benzaldoxime changed the k_{obs} value by 1 order of magnitude maximally. The calculations were always carried out with all the experimental k_{obs} values obtained by measurements at all pH values and all concentrations of the given benzaldoxime. The calculations used the experimental values of dissociation constants $K_{a,oxime}$ of benzaldoximes and experimental values of observed rate constants k_{buffer} obtained by measuring the PNPA cleavage in the absence of benzaldoxime under otherwise identical conditions. The results were statistically evaluated, the statistically insignificant rate constants in kinetic models were omitted and the calculation was repeated. The criteria for selection of the most appropriate model involved the residual standard deviation and positive values of rate and/or equilibrium constants as the optimized parameters. The calculation of correlation equations parameters for interpretation of substituent effects used the linear and non-linear regression depending on the type of regression model; the substituent constants were taken from literature[30,31]. The calculations in this section were carried out using the OPgm program[32].

RESULTS AND DISCUSSION

The interpretation of the role of benzaldoximes **1a**–**1k** in the cleavage of PNPA adopted three mutually complementary approaches – measurement of dissociation constants, modelling of kinetic dependences, and evaluation of substituent effects.

Effect of Substitution on Dissociation Constants of Benzaldoximes

Table I presents the dissociation constants p$K_{a,oxime}$ of benzaldoximes **1a**–**1k** measured in 10% (v/v) aqueous dioxane at 35 °C.

The substituent effects were evaluated with the use of usual correlation equations. The Hammett equation[33] for the benzaldoximes studied reads as follows:

$$\log K_{a,oxime} = -(10.95 \pm 0.02) + (0.910 \pm 0.045)\sigma_p \,, \qquad (2)$$

$$n = 11,\ r = 0.989,\ s = 0.061,\ F(1,9) = 418 \,,$$

where n is the number of experimental values, r is pair correlation coefficient, s is residual standard deviation, and F is Fisher–Snedecore criterion.

The application of the Yukawa–Tsuno equation[34] gives:

$$\log K_{a,oxime} = -(10.95 \pm 0.03) + (0.913 \pm 0.050)[\sigma_p + (0.03 \pm 0.16)(\sigma_p^- - \sigma_p)] , \quad (3)$$

$$n = 11,\ R = 0.989,\ s = 0.065,\ F(2,8) = 186 ,$$

where n, s, and F have the above-mentioned meanings and R is multiple correlation coefficient.

As it can be seen from Eq. (*3*), the term r is statistically insignificant. The separation of effects adopting the constants that describe the inductive (σ_I) and mesomeric (σ_R) effects of substituents results in the correlation equation of the following form:

$$\log K_{a,oxime} = -(10.95 \pm 0.06) + (0.872 \pm 0.133)\sigma_I + (1.226 \pm 0.123)\sigma_R , \quad (4)$$

$$n = 11,\ R = 0.978,\ s = 0.093,\ F(2,8) = 88.9 .$$

For comparison, we also give the results of application of Alternative Interpretation of Substituent Effects (AISE)[31] in the form:

TABLE I
The $pK_{a,oxime}$ values of benzaldoximes **1a**–**1k** in 10% (v/v) aqueous dioxane at 35 °C calculated from Eq. (*1*), their standard deviations $s(pK_{a,oxime})$ and numbers of experimental points n used in calculation of the K_a

X	$pK_{a,oxime}$	$s(pK_{a,oxime})$	n	X	$pK_{a,oxime}$	$s(pK_{a,oxime})$	n
H	11.01	0.02	15	OCH_3	11.16	0.02	16
CH_3	11.05	0.03	18	$N(CH_3)_2$	11.56	0.04	15
CF_3	10.51	0.02	17	$COOCH_3$	10.48	0.01	15
F	10.96	0.02	15	CN	10.27	0.01	15
Cl	10.66	0.01	17	NO_2	10.28	0.02	16
Br	10.79	0.02	17				

$$\log K_{a,oxime} = -(10.29 \pm 0.07) + (1.296 \pm 0.111)_{(I)}[\sigma^i - (0.553 \pm 0.045)] +$$

$$(2.727 \pm 0.268)_{(N)}[\sigma^i - (0.553 \pm 0.045)] + (0.665 \pm 0.279)_{(E)}[\sigma^i - (0.553 \pm 0.045)] , \quad (5)$$

$$n = 11,\ R = 0.991,\ s = 0.069,\ F(4,6) = 81.9 ,$$

where the subscripts (I), (N), and (E) denote the reaction constants for the substituents of class I (inductive effect), class II (inner nucleophiles), and class III (inner electrophiles), respectively, according to AISE. The results presented show that the dependences of log $K_{a,oxime}$ on substituent constants are close to each other except for Eq. (*4*), based on the separation of substituent effects. The Hammett equation (*2*) is fulfilled within its usual validity for dissociation equilibria[30]. The value of the reaction constant in the Hammett equation is higher than expected for the given distance between the substituent and the reaction centre. Hence, the substituent effects are only slightly weakened by their transmission through the grouping –CH=N–O–. The transmission coefficient ε is approximately equal to 0.91, being practically identical with that of grouping –CH=CH– (ε = 0.89 (ref.[35])). The statistically insignificant value of parameter *r* in the Yukawa–Tsuno equation indicates that there is no direct conjugation between the reaction centre and substituent, and this fact is also confirmed by the low value of reaction constant ρ_E, expressing the sensitivity to inner electrophiles according to AISE. Obviously, the reason lies in the preferential localization of electrons in the area of grouping –CH=N–$O^{(-)}$ possessing two electronegative atoms simultaneously with efficient stabilization of this anion by solvent and other effects[6b].

Kinetic Model

Both the published results[1a,1d,3d,4a] and the measurements carried out in this work show a distinct catalytic effect of the substituted benzaldoximes added to the reaction mixture and influence of pH. This fact is clearly illustrated on example of the parent compound **1a** depicted in Fig. 1. All other compounds **1b**–**1k** afforded the same type of the k_{obs} *vs* c_{oxime} plot.

At higher pH values, the observed rate constants k_{obs} are markedly increased in the region of low analytical concentrations of benzaldoxime, c_{oxime}, which changes into a linear dependence in the region of higher analytical concentrations of benzaldoxime. At lower pH values the dependence

is linear in the whole range of the benzaldoxime analytical concentrations used. From this finding it can be deduced that the dissociated form of oxime (*i.e.* oximate) is responsible for the increase of the observed rate constant: the actual concentration of oximate in the reaction mixture increases with increasing pH. The distinct increase in the observed rate constants at lower oxime concentration and higher pH indicates a change in the rate-limiting step associated with formation of some intermediate whose actual concentration does not change any more on increasing the analytical concentration of benzaldoxime, and/or it can indicate the existence of a side equilibrium. On the basis of the considerations given, a number of probable kinetic models have been suggested and their suitability for interpretation of our experimental data was evaluated according to the criterion of the lowest residual standard deviation and analysis of residua. The kinetic models analyzed differed markedly in these factors, but some of them were statistically identical and thus kinetically indistinguishable.

The most suitable kinetic model for the reactions of compounds **1a**–**1k** corresponds to the mechanism given in Scheme 1.

In the first fast reversible reaction step, oximate reacts with PNPA (rate constant k_1) to give the tetrahedral intermediate THI. The latter is either decomposed back to educts (k_{-1}), or reacts further in the rate-limiting step (k_2) to give the substitution product, *i.e. O*-acetylated benzaldoxime[1a], or in an equilibrium reaction with water produces the conjugated acid THIH and

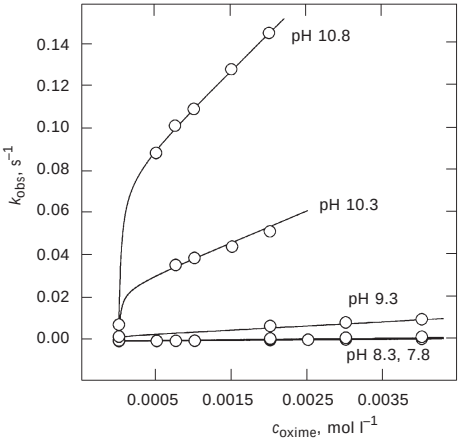
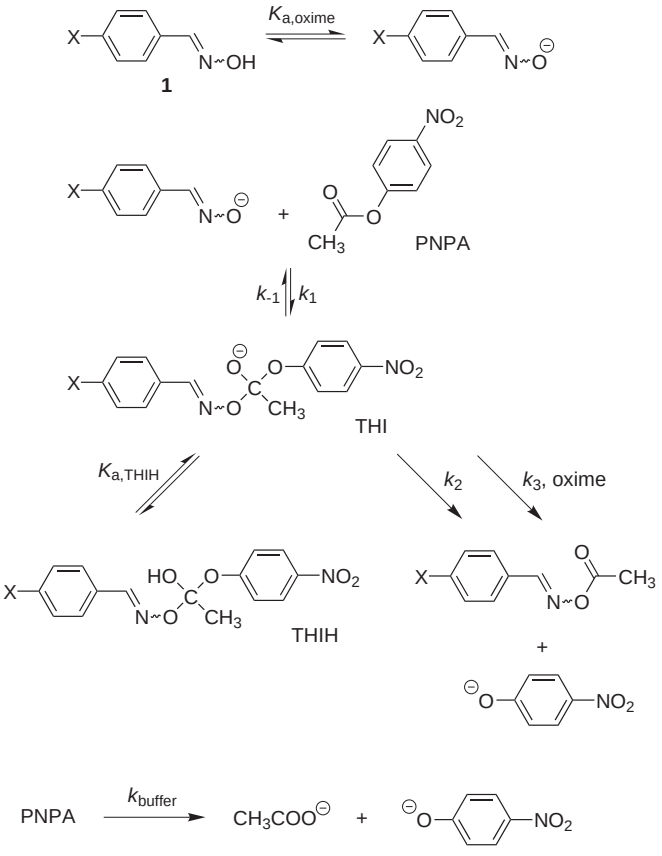


FIG. 1

Dependence of the pseudo-first order rate constant, k_{obs} (s^{-1}) of the PNPA reaction with benzaldoxime (**1a**) in 10% (v/v) aqueous dioxane at 35 °C on the oxime concentration, c_{oxime} (mol l^{-1}) and pH. Circles, experimental values; lines, calculated from Eq. (*13*) using Eq. (*10*)



SCHEME 1

hydroxide ion (dissociation constant $K_{a,THIH}$). In addition, the decomposition of THI to the substitution products is subject to general acid catalysis by the oxime (proton transfer on the oxygen of the leaving *p*-nitrophenolate, catalytic constant k_3). If k_1, $k_{-1} > k_2$, k_1, $k_{-1} > k_3$ and if the values of dissociation constant $K_{a,THIH}$ are low, the actual concentration of THI in the solution is negligible compared with the other intermediates. Assuming the equilibrium between PNPA, oximate, and THI (Eq. (*6*)) and using the dissociation constants $K_{a,oxime}$ and $K_{a,THIH}$ the actual concentrations of PNPA (Eq. (*7*)) and THI (Eq. (*8*)) under the experimental conditions used can be expressed as follows:

$$\frac{k_1}{k_{-1}} = \frac{[\mathrm{THI}]}{[\mathrm{oximate}][\mathrm{PNPA}]}, \qquad (6)$$

$$[\mathrm{PNPA}] = \frac{K_{\mathrm{THIH}}}{K_{\mathrm{THIH}} + [\mathrm{oxime}]} c_{\mathrm{PNPA}} \qquad (7)$$

and

$$[\mathrm{THI}] = \frac{K_{\mathrm{a,THIH}}[\mathrm{oxime}]}{[\mathrm{H}^+](K_{\mathrm{THIH}} + [\mathrm{oxime}])} c_{\mathrm{PNPA}} \,, \qquad (8)$$

where

$$K_{\mathrm{THIH}} = \frac{k_{-1} K_{\mathrm{a,THIH}}}{k_1 K_{\mathrm{a,oxime}}} \qquad (9)$$

and c_{PNPA} is analytical concentration of PNPA at a given time. The actual concentrations of oxime and oximate depend on pH according to the following equations:

$$[\mathrm{oxime}] = \frac{[\mathrm{H}^+]}{K_{\mathrm{a,oxime}} + [\mathrm{H}^+]} c_{\mathrm{oxime}} \qquad (10)$$

and

$$[\mathrm{oximate}] = \frac{K_{\mathrm{a,oxime}}}{K_{\mathrm{a,oxime}} + [\mathrm{H}^+]} c_{\mathrm{oxime}} \,, \qquad (11)$$

where $K_{\mathrm{a,oxime}}$ is the dissociation constant of the respective benzaldoxime and c_{oxime} is its analytical concentration. This model, respecting the decomposition of PNPA in the buffer alone, leads to the following expression for the reaction rate:

$$\text{reaction rate} = k_{\mathrm{buffer}}[\mathrm{PNPA}] + k_2[\mathrm{THI}] + k_3[\mathrm{THI}][\mathrm{oxime}] \,, \qquad (12)$$

where k_{buffer} is the observed rate constant of decomposition of PNPA without added benzaldoxime. After introducing [PNPA] and [THI] from Eqs (*7*) and (*8*) into Eq. (*12*) we obtain for observed rate constant Eq. (*13*):

$$k_{\mathrm{obs}} = \frac{k_{\mathrm{buffer}} K_{\mathrm{THIH}}[\mathrm{H}^+] + k_2 K_{\mathrm{a,THIH}}[\mathrm{oxime}] + k_3 K_{\mathrm{a,THIH}}[\mathrm{oxime}]^2}{[\mathrm{H}^+](K_{\mathrm{THIH}} + [\mathrm{oxime}])} \,. \qquad (13)$$

The calculated course of the dependence of k_{obs} on analytical concentration of benzaldoxime, c_{oxime}, and on pH for compound **1a** according to Eq. (*13*) with the use of Eq. (*10*) is represented by the curve in Fig. 1. A similarly close coincidence of experimental points with calculated curves was obtained also for other substitution derivatives of benzaldoxime **1b**–**1k**.

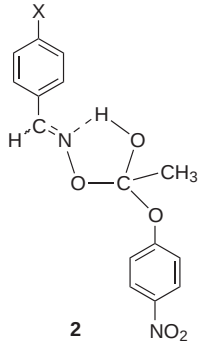
The rate and equilibrium constants calculated by weighted non-linear regression according to Eq. (*13*) are given in Table II.

The existence of a stable tetrahedral intermediate under suitable reaction conditions is typical for reactions of esters (including of *p*-nitrophenyl acetate) with amines[36–41], phenolates[42,43] and other reagents[44,45] that are both good nucleophiles and good nucleofuges, so the equilibrium between the educts and THI is established rapidly. It is not surprising in this context that we have found the existence of a stable tetrahedral intermediate for oximates as α-nucleophiles. The easy formation and the stability of tetrahedral intermediates are explained in literature by formation of hydrogen bond[38,40,44] or by non-bonding interactions[40,46]. From our kinetic scheme it follows that there exists equilibrium between the educts and non-ionized tetrahedral intermediate THIH. The latter can be stabilized either by a hydrogen bond between hydroxyl group and the free electron pair at nitrogen atom of oxime goup (structure **2**), or by non-bonding interaction between the lone pairs at oxygen atom in hydroxy group and the electron-deficient carbon atom (structure **3**).

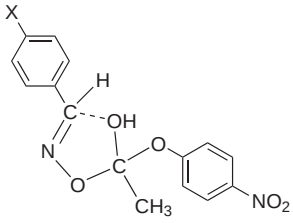
TABLE II

The values of constant K_{THIH} (mol l^{-1}) in Eq. (*8*) and values of constants $k_2K_{a,THIH}$ (s^{-1}) and $k_3K_{a,THIH}$ (s^{-1} l mol^{-1}) in Eq. (*11*) for the decomposition of PNPA in 10% (v/v) dioxane at 35 °C catalyzed by benzaldoximes **1a**–**1k**; the values were obtained by weighted non-linear regression from Eq. (*11*), *s* are weighted residual standard deviations and *n* are the numbers of observed rate constants k_{obs} used for calculation

X	$K_{THIH} \times 10^5$	$k_2K_{a,THIH} \times 10^{12}$	$k_3K_{a,THIH} \times 10^{10}$	$s \times 10^5$	*n*
H	2.34	1.25	8.82	1.475	27
CH_3	2.79	1.20	8.07	1.996	25
CF_3	3.90	1.63	18.5	2.425	27
F	2.47	1.68	7.44	2.160	27
Cl	3.52	1.25	10.9	0.695	22
Br	2.89	1.39	12.4	1.699	25
OCH_3	2.01	1.10	4.64	1.210	21
$N(CH_3)_2$	1.40	1.14	5.32	1.351	25
$COOCH_3$	3.77	1.61	20.9	1.755	27
CN	4.55	2.15	31.2	1.935	24
NO_2	5.35	1.96	42.2	3.800	19



2



3

The first kind of stabilization is more likely with regard to suitable geometry of the participating atoms. The hydrogen atom in the hydroxy group of THIH is expected to be relatively acidic. For example, literature[37] reports an estimate of $pK_a = 6.8$ for the protonated form of the tetrahedral intermediate resulting from the attack of 2,4-dinitrophenyl acetate with cyclic secondary amines. The species THIH probably exhibit higher $pK_{a,THIH}$ values, nevertheless sufficient for formation of the hydrogen bond mentioned.

Effect of Substitution on Rate and Equilibrium Constants in Kinetic Model

The evaluation of substituent effects on the rate and equilibrium constants in kinetic model was carried out with application of the Hammett equation, the Yukawa–Tsuno equation, the correlation equation based on separation of effects, and the correlation based on AISE. The *r* constant in the Yukawa–Tsuno equation was statistically insignificant in all the correlations, and AISE gave collinear dependences for all three types of substitution; therefore, the results of these calculations are not presented. The substituent effects were evaluated separately for the individual kinetically determinable equilibrium and rate constants. This procedure gave the corresponding reaction constants providing information about the elementary processes taking place, not only a single overall reaction constant, which can logically be considered anomalous[47].

The values of equilibrium constant K_{THIH} from Table II depend on the Hammett substituent constants σ_p as follows:

$$\log K_{THIH} = -(4.59 \pm 0.01) + (0.376 \pm 0.031)\sigma_p \,, \qquad (14)$$

$$n = 11,\ r = 0.970,\ s = 0.043,\ F(1,9) = 145 \,.$$

The correlation equation based on the separation of effects reads as follows:

$$\log K_{\mathrm{THIH}} = -(4.58 \pm 0.03) + (0.328 \pm 0.078)\sigma_{\mathrm{I}} + (0.527 \pm 0.072)\sigma_{\mathrm{R}} , \quad (15)$$

$$n = 11,\ R = 0.957,\ s = 0.055,\ F(2,8) = 43.7 .$$

According to the residual standard deviation, both dependences are relatively close.

According to Eq. (*9*), the reaction constant ρ(THIH) of the Hammett equation can be expressed as:

$$\rho(\mathrm{THIH}) = \rho(k_{-1}/k_1) + \rho(K_{\mathrm{a,THIH}}) - \rho(K_{\mathrm{a,oxime}}) . \quad (16)$$

After introducing the reaction constant $\rho(K_{\mathrm{a,oxime}})$ from Eq. (*2*) it is $\rho(k_{-1}/k_1) + \rho(K_{\mathrm{a,THIH}}) \cong 1.29$. As the value of $\rho(K_{\mathrm{a,THIH}})$ is obviously small and positive, it can be estimated that the $\rho(k_{-1}/k_1)$ value will be close to 1. The effect of substitution on the equilibrium between the oximate and PNPA, (k_{-1}/k_1), is somewhat larger than that on the equilibrium between oximate and proton ($K_{\mathrm{a,oxime}}$).

The values of constants $k_2K_{\mathrm{a,THIH}}$ from Table II depend on the Hammett substituent constants σ_{p} as follows:

$$\log k_2K_{\mathrm{a,THIH}} = -(11.87 \pm 0.02) + (0.195 \pm 0.037)\sigma_{\mathrm{p}} , \quad (17)$$

$$n = 11,\ r = 0.869,\ s = 0.051,\ F(1,9) = 27.7.$$

The correlation equation based on the separation of effects reads as follows:

$$\log k_2K_{\mathrm{a,THIH}} = -(11.90 \pm 0.03) + (0.257 \pm 0.064)\sigma_{\mathrm{I}} + (0.231 \pm 0.060)\sigma_{\mathrm{R}} , \quad (18)$$

$$n = 11,\ R = 0.912,\ s = 0.045,\ F(2,8) = 19.8 .$$

Also in this case the dependences are relatively close judging from the residual standard deviation. The reaction constants are small and, unexpectedly, have positive signs. The comparable magnitudes of constants ρ_{I} and ρ_{R} in Eq. (*18*) indicate low manifestation of mesomeric effects. As already stated, the reaction constant $\rho(K_{\mathrm{a,THIH}})$ is obviously small and positive.

Therefrom it can be concluded that the reaction constant $\rho(k_2K_{a,THIH})$ predominantly reflects the substitution effect on dissociation of THIH, the influence of substituents on decomposition of THI being negligible. In this case, no significant changes in electron density at the reaction centre take place during the decomposition of THI. This can be due to the small extent of splitting of the bond to nucleofuge in transition state of reaction, to general acid catalysis by water, and to efficient solvation of the leaving *p*-nitrophenoxide.

The values of constant $k_3K_{a,THIH}$ from Table II depend on the Hammett substituent constants σ_p as follows:

$$\log k_3K_{a,THIH} = -(9.03 \pm 0.03) + (0.674 \pm 0.074)\sigma_p \,, \qquad (19)$$

$$n = 11,\ r = 0.949,\ s = 0.102,\ F(1,9) = 81.9.$$

The correlation equation based on separation of effects reads as follows:

$$\log k_3K_{a,THIH} = -(9.00 \pm 0.58) + (0.583 \pm 0.113)\sigma_I + (1.000 \pm 0.105)\sigma_R \,, \quad (20)$$

$$n = 11,\ R = 0.974,\ s = 0.787,\ F(2,8) = 72.8 \,.$$

The values and signs of reaction constants confirm the presumption of participation of non-dissociated benzaldoxime as a general acid facilitating the splitting off of *p*-nitrophenoxide from the reaction centre.

CONCLUSION

Both the determined dissociation constants $K_{a,oxime}$ of the *p*-substituted benzaldoximes and the pseudo-first order rate constants k_{obs} of the PNPA cleavage with these oximes are affected by the substituents in *p*-position of the benzaldoxime. The observed substituent effects correlate with the Hammett and Yukawa–Tsuno equation as well as with the Alternative theory of substitution effects (AISE). Based on the obtained kinetic data, a plausible kinetic model of the PNPA cleavage by *p*-substituted benzaldoximes in buffered aqueous solutions was proposed. We have found the hitherto generally accepted kinetic model assuming the formation of the tetrahedral intermediate (THI) as the rate determining step is valid only if pH of the reaction mixture is lower than $pK_{a,oxime}$ of the oxime at least by 1–2 units. At higher pH values, the rate determinining step of the PNPA cleavage is decomposition of the tetrahedral intermediate THI.

Financial support for this work was provided by the Grant Agency of the Czech Republic (grant No. 303/01/1093) and the Ministry of Education, Youth and Sports of the Czech Republic (grant No. MSM 223100001). The authors thank Ms M. Kovandová for her technical assistance.

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