

# Influence of hydrogen bonds on acid-base properties and polarographic reduction of amide oximes

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The presence of hydrogen bonding between amide oximes and solvent was ascertained by infrared spectroscopy. On the basis of solvation of the functional groups, the changes in  $pK$  and half-wave potentials of the polarographic reduction due to substitution were cleared up. The dependence of  $pK$  on the reciprocal value of relative permittivity of solvent was investigated. A very good correlation between  $pK$  and  $^1H$ -n.m.r. spectra of the substances was observed.

С помощью ИК спектроскопии были обнаружены водородные связи амидоксимов с растворителем. На основании сольватации функциональной группы были объяснены изменения  $pK$  и потенциалов полуволны полярографического восстановления с замещением. Была исследована зависимость  $pK$  на обратном значении относительной пермиттивности растворителя. Обнаружена очень хорошая корреляция  $pK$  со спектрами  $^1H$ -ЯМР соединений.

The dependence of  $pK$  on the reciprocal value of relative permittivity of solvent may be derived on the basis of electrostatic considerations. Provided only electrostatic substrate—solvent interaction is effective, the theoretical relationships are in very good agreement with experiment on condition that they have been several times verified [1]. If the change of solvent is also accompanied by other than electrostatic effects, e.g. change in isomerization equilibrium [2] or change in solvation of substrate [3], these effects manifest themselves by deforming the relationship between  $pK$  and the reciprocal value of relative permittivity of solvent. The solvation of substrate also influences the half-wave potential of its polarographic reduction [4, 5]. This communication is concerned with the study of the solvation of amide oximes the isomerism of which is well-known [6—8].

## Experimental

Benzamide oxime (I) [9], *O*-methylbenzamide oxime (II) [10], *O*-ethylbenzamide oxime

(III) [9], *N*-phenylbenzamide oxime (IX) [11], *N,N*-diethylbenzamide oxime (XI) [12], *p*-nitrobenzamide oxime (XII) [13], *p*-chlorobenzamide oxime (XIII) [14], *p*-bromobenzamide oxime (XIV) [15], and *p*-methylbenzamide oxime (XV) [16] were prepared according to literature. Their melting points and content of C, H, N determined by elemental analysis are in agreement with literature.

*O*-Butylbenzamide oxime (IV) and *O*-benzylbenzamide oxime (V) were synthesized by alkylating substance I with 1-*n*-butyl iodide or benzyl chloride (both anal. grade reagents, Lachema, Brno) according to the method described in literature [9]. *N*-Alkylamide oximes were prepared by aminolysis of benzhydroxamic chloride [17] in ether. In this way, *N*-methylbenzamide oxime (VI), *N*-ethylbenzamide oxime (VII), *N*-benzylbenzamide oxime (VIII), and *N*-cyclohexylbenzamide oxime (X) were prepared. Substances VII and X were obtained in the form of chlorides, the others in the form of free bases. *m*-Methoxybenzamide oxime (XVI) and *p*-dimethylaminobenzamide oxime (XVII) were prepared by adding hydroxylamine to nitrile [18]. The results of analyses and melting points of these newly prepared substances are given in Table 1.

Table 1  
Characterization of the substances

Substance	Formula	<i>M</i>	Calculated/found			Yield %	M.p. °C
			% C	% H	% N		
IV	C <sub>11</sub> H <sub>16</sub> N <sub>2</sub> O	192.25	68.72	8.39	14.57	95	38—40
			68.57	8.10	14.63		
V	C <sub>14</sub> H <sub>14</sub> N <sub>2</sub> O	226.27	74.31	6.24	12.38	92	84—86
			74.45	6.35	12.42		
VI	C <sub>8</sub> H <sub>10</sub> N <sub>2</sub> O	150.18	63.98	6.71	18.66	65	153—154
			63.86	6.72	18.86		
VII	C <sub>9</sub> H <sub>13</sub> ClN <sub>2</sub> O	200.66	53.87	6.53	13.96	73	167—170
			53.80	6.43	13.94		
VIII	C <sub>14</sub> H <sub>14</sub> N <sub>2</sub> O	226.27	74.31	6.24	12.38	81	116—117
			74.48	6.41	12.59		
X	C <sub>13</sub> H <sub>19</sub> ClN <sub>2</sub> O	248.61	62.81	5.27	11.27	87	158—161
			62.69	5.23	11.07		
XVI	C <sub>8</sub> H <sub>10</sub> N <sub>2</sub> O <sub>2</sub>	166.17	57.82	6.07	16.86	73	103—104
			57.63	6.26	16.58		
XVII	C <sub>9</sub> H <sub>13</sub> N <sub>3</sub> O	179.21	60.31	7.31	23.45	60	160—161
			60.13	7.43	23.38		

### Electrochemical measurements

The pH values were measured as described earlier [4]. The p*K* values were calculated from the data obtained by titration by means of the relations presented in [4]. In this calculation, the activity coefficients were assumed to equal one. Polarographic measure-

ments were performed with  $1 \times 10^{-3}$  M solutions of the substances in 50% (by weight) ethanol. For polarographic recording, these solutions were mixed with equal volume of a buffer solution of the ionic strength  $0.5 \text{ mol dm}^{-3}$  prepared also in 50% (by weight) ethanol. The ionic strength was maintained constant with sodium perchlorate (Lachema, Brno) for improving the conductivity of solvent. The citrate, triethanolamine, and glycine buffer solutions used (Lachema, Brno) [3] as well as the polarographic equipment [4] were described earlier.

### Spectral measurements

The infrared spectra were taken on a spectrophotometer UR-20 (Zeiss, Jena). For these measurements, 5% solutions of the substances in chloroform, carbon tetrachloride, 1,4-dioxan, a chloroform—dioxan (1 1) or tetrachloromethane—dioxan (1 1) mixture and 0.4 cm cells were used.  $^1\text{H-n.m.r.}$  spectra were measured on a Varian T-60 instrument at  $34^\circ\text{C}$  using hexadeuterodimethyl sulfoxide and tetramethylsilane (5% w/v) as internal standards. The chemical shifts were read on a frequency counter and are given in the  $\delta$  scale.

### Results and discussion

Substance *I* exhibited intensive  $\nu(\text{O—H})$  absorption at  $3595 \text{ cm}^{-1}$  in chloroform and at  $3610 \text{ cm}^{-1}$  in carbon tetrachloride. The symmetric and asymmetric stretching  $\text{N—H}$  vibrations were in both solvents at  $3405$  and  $3510 \text{ cm}^{-1}$ , which is in harmony with literature [7, 8, 12]. Only one broad absorption band corresponding to the  $\text{O—H}$  and  $\text{N—H}$  bonds engaged in hydrogen bonding was found at  $3360 \text{ cm}^{-1}$  for substance *I* dissolved in mixed solvents containing dioxan or in pure dioxan.

Table 2

pK Values of the substances in water and mixed water—ethanol solvents  
Laboratory temperature, ionic strength  $\mu = 0.5 \text{ mol dm}^{-3}$

Substance	Weight % of ethanol in mixture			
	0	10	30	50
<i>I</i>	4.98	4.73	4.68	4.57
<i>II</i>	3.81	3.65	3.42	3.14
<i>III</i>	—	3.86	3.74	3.44
<i>IV</i>	—	—	3.61	3.24
<i>V</i>	—	—	—	3.10
<i>VI</i>	5.54	5.37	5.33	5.02
<i>VII</i>	5.49	5.30	5.23	4.91
<i>VIII</i>	—	—	—	4.29
<i>IX</i>	—	—	—	3.10
<i>X</i>	—	—	5.03	4.66
<i>XI</i>	5.71	5.58	5.38	4.90

The  $pK$  values given in Tables 2 and 3 were found by titration and represent mean values of four measurements. Their dependence on the reciprocal value of relative permittivity of solvent [19] is represented in Fig. 1. It is evident that alkylation of amide oximes on the oxygen atom shifts their  $pK$  to smaller values. It follows from these infrared spectra that amide oximes form strong hydrogen bonds with electron-donating atoms of the solvent through their hydroxyl group. Hence, the  $pK$  shift which is due to alkylation of the hydroxyl group is comprehensible. The induction effect of the electron pair which forms the hydrogen bond with the hydroxyl group of amide oximes is transferred through oxygen to the oxime nitrogen and increases its electron density. Therefore the derivatives containing a hydroxyl group are usually more basic than the *O*-alkylated derivatives the alkoxy group of which does not exhibit electron-withdrawing properties. A similar effect was previously observed with the derivatives of hydroxylamine [4]. The change in  $pK$  due to alkylation on oxygen is approximately equal for hydrox-

Table 3

$pK$  Values of the substances in 50% (w/w) ethanol  
Laboratory temperature, ionic strength  $\mu = 0.5 \text{ mol dm}^{-3}$

Substance	XII	XIII	XIV	XV	XVI	XVII
$pK$	3.02	4.03	3.95	4.74	4.35	5.80

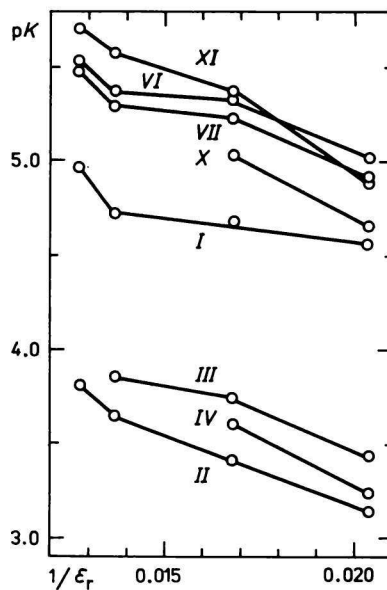
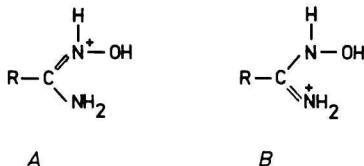


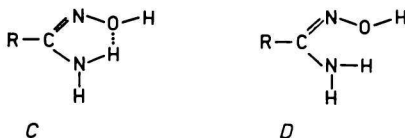
Fig. 1.  $pK$  Value of amide oximes as a function of reciprocal value of relative permittivity of the solvent.

Laboratory temperature, ionic strength  $\mu = 0.5$ .

ylamines and amide oximes. Therefore we may suppose that mesomeric formula *A* describes the structure of protonated amide oximes better than formula *B*



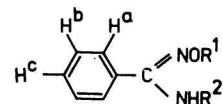
The alkylation on nitrogen brings about a slight increase in  $pK$  and the substitution of benzyl for hydrogen reduces the  $pK$  value. Similar effects have been also revealed with thioamides [5, 20]. They correspond to the solvation of hydrogen in the N—H group which has been confirmed by infrared spectra. Further alkylation on nitrogen shifts  $pK$  again into more alkaline region which may be demonstrated by comparing the values found for substance *VII* with those found for substance *XI*. The change in the  $pK$  value of substance *XI* caused by the change of solvent is somewhat greater than that of hydroxylamines [4], but it is substantially smaller than that of benzoic acid [2]. Only in case of substance *XI*,  $pK$  is approximately a linear function of the reciprocal value of relative permittivity of solvent while it considerably changes with transition from aqueous medium to 10% ethanol in case of other amide oximes. This effect may be related to splitting of the intramolecular hydrogen bond of structure *C* [6] by action of the solvent which is accompanied by simultaneous shift of the equilibrium in the sense of structure *D*



At the same time, it may be expected that the abolition of the intramolecular hydrogen bond in structure *C* and further solvation of the  $\text{NH}_2$  group of structure *D* has influence on  $pK$ . If we adopt this idea, we can comprehend the change in  $pK$  due to alkylation of the second hydrogen in the  $\text{NH}_2$  group. The induction effect of alkyl is not expected to be distinct because the induction effects are poorly transferred through nitrogen of the amide group [21, 22]. The changes in  $pK$  produced by substitution in the aromatic ring (Table 3) fulfil the Hammett equation with the constant  $\rho = 2.02$ . This value is higher than the values corresponding to carboxylic acids of the benzene series, but the  $pK$  value of aniline ions, too, is affected by substitution more than the  $pK$  value of phenols [23].

The chemical shifts corresponding to hydrogen atoms of the investigated compounds are presented in Table 4. The chemical shifts of hydrogen atoms in the

Table 4

<sup>1</sup>H-N.m.r. spectral data of the substituted benzamide oximes

Substance	R <sup>1</sup>	R <sup>2</sup>	H <sup>a</sup>	H <sup>b</sup> H <sup>c</sup>	NHR <sup>2</sup>	NH <sub>2</sub>	NOH	R <sup>1</sup>	R <sup>2</sup>
I <sup>a</sup>	H	H	7.1—7.5 (3H) 7.5—7.8 (2H)	—	5.75	9.57	—	—	—
II	CH <sub>3</sub>	H	7.73 dd	7.35—7.50 m	—	6.05 s	—	3.82 s (CH <sub>3</sub> )	—
III	C <sub>2</sub> H <sub>5</sub>	H	7.73 dd	7.33—7.50 m	—	5.96 s	—	4.06 q (CH <sub>2</sub> —CH <sub>3</sub> ) 1.27 t (CH <sub>2</sub> —CH <sub>3</sub> )	—
IV	C <sub>4</sub> H <sub>9</sub>	H	7.73 dd	7.33—7.50 m	—	5.95 s	—	1.16—1.83 m (CH <sub>2</sub> ) <sub>2</sub> 3.99 t (CH <sub>2</sub> ), 0.94 t (CH <sub>3</sub> )	—
V	CH <sub>2</sub> Ph	H	7.74 dd	7.24—7.55 m	—	6.13 s	—	7.60 m (CH <sub>2</sub> —Ph) 5.06 s (CH <sub>2</sub> —Ph)	—
VI	H	CH <sub>3</sub>	7.41 m	5.73 q	—	9.56 s	—	2.59 d (CH <sub>3</sub> )	—
VII	H	C <sub>2</sub> H <sub>5</sub>	7.40 m	5.65 t	—	9.66 s	—	2.98 k (CH <sub>2</sub> —CH <sub>3</sub> ) 0.95 t (CH <sub>2</sub> —CH <sub>3</sub> )	—
VIII	H	CH <sub>2</sub> Ph	7.40 m	6.29 t	—	9.81 s	—	7.23 m (CH <sub>2</sub> —Ph) 4.20 d (CH <sub>2</sub> —Ph)	—
IX	H	Ph	7.37 m	8.23 s	—	10.52 s	—	6.57—7.26 m (Ph)	—
X	H	C <sub>6</sub> H <sub>11</sub>	7.43 m	5.35 d	—	9.80 s	—	0.87—1.96 m (C <sub>6</sub> H <sub>11</sub> )	—
XI	H	(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub>	7.38 m	—	—	8.87 s	—	3.03 q (CH <sub>2</sub> —CH <sub>3</sub> ) 1.01 t (CH <sub>2</sub> —CH <sub>3</sub> )	—

a) Taken from literature [27]; b) substance XI.

s — singlet, d — doublet, dd — doublet of doublets, t — triplet, m — multiplet, q — quartet, k — quintet.

NH and NOH groups of the *N*-substituted derivatives differ appreciably while the signals of the NH<sub>2</sub> protons in the *O*-substituted derivatives do not practically change owing to substitution. The chemical shifts corresponding to heteroatomic hydrogen cannot be correlated with the Taft  $\sigma^*$  and  $E_s$  constants of the substituents. It is interesting that a significant correlation between the chemical shifts of hydrogen atoms in the NOH and NH groups and the dissociation constants measured in 50% ethanol exists for the *N*-substituted derivatives. This correlation is governed by the equation  $\text{p}K = 16.12 - 0.99 \delta_1(\text{NOH}) - 0.32 \delta_2(\text{NH})$ , the correlation coefficients being  $r_1$  0.953 and  $r_2$  0.955 ( $n = 6$ , 98% level of probability). The change in  $\text{p}K$  produced by substitution is accompanied by a change in the position of signals of hydrogen atoms in the NOH and NH groups. But the changes in position of the signals of hydrogen atom in the NOH group are more significant. Therefore it seems that the protonation of amide oximes takes place preferentially on the nitrogen atom of the oxime group (mesomeric formula A).

Amide oximes are reduced in two-electron reduction at the dropping mercury electrode to give amidines [24]. Provided the pH value of solution is smaller than  $\text{p}K$ , the protonated form of amide oxime is reduced and the half-wave potentials are only slightly dependent on pH. Provided the pH value of solution is greater than  $\text{p}K$  of amide oxime, a formation of the protonated form owing to recombination precedes its reduction. In this case, the half-wave potential is significantly dependent on the pH value of solution [25, 26]. In neutral region, the reduction wave of amidines [24—26] appears behind the wave of amide oximes. Our results are in agreement with this information from literature (Table 5). For the discussion of the influence of solvation on half-wave potential of polarographic reduction, it is suited to choose such medium where the reduction mechanism of the complete series studied is equal, *i.e.* a medium with pH smaller (in 50% ethanol) than 3.10 or greater than 5.02 because all substances listed in Table 2 are in equal state in this case. The relationship between solvation and recombination effects is not known and for this reason, the discussion should be limited to the region of lower pH values. It is obvious from the measured data (Table 5) that the most negative half-wave potential belongs to substance *I*. The alkylation on oxygen or nitrogen brings about equal shifts of the half-wave potential to more positive values in the range of experimental errors while the substitution of alkyls for both hydrogen atoms in the NH<sub>2</sub> group results in further shift in half-wave potential to more positive values (*cf.*  $E_{1/2}$  of *I*, *III*, and *XI*). An appreciable change in half-wave potential was attained by substituting phenyl in the functional group (*cf.*  $E_{1/2}$  of *I* and *IX*). Alkyl and aryl have equal effect on reduction. This may be comprehended only if it is assumed that the solvated molecules of the protonated form of amide oxime are subject to reduction. Then owing to substitution of alkyl or aryl for hydrogen, the functional group loses its ability to form hydrogen bonds. The induction effect of the electron pairs which have participated in hydrogen bonding

Table 5

Half-wave potentials against SCE and currents of polarographic reduction of the  $5 \times 10^{-4}$  M solutions of amide oximes in 50% (w/w) ethanol at laboratory temperature

Substance	pH 2.45		pH 3.09		pH 4.03		pH 5.22		pH 5.94	
	$-E_{1/2}$ , V	$i_d$ , $\mu$ A	$-E_{1/2}$ , V	$i_d$ , $\mu$ A	$-E_{1/2}$ , V	$i_d$ , $\mu$ A	$-E_{1/2}$ , V	$i_d$ , $\mu$ A	$-E_{1/2}$ , V	$i_d$ , $\mu$ A
I	—	—	1.15	2.6	1.16	2.4	1.21	2.4	1.25	2.3
II	1.04	2.9	1.05	2.6	1.11	2.8	1.48 <sup>a</sup>	6.6 <sup>a</sup>	1.50 <sup>a</sup>	4.3 <sup>a</sup>
III	1.06	2.7	1.07	2.4	1.11	2.6	1.48 <sup>a</sup>	6.6 <sup>a</sup>	1.50 <sup>a</sup>	3.0 <sup>a</sup>
IV	1.05	5.3 <sup>b</sup>	1.05	3.7 <sup>b</sup>	1.08	2.4	1.19	2.5	1.26	1.9
V	1.02	4.4 <sup>b</sup>	1.02	4.1 <sup>b</sup>	1.05	2.3	1.47 <sup>a</sup>	8.2 <sup>a</sup>	1.50 <sup>a</sup>	3.3 <sup>a</sup>
VI	—	—	1.08	2.4	1.07	2.5	1.18	2.4	1.25	1.7
VII	—	—	1.06	2.3	1.09	2.5	1.48 <sup>a</sup>	6.4 <sup>a</sup>	1.50 <sup>a</sup>	3.1 <sup>a</sup>
VIII	0.98	1.9	0.98	2.2	1.02	2.2	1.12	2.2	1.22	1.9
IX	0.88	2.1	0.90	2.1	0.95	2.1	1.48 <sup>a</sup>	6.4 <sup>a</sup>	1.50 <sup>a</sup>	3.0 <sup>a</sup>
X	—	—	1.08	2.4	1.07	2.5	1.12	2.4	1.15	2.4
XI	0.92	2.2	0.97	2.2	0.99	2.5	1.15	2.6	1.15	2.5
									1.56 <sup>a</sup>	3.7 <sup>a</sup>
									1.58 <sup>a</sup>	4.9 <sup>a</sup>
									1.11	2.1
									1.57 <sup>a</sup>	3.7 <sup>a</sup>
									1.09	1.8
									1.31 <sup>a</sup>	4.5 <sup>a</sup>
									1.17	2.0
									1.60 <sup>a</sup>	4.4 <sup>a</sup>
									1.12	2.3
									1.60 <sup>a</sup>	5.3 <sup>a</sup>

a) Half-wave potentials and currents of the second wave.

b) Partially diffuse and partially catalytic wave.



disappears and thus a shift in half-wave potential to more positive values appears. The polarographic data in Table 5 do not exhibit a significant correlation with the potentiometric data given in Table 2. This may be due to the fact that the acid-base equilibrium involves the base as well as the protonated form and either is subject to solvation whereas the polarographic reduction involves solely the protonated form. Another reason may consist in the circumstance that the induction and mesomeric effects of a substituent can manifest themselves in acid-base equilibrium and reduction to a different degree. Therefore it may be stated in conclusion that the solvation effects manifest themselves appreciably in the polarographic reduction of amide oximes but their correlation with acid-base properties is not so significant as the correlation with  $^1\text{H}$ -n.m.r. spectra.

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