

Polarographic behaviour and acid-base properties of *O*-benzoylbenzamide oximes

F. GRAMBAL and J. LASOVSKÝ

Department of Inorganic and Physical Chemistry, Faculty of Natural Sciences,
Palacký University, 771 46 Olomouc

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The polarographic reduction and basicity of a series of 27 *O*-(4-*R'*-)benzoyl-4-*R*-benzamide oximes in 50% aqueous ethanol has been studied. It has been found that the studied substances undergo a two-electron reduction to give amidines. The effect of pH upon $E_{1/2}$ is discussed. Under the conditions of the investigation the substances behave as weak bibasic bases. The found half-wave potentials of the polarographic reduction ($E_{1/2}$) as well as the dissociation constants (pK_{a2}) correlate with σ_p constants of the substituents on the aromatic amide oxime ring.

Изучалось полярографическое восстановление и основность 27 *O*-(4-*R'*-)бензоил-4-*R*-бензамидоксимов в 50%-ном этаноле с водой. Было найдено, что эти соединения восстанавливаются двухэлектронно до амидинов. Обсуждается влияние pH на $E_{1/2}$. В той же среде ведут себя изучаемые соединения как очень слабые двухосновные основания. Потенциалы полуволны полярографического восстановления ($E_{1/2}$) и константы диссоциации (pK_{a2}) находятся в корреляции с константами Гаммета σ_p ароматического ядра амидоксима.

The behaviour under the polarographic conditions and the basicity of *p*-substituted benzamide oximes have been previously studied [1—3]. It has been proved that the reduction on a mercury drop electrode at pH 2—10 occurs as a simple two-electron process to give the corresponding amidines. The reduction occurs on the protonized form of the depolarizator and the turning point on the dependence $E_{1/2}$ vs. pH coincides roughly with the pK_a values determined by titration [1].

p-Substituted benzamide oximes and their *N*- and *O*-alkyl derivatives behave in aqueous alcohol as weak monobasic bases [1, 3]. Their dissociation constants pK_a are within 3—6 and from their dependence upon the reversible value of relative permittivity conclusions have been drawn about the effect of *O*- and *N*-alkyls upon pK_a and the cleavage of the intramolecular hydrogen bonding of amide oximes [3]. The dissociation constants are affected markedly by the substituents on the

aromatic ring. The pK_a values correlate linearly with the Hammett σ_p constants of the substituents and the reaction constant is relatively high (2.02) [3].

Recently some *O*-benzoylbenzamide oximes were prepared and their i.r. and u.v. [4], and ^1H -n.m.r. spectra [5] have been studied. The objective of the present work was to study the polarographic behaviour and to determine the dissociation constants of this class of substances.

Experimental

The 4- and 4'-substituted *O*-benzoylbenzamide oximes (*I*—XXVIII) have been described [4]. To study their polarographic behaviour 5×10^{-4} M solutions in 50% (w/w) ethanol were prepared and, prior to the measurements, mixed with an equal volume of a buffer prepared in the same solvent. The pH was adjusted by means of a perchloric acid—sodium perchlorate mixture and Britton—Robinson buffer (I 0.5). Before the measurements were run gelatine (0.1%) was added to suppress the maximum, the solution was deoxygenated with nitrogen which was purified by passing through an alcoholic solution of pyrogallol. The polarographic measurements were carried out using a Kalousek vessel equipped with a separated calomel electrode. The curves were recorded using an LP 7 polarograph connected to an EZ 7 (Laboratorní přístroje, Prague) recorder. At the mercury reservoir height of 50 cm the capillary constants were as follows: $m = 2.88 \text{ mg Hg s}^{-1}$, $t = 2.9 \text{ s}$ in 0.1 M-KCl at 0.0 V (SCE).

For the reversibility studies a Kalousek switch [6] ($f = 6 \text{ c s}^{-1}$) was used. Constant potential was supplied from another polarograph (I and II connection [7]).

The dissociation constants of *O*-benzoylbenzamide oximes *I*—XXVIII in 50% (w/w) ethanol were determined spectrophotometrically. For $\text{pH} \geq 1$ the ion strength *I* was adjusted to 0.1 with sodium perchlorate. The pH was measured with a PHM 64 (Radiometer, Copenhagen) instrument. A hydrogen electrode (for $\text{pH} \geq 1$ a glass electrode) was used as an indication electrode, and a silver chloride electrode filled with 0.1 M sodium chloride in 50% (w/w) ethanol was used as the reference electrode. The system was calibrated by means of standard buffers [8]. The pH was adjusted with appropriate solutions of perchloric acid and buffers (various ratios of 0.01 M citric acid + 0.003 M sodium hydroxide).

Coulometric determinations were done using an OH 404 (Radelkis, Budapest) instrument. Compound *I* (240 mg; 0.001 M) was dissolved in Britton—Robinson buffer in 50% (w/w) ethanol (100 ml) (pH 2.21) and reduced with stirring on a large-surface mercury electrode at a potential difference of 1.1 V vs. SCE. The number of electrons exchanged, $n = 2.05$, was calculated from the amount of the electric charge. When the reduction was complete the solution was adjusted to $\text{pH} \sim 8$ with sodium carbonate and extracted with ether. The ethereal solution was dried with calcium chloride, filtered and dry hydrogen chloride was passed through the solution to precipitate benzamidine hydrochloride (140 mg; 90%).

The statistical evaluation of the results was done at Computing Laboratory, Palacký University, with Tesla 200 computer.

Results and discussion

The studied *O*-benzoylbenzamide oximes were submitted to electroreduction on a mercury drop electrode at pH 0.9–7.00. As usual for diffusion-governed polarographic waves a linear dependence of the wave height upon the second root of the height of the mercury reservoir and concentration was found for compound *I* (pH 1.16 and 5.18), *III* (pH 4.57), and *XIV* (pH 3.97). From the comparison of the wave height observed with an internal standard for the nitro group and the coulometric determination, the number of electrons exchanged with compounds *VI*, *XIII*, and *XX* was found to be equal to 2. With all compounds studied the waves were irreversible in the whole range of pH. The irreversibility was proved by means of switched waves produced with a Kalousek switch in both connections. These results are in agreement with *Lund's* work [9] who showed that the azomethine group $R_1R_2C=N-Y-R$, in the case of nonalkylated amide oximes, gives the same results.

The reduction on a mercury drop electrode of all compounds under investigation shows a considerable dependence of $E_{1/2}$ vs. pH. At pH 0.9–1.44 $d(E_{1/2})/d(pH)$ up to 600 mV was observed, which is in agreement with acid-base properties of the studied substances showing a shift of protonation to low pH values. At pH 1.44–7.00 the $E_{1/2}$ shows a less pronounced dependence upon pH [$d(E_{1/2})/d(pH) = 53\text{--}100$ mV]. With the increasing pH, when the amount of the protonized form diminishes, the diffusion wave height decreases as well and disappears at pH 5–7.

With the exception of compounds *VII* and *XIV* and the nitro compounds (*VI*, *XIII*, *XX*, *XXII*–*XXVII*) the $E_{1/2}$ vs. pH dependence agrees with the common conception of reduction preceded by protonation [10] (Fig. 1). Since the ionization constants pK_{a_2} show low values (Table 1) the totally protonized form occurs at $pH \sim 0$.

Compound *VII* shows another turning point (pH 3.3; Fig. 1) on the curve $E_{1/2}$ vs. pH, which can be attributed to the protonation of the dimethylamino group at the position 4, resulting in the change of the electrode mechanism as a consequence of the processes occurring at the boundary between the mercury drop and the solution [11]. Compound *XIV* shows two turning points at pH 2.2 and 4.5. The first value agrees well with pK_{a_1} (2.54) of the dimethylamino group found photometrically.

A similar complication of the dependence $E_{1/2}/pH$ (Fig. 2) was observed with the nitro derivatives where the reduction of the nitro group precedes the hydrogenolysis of the N–O linkage of the acyloximino group. Similarly to nitrobenzoic acids [12] the pH values corresponding to these turning points are rather far away from pK of phenylhydroxylamines.

Table 1. Half-wave potentials and limiting currents for 4,4'-substituted *O*-benzoylbenzamide oximes

Compound	R	R'	$-E_{1/2}$, V		$-E_{1/2}$, V		$-E_{1/2}$, V		pK _{a2}	pK _{a1} (CH ₃) ₂ N
			i _d /mmol, μA pH 0.9	i _d /mmol, μA	i _d /mmol, μA pH 2.21	i _d /mmol, μA	i _d /mmol, μA pH 5.18	i _d /mmol, μA		
I	H	H	0.79	3.5	0.96	3.4	1.26	1.9	2.10	
II	Cl	H	0.72	3.7	0.93	3.5	1.20	2.4	1.89	
III	Br	H	0.71	3.1	0.92	3.1	1.16	2.5	1.89	
IV	CH ₃	H	0.81	4.0	0.98	4.4	1.26	3.4	2.24	
V	OCH ₃	H	0.77	4.2	0.99	3.0	1.35	1.0	2.31	
VI	NO ₂	H	0.80	4.0	1.00	2.4	1.32	3.1	1.52	
VII	N(CH ₃) ₂	H	0.71	3.1	0.85	2.85	1.13	1.9	1.43	2.495
VIII	H	OCH ₃	0.76	3.4	0.93	3.50	1.21	3.0	2.25	
IX	Cl	OCH ₃	0.69	3.6	0.89	3.9	1.15	2.7	1.86	
X	Br	OCH ₃	0.665	3.7	0.87	3.6	1.135	2.6	1.92	
XI	CH ₃	OCH ₃	0.76	3.4	0.94	3.6	1.21	2.5	2.50	
XII	OCH ₃	OCH ₃	0.77	3.1	0.96	3.2	1.235	2.8	2.75	
XIII	NO ₂	OCH ₃	0.78	3.6	0.98	2.3	1.30	4.0	1.21	
XIV	N(CH ₃) ₂	OCH ₃	0.72	3.2	0.80	3.2	1.085	2.3	1.63	2.54
XV	H	Cl	0.72	3.8	0.93	3.6	1.25	2.0	1.96	
XVI	Cl	Cl	0.70	3.6	0.91	3.9	1.21	1.6	1.88	
XVII	Br	Cl	0.67	3.0	0.89	3.6	1.11	1.3	1.68	
XVIII	CH ₃	Cl	0.74	3.0	0.95	3.3	1.23	2.1	2.35	
XIX	OCH ₃	Cl	0.73	3.7	0.96	3.5	1.19	2.3	2.51	
XX	NO ₂	Cl	0.78	3.1	0.97	2.05	1.29	2.2	1.28	
XXI	N(CH ₃) ₂	Cl							1.33	2.325
XXII	H	NO ₂	0.86	3.6	0.96	2.2	1.295	0.6	1.64	
XXIII	Cl	NO ₂	0.79	3.0	0.94	2.7	1.30	1.2	1.45	
XXIV	Br	NO ₂	0.75	3.0	0.93	2.4			1.35	
XXV	CH ₃	NO ₂	0.82	3.0	0.97	2.0	1.315	0.9	1.75	
XXVI	OCH ₃	NO ₂	0.85	2.9	0.99	2.3	1.36	0.9	1.94	
XXVII	NO ₂	NO ₂	0.81	3.0	0.935	3.6	1.32	0.7	1.06	
XXVIII	N(CH ₃) ₂	NO ₂								1.94

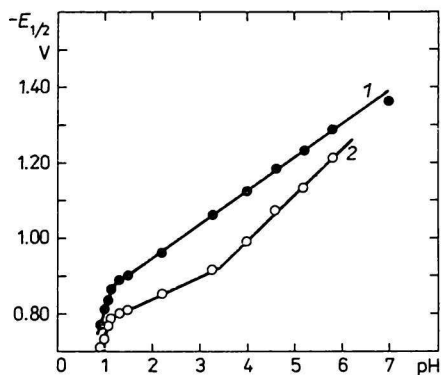


Fig. 1. The $E_{1/2}$ vs. pH dependence.

1. *p*-Methoxybenzoyl-*p*-methoxybenzamide oxime; 2. benzoyl-*p*-dimethylaminobenzamide oxime.

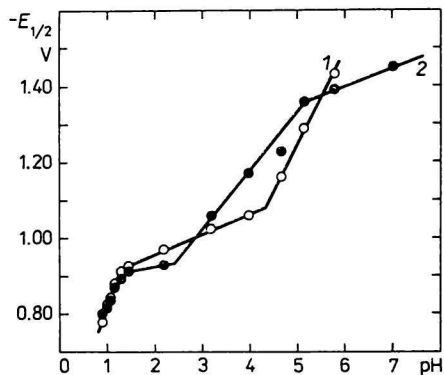
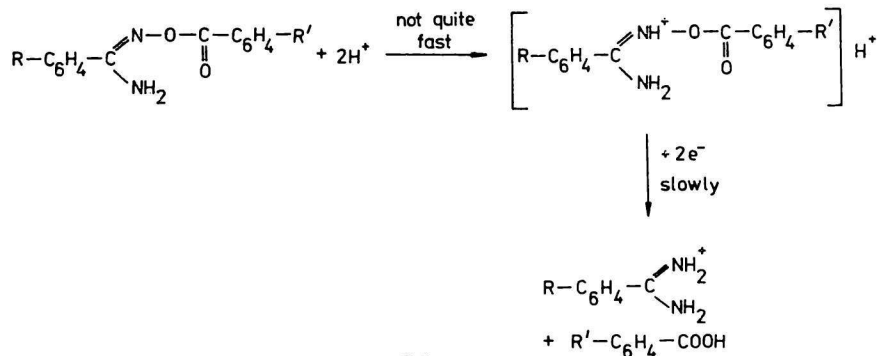


Fig. 2. The $E_{1/2}$ vs. pH dependence.

1. *p*-Chlorobenzoyl-*p*-nitrobenzamide oxime; 2. *p*-nitrobenzoyl-*p*-nitrobenzamide oxime.

In cases with preceding reduction of the nitro group at the position 4' the turning point on the dependence $E_{1/2}/\text{pH}$ occurs at pH 2.2—2.5 with all compounds studied, which is in agreement with the lower $\text{p}K$ of the hydroxylamino group located at the *p*-position towards the benzoyl group. In the case of the hydroxylamino group at the *p*-position towards the amide oxime group the turning point is shifted to pH 3.3—4.2.

Based upon the $E_{1/2}$ vs. pH dependence (Fig. 1) and the acid-base properties, as well as on the large-scale reduction on a large-surface electrode the general Lund scheme and the polarographic behaviour of the nonacylated amide oximes [1] may be described by the two-electron reduction scheme of benzoylated benzamide oximes (Scheme 1)



Scheme 1

The protonation of *O*-benzoylbenzamide oximes takes place in strongly acid medium and at positive pH it is impossible to determine the molar absorption coefficients of the protonized form. Let us assume an equilibrium (A) characterized by a dissociation constant K_{a_n} (1). For the sake of simplicity the ion charges are not given.



$$K_{a_n} = [L][H]^n [H_nL]^{-1} \quad (1)$$

Using the expression for simultaneous absorbance of both forms (2) and the overall analytical concentration (3) it is possible to obtain the linear transformation (4) by means of which the molar absorption coefficient of the protonized form can be calculated [13].

$$A = \varepsilon_L[L] + \varepsilon_{H_nL}[H_nL] \quad (2)$$

$$c_L = [L] + [H_nL] \quad (3)$$

$$A/c_L = \varepsilon_{H_nL} - \frac{K_{a_n}(A - \varepsilon_L c_L)}{c_L [H]^n} \quad (4)$$

The absorbances were measured at 240–280 nm where there is the most pronounced difference between the molar absorption coefficients of the acid-base forms. The transformation (4) showed, for all compounds studied, at pH 0–2 a linear course only for $n = 2$. From the known values ε_{H_2L} and ε_L the dissociation constants were calculated numerically

$$K_{a_2} = \frac{A - \varepsilon_{H_2L} c_L}{\varepsilon_L c_L - A} [H]^2 \quad (5)$$

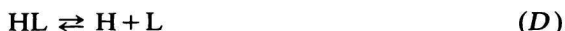
Also the Henderson—Hasselbalch equation (6) gave constant pK_{a_2} values for $n = 2$ and showed a linear course with the tangency corresponding to two cleaved off protons (B).

$$pK_{a_2} = 2pH + \log \frac{A - \varepsilon_L c_L}{\varepsilon_{H_2L} c_L - A} \quad (6)$$



The tabulated values of the dissociation constants are mean values of 6–8 measurements transformed to a logarithmic scale. The observed variations never exceeded a value of 0.1 pK_a (Table 1).

The evaluation of the acid-base reaction at the dimethylamino group of compounds VII, XIV, XXI, and XXVIII is easy. It is possible to formulate two equilibria of which the first applies to the $-\text{C}(\text{NH}_2)\text{NOCO}-$ arrangement (C) (5) and the second to the dimethylamino group (D) (7).



$$K_{a_1} = [\text{H}][\text{L}][\text{HL}]^{-1} \quad (7)$$

The totally deprotonized forms of these substances show intense absorption bands at 300—310 nm [4] where the molar absorption coefficient of the H_3L form is equal to zero and of the HL form is small

$$A = \varepsilon_{\text{HL}}[\text{HL}] + \varepsilon_{\text{L}}[\text{L}] \quad (8)$$

On the other hand, the molar absorption coefficient for the HL form can be determined using the transformation (4) ($n = 1$). The dissociation constants can be then calculated in the usual manner using the Henderson—Hasselbalch equation [14] (Table 1). Since the equilibria cannot be considered fully isolated calculations of the dissociation constants have been carried out taking into account the interactions of the equilibria (C) and (D). For compound XIV the absorption curves went through the isosbestic point ($\lambda_{\text{iso}} = 286 \text{ nm}$) corresponding to the equilibrium (C)

$$A = \varepsilon^*([\text{H}_3\text{L}] + [\text{HL}]) + \varepsilon_{\text{L}}[\text{L}] \quad (9)$$

where ε^* is the molar absorption coefficient of the H_3L or HL form, and ε_{L} is the molar absorption coefficient of the deprotonized form L.

The $\frac{[\text{L}]}{c_{\text{L}}} = \alpha_0$ relationship can be then easily calculated using the expression [15]

$$\alpha_0 = \frac{\varepsilon - \varepsilon^*}{\varepsilon_{\text{L}} - \varepsilon^*} \quad (10)$$

By characterizing the equilibria (C) and (D) by the overall stability constants β_1 and β_3

$$\beta_1 = [\text{HL}][\text{L}]^{-1}[\text{H}]^{-1} \quad (11)$$

$$\beta_3 = [\text{H}_3\text{L}][\text{L}]^{-1}[\text{H}]^{-3} \quad (12)$$

it can be written

$$\frac{1 - \alpha_0}{\alpha_0[\text{H}]} = \beta_1 + \beta_3[\text{H}]^2 \quad (13)$$

It has been found that the right side of eqn (13) is, within experimental errors, constant for different [H] values and that $\log \beta_1$ does not differ from $\text{p}K_{a_1}$ determined in the usual way.

The correlation of the half-wave potentials ($E_{1/2}$) of the polarographic reduction and the dissociation constants ($\log K_{a_2}$) with the Hammett constants of the

substituents at the position 4 can be divided into four classes, according to the nature of the substituents at the position 4'. To evaluate the polar effects of the substituents at both positions, a biparametric equation, taking into account their different effects, has been used.

$$x_{i,j} = x_0 + \rho\sigma_{p,i} + \rho'\sigma_{p,j} \quad (14)$$

where $\sigma_{p,i}$ and $\sigma_{p,j}$ are the Hammett constants of the substituents at the positions 4 and 4', respectively and ρ and ρ' are the corresponding reaction constants. In both cases the correlations are statistically important (P 99.9%) for substituents at the position 4, whereas the 4'-substituents do not correlate with the experimentally found values. The reaction constant ρ ($\log K_{a_2}$) is almost equal (0.956) to that observed with aqueous benzoic acids [16]. In agreement with general chemical experience the effect of the substituent R' diminishes, as a result of the presence of the —OCO— arrangement, through which the transfer of the electronic effects of the substituents occurs less easily. The influence of the effects unaffected by the Hammett equation becomes then more pronounced and the correlation is less satisfactory (Table 2). The same conclusion could be drawn about the effect of both classes of substituents when the correlation of the chemical shifts of protons of the NH_2 group was studied [5]. The linear correlations between all measured equilibrium values ($E_{1/2}$, $\text{p}K_{a_2}$, δ) have been compared. It has been found that all the pairs

Table 2

Correlation of the half-wave potentials and the dissociation constants with the σ_p constants of the substituents

$x_{i,j} = x_0 + \rho\sigma_{p,i} + \rho'\sigma_{p,j}$										
$x_{i,j}$	x_0	n	ρ	ρ'	r	P	r'	P'	R	F
$E_{1/2}$	-0.939	25 ^a	0.135	0.00877	0.914	99.9	+0.039	<95	0.915	56.83 (0.975)
$\log K_{a_2}$	-2.13	27	0.956	0.554	0.824	99.9	0.402	<95	0.954	121.2 (0.99)
R	H	Cl	Br	CH ₃	OCH ₃	NO ₂	(CH ₃) ₂ N	NHOH		
σ_p [17, 18]	0.00	0.227	0.232	-0.17	-0.268	0.778	0.83	-0.34		

a) Due to sparing solubility compounds XXI and XXVIII were not measured. Compound XXVII is not included owing to the complex electrode phenomena observed.

n — number of determinations,

r, r' — correlation coefficients,

P, P' — probability level (%).

R — correlation coefficient between the depending parameter and the regression,

F — Fisher probability level criterion.

Table 3

Correlation of the half-wave potentials ($E_{1/2}$), dissociation constants (pK_{a2}), and chemical shifts of the amide group

$Y = kx + q$								
Y	x	k	τ_k	q	τ_q	n	r	P
$E_{1/2}$	pK_{a2}	0.10839	± 0.04858	-0.6970	± 0.0968	17	0.7753	99.9
$E_{1/2}$	δ	-0.27035	± 0.10885	-2.8006	± 0.75195	15	0.8299	99.9
δ	pK_{a2}	-0.28326	± 0.05919	7.5041	± 0.1146	24	0.9041	99.9

τ_k — regression coefficient reliability interval,

τ_q — absolute member reliability interval,

n — number of pairs of determination,

r — correlation coefficient,

P — probability level (%).

of the experimental data correlate linearly with each other to the probability level of 99.9% (Table 3). This can be attributed to the localization of all equilibrium phenomena in the azomethine proton of the molecule.

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