CYCLIZATION OF O-BENZOYLBENZAMIDOXIME DERIVATIVES IN WATER–ALCOHOL MEDIA

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Received March 23rd, 1985

O-Benzoylated benzamidoximes give 1,2,4-oxadiazoles (yields above 90%) in water–alcoholic media of pH = 2·45 to 6·20. The cyclization rate has been studied with 28 derivatives containing different substituents. The reaction is accelerated by electron-donor substituents at 4-position of benzamidoxime and by electron-acceptor substituents at 4′-position of benzoyl. The dependence of the rate constants *vs* σ values of the substituents fulfils the two-parameter Hammett equation at a 99% probability level. The activation parameters have been determined, and effects of polarity of medium, kinetic isotopic effect, and the reaction mechanism are discussed.

Acylated amidoximes are intermediates in synthesis of 1,2,4-oxadiazoles which found application as optical brightening agents[1,2]. About 20 years ago[3,4] their antipyretic and antiphlogistic effects were determined and, at the present time, their syntheses are paid the main attention[5,6].

O-Acylated amidoximes are easily hydrolyzed to the parent amidoximes and easily cyclized to the corresponding oxadiazoles[7]. Although basic reports[8,9] dealing with these compounds were published as early as in 1884, mechanism of their reactions has not been solved yet[10]. A recent paper[11] deals with mechanism of formation of 3,5-disubstituted 1,2,4-oxadiazoles from O-acetyl and O-aroylamidoximes in non-polar media.

A possibility is suggested in literature[12] that the cyclization reactions of acylated amidoximes to corresponding 1,2,4-oxadiazoles are subject to acid catalysis. In context with the research of this reaction in acid medium (where solvolysis is operating), we have carried out a part of kinetic studies in media of pH 2·45 – 6·20, where the compounds examined are present as neutral molecules and the cyclization rate is pH-independent. The results are given in this paper.

EXPERIMENTAL

O-Benzoylbenzamidoximes *I – XXVIII* (Table I) were prepared according to ref.[13].

The kinetic measurements were carried out with $5 \cdot 10^{-4}$ mol l^{-1} solutions of the compounds in the Britton–Robinson buffers in 50% w/v aqueous ethanol. The ionic strength μ was adjusted

at the value 0·1 by addition of sodium chloride. The reaction was studied at 343·15 ± 0·05 K in an ultrathermostat (Prüfgeräte, Medingen, GDR). The rate constants were determined from polarographical data by the technique of sample withdrawing: at definite time intervals samples were taken, and concentration of the starting substances was determined therein polarographically. The sample treatment before analysis included acidification with sulphuric acid to pH ~ 1, addition of gelatine, and deareation with nitrogen. At these conditions the compounds *I*—*XXVIII* exhibit the diffusion currents due to their two-electron reduction to amidines[14]. 1,2,4-Oxadiazole does not interfere with the analysis. The rate constant values were calculated from the relation $\ln (i_0/i_t) = k_{exp}t$, where i_0 and i_t mean the limit currents of the reactants at the time $t = 0$ and t, resp.. The values given in Tables are mean values of 15—30 measurements, standard deviation of the rate constant did not exceed 5%. The pH values of aqueous ethanol were measured by a known method[14] using a cell of glass and silver chloride electrodes.

Identification of the products: 1 g compound *I* was dissolved in 400 ml 50% w/v ethanol (or 100 ml methanol) and refluxed 20 h. Then the solvent was evaporated under reduced pressure, and the solid was recrystallized from aqueous ethanol. In both the cases, C,H,N elemental analysis, IR spectrophotometry, and the melting point value 109°C (ref.[8] gives 109—110°C) confirmed the structure of 3,5-diphenyl-1,2,4-oxadiazole which was formed in the yields 0·89 g or 0·87 g, resp., *i.e.* above 90%. Dependences of the rate constant on pH and relative permittivity of solvent were measured at 343·15 K. The activation parameters were calculated from the rate constants measured at 353·15, 348·15, 343·15, and 338·15 K for compounds *I*, *VI*, *VIII*, and *XX* in 50% w/v ethanol at pH 2·45. With respect to higher reaction rates in absolute methanol the temperature interval chosen was lower: 313·15, 308·15, 303·15, and 298·15 K. In all the cases the reaction rates measured agreed with the Arrhenius diagram.

Kinetic isotope effect: The experiments were carried out in 50% *v/v* ethanol to increase the deuterium content. Compound *I* (12 mg) was dissolved in 50 ml ethanol, and 50 ml H_2O or ^2H_2O (99·9%) was added thereto. All subsequent operations were identical with the above-described ones.

Apparatus: An LP 7 polarograph (Laboratorní přístroje, Prague), the Kalousek vessel with a saturated calomel electrode separated from a dropping mercury electrode, a PHM 64 pH-meter (Radiometer, Copenhagen, Denmark).

RESULTS AND DISCUSSION

In all the cases studied the reaction product is 3,5-disubstituted 1,2,4-oxadiazole. The kinetic curves of the O-benzoylated benzamidoximes agree with the formalism of isolated reactions of the 1st order, they are independent of the solution acidity in the pH interval from 2·45 to 6·20. Table I gives the rate constant values which are mean values of 9 results obtained at pH 2·45, 2·60, 2·92, 3·10, 3·56, 4·08, 5·04, 5·50, and 6·20. For estimation of polar effects of substituents on the cyclization reaction the rate constants were correlated by means of the two-parameter equation

$$\log k_{i,j} = \log k_0 + \varrho_1 \sigma_{p,i} + \varrho_2 \sigma_{p,j} ,$$

where $\sigma_{p,i}$ and $\sigma_{p,j}$ are constants of the substituents at the 4- and 4'-positions, resp. (ref.[15]), and ϱ_1 and ϱ_2 are the respective reaction constants (Table II). The significance

level of the regression given estimated by the Fisher criterion is 99%. The polar effect of the substituents in benzamidoxime ring ($\varrho_1 = -1{\cdot}16$) agrees fully with the idea of the amidoxime—NH_2 group acting as a nucleophile (with decreasing electron density at the amidoxime carbon atom). The effect of benzoyl *para* substituents obeys the σ values, and its magnitude is comparable with that of polar effects on ionization of benzoic acids ($\varrho_2 = 0{\cdot}98$). The correlation with σ^+ constants, which would indicate an interruption of conjugation of carbonyl group with aryl ring, was not fulfilled in the given case. The polar effect of the substituents simultaneously present at the 4 and 4′ positions is qualitatively equal to that of *para* substituted benzoylacetamidoximes or *para*-substituted acetylbenzamidoximes, resp., nevertheless, the

TABLE I

Rate constants of cyclization of substituted O-benzoylbenzamidoximes

Compound	$k_n \cdot 10^5$, s^{-1}	Compound	$k_n \cdot 10^5$, s^{-1}
I	3·20	*XV*	1·69
II	3·52	*XVI*	2·00
III	2·17	*XVII*	1·00
IV	2·07	*XVIII*	1·20
V	3·49	*XIX*	2·13
VI	0·85	*XX*	0·53
VII	100	*XXI*	68
VIII	5·23	*XXII*	27·6
IX	6·99	*XXIII*	20·0
X	3·17	*XXIV*	15·2
XI	3·20	*XXV*	15·0
XII	6·44	*XXVI*	33·2
XIII	1·41	*XXVII*	3·97
XIV	150	*XXVIII*	250

TABLE II

The substituent polar effects

$\log k_0$	n^a	ϱ_1	ϱ_2	r_1	P_1	r_2	P_2	R	F
−4·400	28	−1·16	0·98	−0·7738	99·9	0·5399	99	0·9436	101·5

[a] n Number of elements; r_1, r_2 the correlation coefficients; P_1, P_2 the probability level (%); R the correlation coefficient between the dependent variable and the regression; F the value of the Fisher F-criterion.

absolute values of reaction constants given in ref.[11] are lower. The simultaneous influence of substituents transmitted by the aromatic rings from both the sides allows a more sensitive and larger-scale control of the cyclization rate. The rate constant of compound *XXVIII* is 78 times greater than that of the parent derivative *I*, the rate ratio being as large as 472 with respect to the "slowest" derivative *XX*. This fact can be simply explained by simultaneous action of the two substituents with opposite polar effects.

The activation parameters were determined for compounds *I*, *VI*, *VIII*, *XVI*, and *XX* (Table III). In the less polar methanolic medium the activation enthalpy found for compound *II* was $\Delta H^{\neq} = 163{\cdot}6$ kJ mol^{-1}, the activation entropy being $\Delta S^{\neq} = 213{\cdot}3$ J K^{-1} mol^{-1} at 313·15 K. The activation entropy value confirms monomolecular reaction mechanism in the rate-limiting step[16]. The activation entropy lowering accompanying addition of —NH_2 group to carbonyl is fully understandable, if lowering of rotational energy of the two partners is taken into account. The $\Delta S^{\neq}$ values involve the reorganization of the solvation sphere during the reaction, and this

TABLE III

The activation parameters for pH = 2·45; 343·15 K, 50% w/v ethanol

Compound	*I*	*VI*	*VIII*	*XVI*	*XX*
$\Delta H^{\neq}$, kJ mol^{-1}	110·9	106·9	108·7	110·1	113·1
$\Delta S^{\neq}$, JK^{-1} mol^{-1}	−7·2	−26·8	−8·7	−14·7	−11·1

TABLE IV

Effect of relative permittivity of solvent on the reaction rate

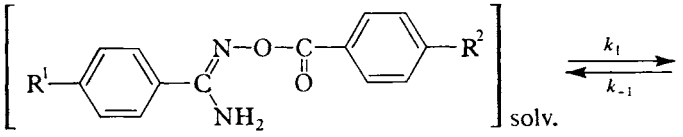
% Ethanol (w/v)	$-\ln k_{exp}$	$\frac{D-1}{2D+1}$[a]
100	8·40834	0·46013
90	9·12416	0·46536
85	9·21034	0·46802
80	9·52642	0·47030
70	9·79733	0·47465
60	10·24035	0·47810
50	10·26302	0·48081

[a] Ref.[22].

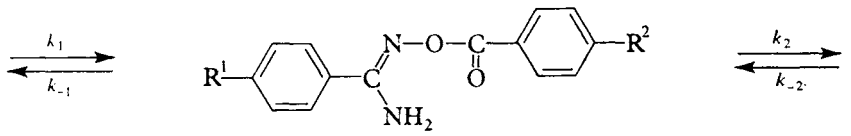
fact is especially significant when using methanol as the reaction medium. The low $\Delta S^{\neq}$ value confirms the addition mechanism, because a considerable entropy decrease would have to accompany any elimination of water in the rate-limiting step[17]. The $\Delta H^{\neq}$ value of compound *VIII* is lower than those of *I*, *XVI*, and *XX* in accordance with the addition to carbonyl group, where the electron-acceptor substituents lower the activation enthalpy[18]. Predominant effect of the lower activation enthalpy on the reaction rate increase is observed with exception of compound *VI*. Such behaviour of nitro derivatives in cyclization reactions has already been observed[19] in connection with preferred formation of 5-acetonyl-1,2,4-oxadiazole. Both the preferred splitting off of water and larger $\Delta H^{\neq}$ decrease with higher $\Delta S^{\neq}$ could be understood as a consequence of the concerted mechanism involving simultaneous addition and splitting off of hydrogen from the amidic group. It can thus be concluded that the cyclization is governed by addition of amino group to carbonyl group of the O-benzoylated benzamidoximes.

Influence of relative permittivity of solvent was studied in water–alcohol mixtures in the range of 50–100% w/v. Table IV summarizes the results obtained with solution of $5 \cdot 10^{-4}$ mol l^{-1} compound *I* at 343·15 K. The rate constant values found obey the linear relation $\ln k_{exp} = 32{\cdot}71 - 89{\cdot}65(D - 1)/(2D + 1)$. In order to estimate the effect of heavy water on the reaction rate, we determined the kinetic isotope effect for compound *I*. In the first case using H_2O we found the rate constant $k_{expH} = 3{\cdot}27 \cdot 10^{-5}\ s^{-1}$. In the second case using ethanolic solution of ^2H_2O (final concentration 87% ^2H) we found $k_{exp\,^2H} = 3{\cdot}95 \cdot 10^{-5}\ s^{-1}$. The kinetic isotope effect $k_{expH}/k_{exp\,^2H} = 0{\cdot}83$.

We studied the effect of ionic strength on the cyclization reaction rate and found that in the interval $\mu = 0{\cdot}01$ to 1·00 the rate constant decreased by 13% ($-\log k_{exp} = 4{\cdot}46 - 4{\cdot}52$). The cyclization reaction of O-benzoylbenzamidoximes is independent of H^+ ion concentration in the pH range given, being very little dependent



A



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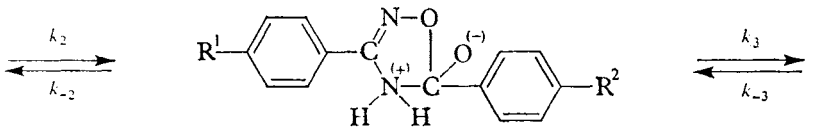

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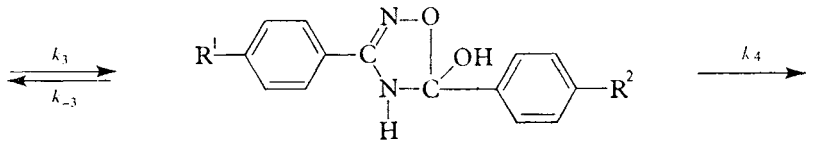
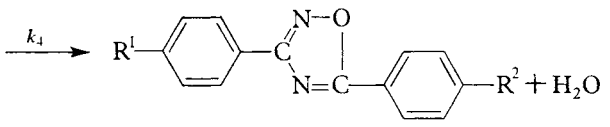


D



E

I, $R^1 = R^2 = H$
II, $R^1 = CH_3$, $R^2 = H$
III, $R^1 = Cl$, $R^2 = H$
IV, $R^1 = Br$, $R^2 = H$
V, $R^1 = CH_3O$, $R^2 = H$
VI, $R^1 = NO_2$, $R^2 = H$
VII, $R^1 = (CH_3)_2N$, $R^2 = H$
VIII, $R^1 = H$, $R^2 = Cl$
IX, $R^1 = CH_3$, $R^2 = Cl$
X, $R^1 = R^2 = Cl$
XI, $R^1 = Br$, $R^2 = Cl$
XII, $R^1 = CH_3O$, $R^2 = Cl$
XIII, $R^1 = NO_2$, $R^2 = Cl$
XIV, $R^1 = (CH_3)_2N$, $R^2 = Cl$
XV, $R^1 = H$, $R^2 = CH_3O$
XVI, $R^1 = CH_3$, $R^2 = CH_3O$
XVII, $R^1 = Cl$, $R^2 = CH_3O$
XVIII, $R^1 = Br$, $R^2 = CH_3O$
XIX, $R^1 = R^2 = CH_3O$
XX, $R^1 = NO_2$, $R^2 = CH_3O$
XXI, $R^1 = (CH_3)_2N$, $R^2 = CH_3O$
XXII, $R^1 = H$, $R^2 = NO_2$
XXIII, $R^1 = CH_3$, $R^2 = NO_2$
XXIV, $R^1 = Cl$, $R^2 = NO_2$
XXV, $R^1 = Br$, $R^2 = NO_2$
XXVI, $R^1 = CH_3O$, $R^2 = NO_2$
XXVII, $R^1 = R^2 = NO_2$
XXVIII, $R^1 = (CH_3)_2N$, $R^2 = NO_2$

SCHEME 1

on ionic strength of the solution. This fact supports the idea that the reaction involves the neutral molecule. The reaction can be presumed to follow the general mechanism of formation of azomethines[20] (Scheme 1).

This reaction is usually considered both from the point of view of possible catalysis[12] and with the aim to find whether the limiting step consists in addition of a nucleophilic particle to carbonyl group or in the subsequent elimination of water.

The dependence of rate constants on composition of solvent (*i.e.* the decrease of the reaction rate with increasing water content) indicates that increasing water content not only will make itself felt in a change of relative permittivity, but, at the same time, higher proton-donor ability of water (as compared with ethanol) will also play its part[21]. Increased solvent polarity results in a decrease of activation enthalpy and corresponds to increased solvation of the more polar transition state as compared with the starting substances. The reaction rate, however, is lower with respect to the entropy term. A marked entropy increase in less polar methanolic medium can be taken as a confirmation of less solvated starting substances as compared with aqueous ethanolic medium. As the cyclization reaction does not represent a one-step condensation, it is affected by both the initial equilibrium and the subsequent reactions which follow. The effect of medium will make itself felt to some or other extent in all the reaction steps. The lowered reaction rate with increasing water concentration in ethanol is understandable with regard to lowered nucleophilicity of the solvated $—NH_2$ group.

The change in solvent also results in a change in the rate-limiting reaction step. A more polar medium shifts the mechanism of the reaction of O-benzoylated benzamidoximes from a proton-transfer reaction to a nucleophilic addition to carbonyl group. The proton transfer is fast in aqueous-ethanolic medium, and, in accordance with the isotope effect found, the rate-limiting step consists in addition of amino group to carbonyl group of O-benzoylated benzamidoximes. This fact seems to be decisive for estimation of the rate-limiting step.

The initial equilibrium k_1/k_{-1} (Scheme 1) is shifted in favour of the solvated molecules, and the reaction rate is equal to the product $(k_1/k_{-1})\,k_2$. With respect to what was said above it can be expected that the transition state will be more polar than the starting compounds and will approach *C*.

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Translated by J. Panchartek.