Oxidation of organic amide ions by dioxygen
1. Kinetics of base-catalyzed oxidation of secondary amines

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Amide ions generated from secondary aromatic amines with $pK_a > 21$ are readily oxidized by dioxygen in the system KOH+18-crown-6+DMSO at room temperature. It was found that the rate limiting stage of the reaction is the interaction of dioxygen with amide ions. The rate of the reaction is determined by two main factors, varying in opposite directions: the degree of ionization of the amine and the reactivity of the amide ions towards dioxygen.

Key words: aromatic amines, amide ions, oxidation, dioxygen, kinetics.

Ionization of organic compounds in strongly basic media is an efficient and simple way of their activation towards molecular oxygen. This method is being used more and more widely nowadays for selective oxidation of organic compounds under mild conditions, largely owing to the development of the methods of phase-transfer catalysis, which made possible the application of readily available strongly basic systems {alkali + phase-transfer catalysts (crown ethers and their analogs) + aprotic solvents}[1,2] for ionization of even very weak acids ($pK_a > 30$).

However, a series of substrates, for which the preparative capacity and mechanism of anionic oxidation were studied in detail, is mainly restricted to C-H acids, whereas the oxidation patterns for organic anions with the charge centered at heteroatoms including nitrogen (amide ions) have been investigated very scantily[3—5].

In this work, the kinetic patterns of the organic amine oxidation by molecular oxygen in strongly basic media have been studied to elucidate the mechanism of the amide ion autoxidation.

Generation of amide ions from most of the aromatic amines containing electron-acceptor substituents possess no great difficulties. Moreover, it is convenient to use ionization of substituted diphenylamines and anilines for determination of the H_- acidity function values in strongly basic media[6]. However, alkaline oxidation of amines, which contain activated C—H bonds, often proceeds not at the nitrogen but at a carbon atom[5]. In addition, the amide ions generated from primary amines readily enter the reactions of condensation and substitution with the intermediate products of their oxidation[3—5].

The preceding imposes certain limitations on the choice of organic amines, the study of whose oxidation in alkaline media could provide unequivocal information about the kinetics and mechanism of the amide ion interaction with molecular oxygen through the nitrogen atom. Therefore, in this work we studied the oxidation of those secondary amines (SA) that contain no activated C—H bonds or other groups capable of being ionized and oxidized concurrently with the amino group. We used the derivatives of diphenylamine, (2,2-dimethyl)tetrahydroquinoline, and (2,2,6,6,-tetramethyl)piperidine.

Experimental

In this study, we used commercial diphenylamine (analytical grade) and morpholine (reagent grade) as well as SA with 98 % content of the basic substance, synthesized in the laboratory.

Aprotic solvents were purified by distillation or by passing through a column with chromatographic alumina, and stored over desiccants (anhydrous sodium sulfate or calcium chloride). Dimethyl sulfoxide (chemically pure grade) was distilled under reduced pressure and stored over 4 Å molecular sieves. The water content of the purified solvent did not exceed 0.5 %. The KOH was homogenized in benzene using 18-crown-6 ether essentially as described earlier[7].

The kinetics of O_2 consumption was studied in a volumetric unit at constant pressure. In a typical kinetic experiment, 0.2 mmol of SA and 4.5 mL of DMSO were introduced into a 25—100 mL cell equipped with a magnetic stirrer. After purging the cell with oxygen or argon-oxygen mixture, 0.5 mL of 1 *M* KOH+18-crown-6 solution in benzene was added. Nearly constant partial pressure of oxygen in the experiments using argon-oxygen mixtures of different composition was main-

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* The results of investigation of the oxidation products for organic amide ions are presented in the next report.

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tained due to the existence of a large volume excess of the gas mixture in the cell. In all runs, variation of O_2 concentration throughout the reaction did not exceed 5% of the initial value.

The absorption spectra of the compounds in UV and visible region were recorded on a Beckman UV 5270 spectrophotometer. The degree of amine ionization in strongly basic media was determined under argon according to standard analytical procedures.

Results and Discussion

Kinetic patterns of the secondary aromatic amine oxidation in the presence of bases

The main patterns of SA oxidation by molecular oxygen have been studied in the strongly basic system KOH+18-crown-6+DMSO. The oxidation rate of the amines studied, determined from the kinetics of oxygen consumption at room temperature, decreases in the order:

1 > **2** > **3** > **4** > **5**, **6** > **7** > **8** > **9** > **10** ≫ **11**, **12**.

Amines **11** and **12** are oxidized extremely slowly under these conditions, apparently because their NH-acidity is extremely low and the basicity of the system is not sufficient for effective ionization. Secondary aromatic amines **1**—**9** are oxidized rapidly in the presence of strong bases even at room temperature. From the series given above it is shown that the oxidation rate of SA is substantially dependent on the nature of the substituent in the aromatic ring, being enhanced by strong electron-donor substituents (alkoxy groups) and attenuated by electron-acceptor ones (nitro group).

Determination of the amide ion concentration

To determine the amide ion concentration in a solution, the equilibrium of the SA ionization in the KOH+18-crown-6+DMSO system was studied spectrophotometrically. Some characteristics of the absorption spectra of the SA and corresponding amide ions as well as the values of NH-acidity for a number of SA are given in Table 1.

The equilibrium ionization of the secondary amine (R_2NH) in DMSO

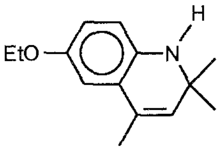
$$R_2NH + OH^- \rightleftharpoons R_2N^- + H_2O$$

is described by the equation

$$K_{exp} = [R_2N^-]_p/[R_2NH]_p \cdot [OH^-]_p, \qquad (1)$$

where $K_{exp} = K_p/[H_2O] \approx$ const.

Water formation in the ionization of SA does not appreciably affect the K_{exp} value because of the substantial water content in the solvent (about 0.3 mol L^{-1}). It remains practically constant because the ionization produces only 10^{-3}—10^{-2} mole of water per liter. How-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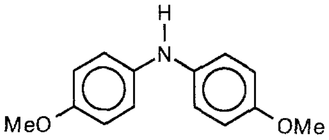
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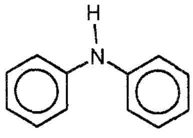
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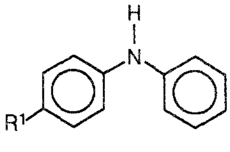
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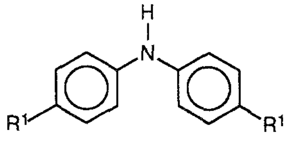
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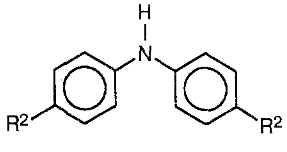
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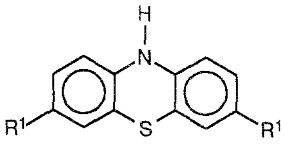
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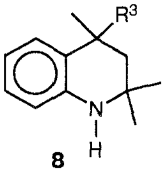
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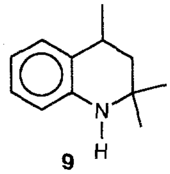
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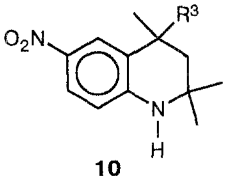
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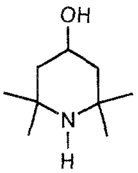
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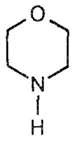
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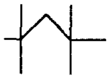
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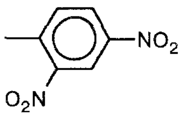

Table 1. Absorption maxima and molar extinction coefficients of amide ions and pK_a values of SA in DMSO

Amine (R_2NH)	$\lambda^{R_2NH}_{max}$/nm	ε^{R_2NH}/mol L^{-1} cm^{-1}	$\lambda^{R_2N^-}_{max}$/nm	$\varepsilon^{R_2N^-}$/mol L^{-1} cm^{-1}	pK_a
2	290	21200	363	29000	23.8
3	289	22500	373	28600	22.4
4	290	23600	370	29000	22.8
5	291	27500	371	30200	23.3
7	320	6000	385	8400	22.1
10	364	20000	427	22200	21.2

ever, the values of equilibrium constants determined for one concentration of the alkaline additive, as a rule, does not make it possible to calculate concentrations of amide ions at other KOH contents in such a way that the calculated values agree with experimental ones satisfactorily. This appears to be so because the basicity of the medium is strongly affected by the additions of water and methanol that are inevitably present in the alkaline additive (KOH+18-crown-6) prepared according to the known procedure[7].

Such a nonlinear variation pattern of the medium basicity with KOH concentration is illustrated in Fig. 1, where the medium basicity is expressed in the form of an H_- acidity function, determined from the spectrophotometric data on ionization of indicator amounts of amines with known pK_a values:

$$H_- = pK_a + \lg([R_2N^-]_p/[R_2NH]_p). \quad (2)$$

Here the indicator used was diphenylamine with pK_a = 22.44[6]. Figure 1 shows that the medium basicity increases linearly with alkali concentration only at $[KOH]_0 < 5 \cdot 10^{-3}$ mol L^{-1}. At higher alkali concentrations, the linearity is violated; at $[KOH]_0 = 1.5 \cdot 10^{-2}$ mol L^{-1}, the function reaches maximal value — $(H_-)_{max} \approx 22.9$ — and then the H_- value decreases appreciably. This qualitatively agrees with the ratio variation between the water content in DMSO ($[H_2O]_{DMSO}$) and the sum of OH-acids (water, methanol, XOH) introduced with an alkaline additive. Indeed, at $[KOH]_0 < 0.5 \cdot 10^{-2}$ mol L^{-1}, when $[XOH] \ll [H_2O]_{DMSO}$, the solvent composition virtually does not change and the medium basicity increases with the amount of alkaline additive. At $[KOH]_0 > 2 \cdot 10^{-2}$ mol L^{-1}, when [XOH] and $[H_2O]_{DMSO}$ are comparable, the solvent composition is significantly altered under the introduction of the alkaline additive, and the basicity of the medium decreases despite the increase in alkali concentration.

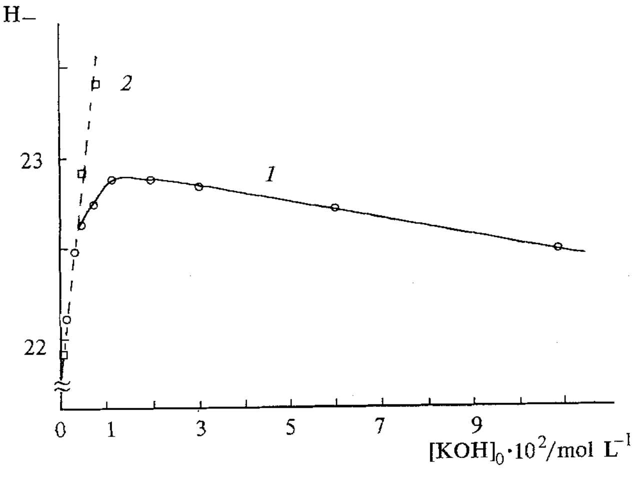

Fig. 1. The dependence of the basicity of the systems DMSO+18-crown-6+KOH (*1*) and DMSO+$Me_4N^+OH^-$ (*2*) on the amount of base added.

For comparison, Fig. 1 displays the plot of medium basicity for the case of tetramethylammonium hydroxide pentahydrate (Janssen Chimica). Introduction of this base does not appreciably alter the solvent composition up to $[OH^-] = (1—2) \cdot 10^{-2}$ mol L^{-1}, and the medium basicity increases linearly with the amount of the base added.

Thus, when calculating the amide ion concentration, one should take into account the water content in the solution. Experimentally, to determine the $[R_2N^-]$, the most convenient way is to use the dependence of H_- on $[KOH]_0$ taking into account the relation (2) between $[R_2N^-]$ and H_-, which is satisfied well under the conditions when $H_- \ll pK_a$ or $[R_2NH]_0 \ll [KOH]_0$.

Kinetics of the diphenylamine derivative oxidation

4,4′-Di-*tert*-butyl diphenylamine (**5**) was chosen as a model compound for studying kinetics of the SA base-catalyzed oxidation.

The activation energy for base-catalyzed oxidation of **5** in DMSO is 6.5 kcal mol^{-1}. The oxidation rate increases linearly with partial pressure of oxygen in a range of 0.2—1.0 atm, which is the evidence of the involvement of dioxygen in the rate-limiting step of the process (see Fig. 2, dependence *1*).

The reaction displays fractional orders with respect to the amine and base concentrations: approximately 0.3 and 0.4, respectively. The derived reaction orders do not conflict with the suggestion that the rate-limiting step is the interaction between dioxygen and the amide ion, which was formed at the equilibrium step of amine

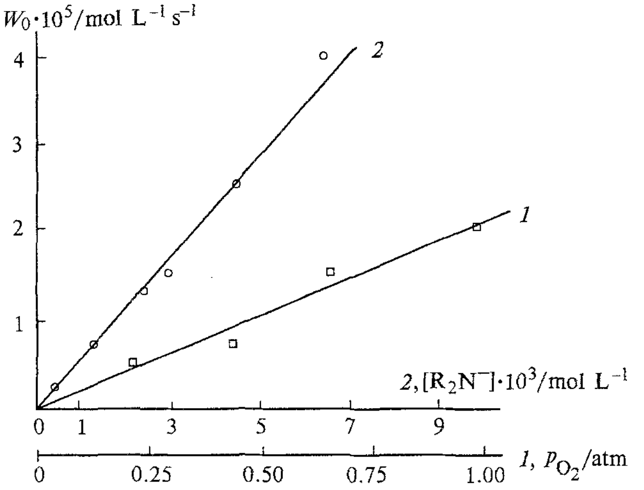

Fig. 2. The dependence of the initial rate of amine **5** alkaline oxidation on partial oxygen pressure (*1*) and amide ion concentration (*2*). DMSO, 25°C; *1*, $[R_2NH]_0 = 0.02$ mol L^{-1}, $[KOH]_0 = 0.023$ mol L^{-1}; *2*, $[R_2NH]_0 \ll [KOH]_0$.

ionization. This is confirmed by the linear dependence of the oxidation rate vs. the amide concentration (see Fig. 2, dependence *2*).

Thus, the rate of 4,4′-di-*tert*-butyl diphenylamine oxidation in DMSO+KOH+18-crown-6 system is described by the equation

$$W^0_{O_2} = k\cdot[R_2N^-]_0\cdot p_{O_2} \qquad (3)$$

with the average value of $k = (5.5\pm0.3)\cdot10^{-3}$ s^{-1} atm^{-1} (25°C).

The nature of the solvent severely affects the oxidation rate of the SA. At room temperature, SA are oxidized extremely slowly in proton-donor solvents (water, primary alcohols) even at $[KOH]_0 > 1$ mol L^{-1}.

In aprotic media, the rate of **5** oxidation increases with solvent polarity in the order (dielectric constants given in parentheses): dioxane ($\varepsilon = 2.2$) < dimethoxyethane (7.2) < THF (7.8) < benzene (2.28) < toluene (2.34) < chlorobenzene (5.62) < acetonitrile (37.5) < DMSO (46.7). The trend for increasing oxidation rate with the solvent's polarity is strictly observed only among solvents of similar chemical nature (ethers, aromatic hydrocarbons). Aromatic solvents drop out of this trend, possibly in connection with the specific solvation of amide ions by π-donating molecules. Due to such solvation, the reactivity of amide ions increases.

According to equation (3), the initial rate of SA oxidation is determined by two factors: the concentration of amide ions and their reactivity towards molecular oxygen (k). Having estimated the concentration of amide ions at a certain basicity of the medium and the effective rate constants of the reaction, $k_{eff} = k\cdot p_{O_2}$, using the initial rates of oxygen consumption, one can compare the reactivity of amide ions of different structure towards molecular oxygen (see Table 2).

The pK_a values of amines **1** and **9** can not be determined by the method described in this work because of their low NH-acidity. However, with accuracy sufficient for our purposes, the pK_a values of these amines can be estimated from the published data on the NH-acidity of related compounds and on the influence of the substituents at the nitrogen atom and in the phenyl rings of aromatic amines on pK_a. Thus, taking the value of NH-acidity for amine **10** and considering that the introduction of a *para*-nitro group into phenyl ring of aromatic amine decreases the pK_a value by 7—8 units; the introduction of an alkoxy group raises it by 0.5—1.0, and the replacement of a hydrogen of a primary amino group with an *iso*-alkyl substituent raises the pK_a value by 0.5—1.0 (see, *e.g.*, Ref. 6), one can predict the ranges of pK_a values for amines **1** and **9** with reasonable certainty (see Table 2) and, consequently, the concentrations of the corresponding amide ions in the media of known basicity.

Table 2 shows that there is no one-to-one correspondence between $W^0_{O_2}$ and the degree of amine ionization or the reactivity of amide ions towards oxygen. The rate of base-catalyzed oxidation of the secondary aromatic amines is determined by superposition of both factors. At the same time, there is a clear correlation

Table 2. Kinetic parameters of SA oxidation in the system KOH+18-crown-6+DMSO ($[R_2NH]_0 = 0.04$ mol L^{-1}, $[KOH]_0 = 0.1$ mol L^{-1}, $p_{O_2} = 1.0$ atm, $T = 25$ °C)

Amine	pK_a	$[R_2N^-]_0$*/mol L^{-1}	$W^0_{O_2}\cdot10^5$/mol L^{-1} c^{-1}	$k_{eff}^{R_2NH}$/s^{-1} atm
1	29—30	$(1.3—13)\cdot10^{-9}$	18.0	$(1.4—14)\cdot10^{4}$
2	23.8	$2.6\cdot10^{-3}$	17.0	$6.5\cdot10^{-2}$
3	22.4	$2.3\cdot10^{-2}$	6.3	$2.7\cdot10^{-3}$
4	22.8	$1.4\cdot10^{-2}$	4.7	$3.4\cdot10^{-3}$
5	23.3	$6.5\cdot10^{-3}$	4.0	$(5.5\pm0.3)\cdot10^{-3}$ **
7	22.1	$2.9\cdot10^{-2}$	3.9	$1.3\cdot10^{-3}$
9	28—29	$(1.3—13)\cdot10^{-8}$	3.3	$(2.5—25)\cdot10^{2}$
10	21.2	$3.8\cdot10^{-2}$	0.5	$1.3\cdot10^{-4}$

* Evaluated according to the formula (2).

** The average value obtained for a wide range of the amine and base concentrations.

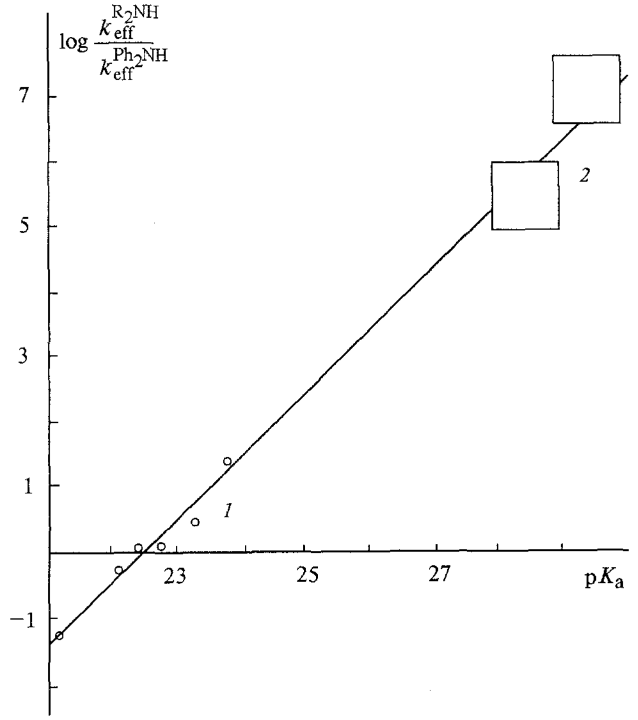

Fig. 3. The dependence of the amide ion reactivity with respect to molecular oxygen on the NH-acidity of corresponding amines (the standard is Ph_2NH): *1,* accurate values[9], *2,* the probable ranges of the values.

between the increasing NH-reactivity of the amide ions towards O_2 and the decreasing NH-acidity (increasing pK_a) of the corresponding amines (Fig. 3). Similar correlations are well-known for many reactions involving carbanions, but it is difficult to relate them to a particular mechanism of the amide ion oxidation, because such correlations were observed both for non-radical reactions of nucleophilic substitution and addition and for single-electron oxidation of carbanions[8,9].

Thus, the general kinetic patterns of the base-catalyzed oxidation of SA established in this study, agree with those found for the oxidation of C-H acids. At the same time, a more complicated set of oxidation products found for the amide ions[3–5,11] as compared to typical set of products known for carbanions[10,11] enables us to suppose a substantial difference between detailed mechanisms of these two reactions. The study of these mechanisms will be the purpose of the following reports.

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