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Deuterium Isotope Effect in the Reaction of Anthrone Oxidation with Molecular Oxygen Catalyzed with Aliphatic Amines

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Abstract—Deuterium isotope effect in the process of the amine-catalyzed anthrone oxidation with molecular oxygen was studied. Reaction proceeds by oxygen insertion in C–H bonds in the position 10. Isotope effect is observed only at the stage of the anthranolate anions reaction with oxygen, and not at the stage of their formation. Therefore it is a secondary isotope effect.

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Anthrone and its derivatives exhibit a pronounced biological activity. For example, knifolone and knifolone-anthrone show antioxidant, antimicrobial, and cytotoxic properties [1]. 9-Anthrones show antipsoriatic action resulting from formation of oxygen-containing active particles in the course of their oxidation [2]. Anthrone oxidation with molecular oxygen catalyzed with amino acids and amines is a model of biosynthesis of antitumor antibiotics of anthracycline series [3]. The suggested mechanism of this process [4] includes proton transfer stages. Therefore the investigation of deuterium isotope effect is important for obtaining more detailed information on the features of oxidation mechanism of [5–8].

Previously we have studied anthrone oxidation with molecular oxygen in polar aprotic solvents under catalysis with aliphatic amines. It was shown that this reaction proceeded through the formation of the anthrone–amine molecular complexes [9].

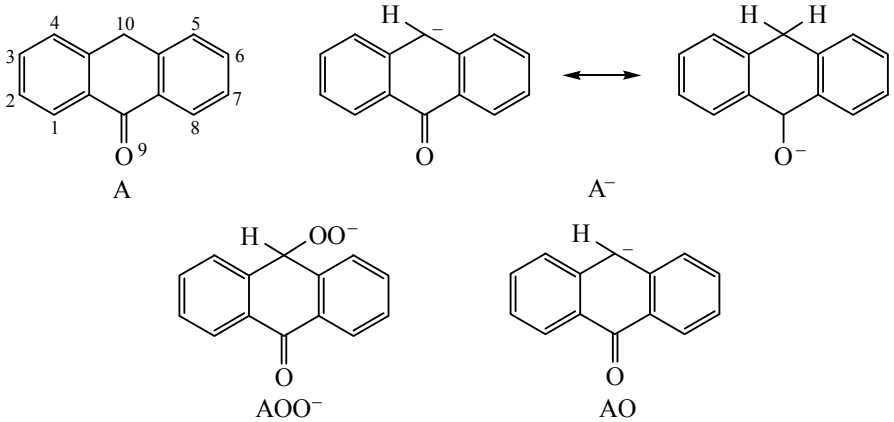
$$2A + Am \rightleftarrows A_2 \cdot Am,\ K_1, \quad (1)$$

$$A_2 \cdot Am \rightleftarrows A^- + A \cdot AmH^+,\ K_2, \quad (2)$$

$$A^- + O_2 \rightarrow AOO^-,\ k_3, \quad (3)$$

$$AOO^- + A \cdot AmH^+ \rightarrow AO + Am + A + H_2O,\ k_4. \quad (4)$$

Here A is anthrone, Am, AmH^+ are the amine and its protonated form, A^- is the anthranolate anion, AOO^- is hydroperoxide anion, AO is anthraquinone.



Kinetic analysis of mechanism [10] provides the equation of the process rate which agrees with the experimental data [Eq. (5)].

$$w = k_3 x_1[O_2] = k_3[A_0][O_2]\sqrt{K_1 K_2[Am_0]}. \quad (5)$$

According to the scheme [Eqs. (1)–(4)] the deuterium atom can take part in ionization [Eq. (2)] or in the stage of the reaction with oxygen [Eq. (3)]. Rate constants of these stages are included in the Eq. (5). The influence of deuterium isotope effect on the rate of oxidation may be direct (primary isotope effect when deuterium atom takes part in ionization of anthrone, and oxygen attacks C^{10}–D bond) and indirect (secondary isotope effect when oxygen attacks not the C^{10}–D bond, but C^{10}–H one adjacent to deuterium). Primary deuterium isotope effect may be traced spectrophotometrically by the rate of formation of intensely colored anthranolate anion.

As we failed to isolate deuteroanthrone pure from the reaction mixture, the preparation was used which contained small amount of non-deuterated substrate. Deuteration degree of anthrone (χ) was established by means of the ^{1}H NMR spectroscopy from the decrease in the intensity of signal of proton in the position 10 of anthrone (8.02 ppm, singlet) against the intensity of signals of protons in the positions 1 and 8 (8.35 ppm, 2H, doublet, J 8.4 Hz) (Fig. 1). The deuteration degree was ~85%.

At the addition of catalyst of basic nature (inorganic alkali or amine) to the solution of anthrone in DMSO the formation of colored anthranolate anion (absorption maximum at 490 nm, Fig. 2a) takes place. If the step of establishing equilibrium (2) (characterized by the equilibrium constant K_2) is sensitive to isotope substitution, the difference in optical density of solutions of anthrone and deuteroanthrone in the presence of catalyst must be observed in the initial stage just after mixing reagents. As seen from the Eq. (5) the rate of the process under study depends on the square root of the catalyst concentration. Measurements of optical density alteration on this wavelength for anthrone-triethylamine and deuteroanthrone-triethylamine systems showed that obtained data can be linearized in optical density–C(triethylamine)$^{0.5}$ coordinates. The observed ratio of slope angles is about 1 within the limits of experimental error (Fig. 2b). Hence, the rate of formation of anthranolate anion in the case of deuterated as well as of non-deuterated derivative is practically the same. The absence of difference in optical densities of anthrone and deuteroanthrone solutions in the presence of catalyst (Fig. 2b) shows that the equilibrium constants of these processes are close. In the case of their difference the amount of colored anthranolate ion and hence optical density of solutions must be also different.

Therefore in the stage of formation of anthranolate ions no primary deuterium isotope effect was observed. But the processes of catalytic anthrone oxidation and deuteroanthrone can proceed with different rate due to the secondary deuterium isotope effect.

To establish the character of influence of the isotope substitution of anthrone on the observed reaction rate the oxidation kinetics was measured by the amount of absorbed oxygen. Kinetic curves are well described by Eq. (6).

$$n(O_2)_t = n(O_2)_\infty(1 - e^{-k_{ef}t}). \quad (6)$$

Here $n(O_2)$ is the amount of oxygen absorbed by 1 L of the reacting solution until the given time, mol; $n(O_2)_\infty$ is the maximum amount of absorbed oxygen at the infinitely long reaction time, mol; k_{ef} is the effective rate constant, s^{-1}; t is time, s.

In the case of oxidation of deuteroanthrone obtained k_{ef} includes effective rate constants of the reactions of catalytic oxidation of deuterated and non-deuterated anthrone (because deuteration degree χ is 85%). If the processes of anthrone oxidation and deuteroanthrone proceed independently k^D_{ef} may be obtained directly by separation of k_{ef} into the components k^D_{ef} and k^H_{ef} according to the Eq. (7) as it was done in [10]:

$$k_{ef} = \chi k^D_{ef} + (1 - \chi)k^H_{ef}. \quad (7)$$

Here k^D_{ef} is the effective rate constant of oxidation of deuterated substrate, s^{-1}; k^H_{ef} is the effective rate constant of oxidation of non-deuterated substrate s^{-1}.

Results of treating of kinetic data within the frames of the Eqs. (6) and (7) are listed in the table.

It must be specially noted that addition of catalyst (isopropoxypropylamine) may accelerate the isotope exchange. It may happen that deuteration proceeds faster than oxidation, and only deuterated anthrone will take part in oxidation. In this case no correction of data according to the Eq. (7) must be done, and k_{ef} may be used directly, namely, $k_{ef} \approx k^D_{ef}$. In the table values of deuterium isotope effect considering the correction according to Eq. (7) as well as without it are presented.

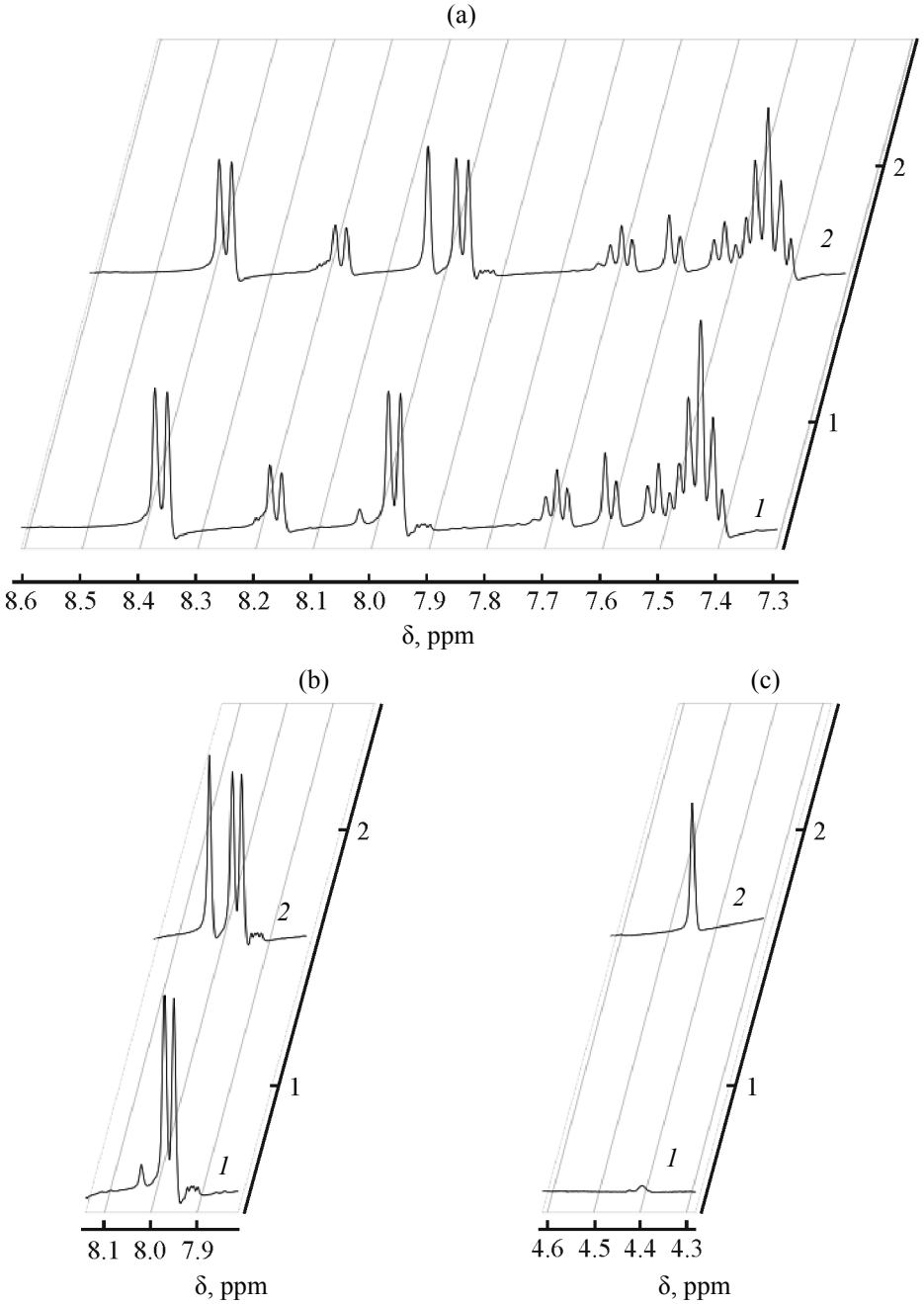
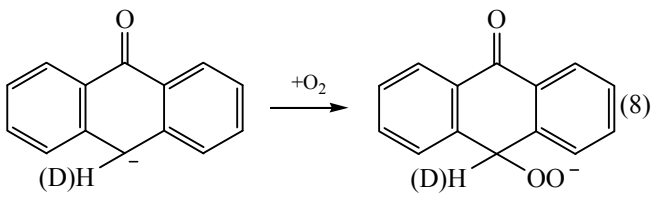


Fig. 1. ^{1}H NMR spectrum (400 MHz) of anthrone solutions in (*1*) DMSO/D_2O and (*2*) DMSO–H_2O mixtures in the range (a) 7.3–8.6 ppm, (b) 7.9–8.1 ppm, and (c) 4.3–4.6 ppm.

Obtained values 1.6 and 1.8 can be regarded as the same within the evaluation errors.

The observed deuterium isotope effect in the reaction of anthrone oxidation with molecular oxygen is evidently the secondary one. It is not connected with the direct proton transfer in the rate determining stage. The change in the reaction rate at the isotope substitution in this case is caused by the fact that insertion of oxygen molecule proceeds directly at the carbon atom where protium is substituted by deuterium [Eq. (8)].



(8)

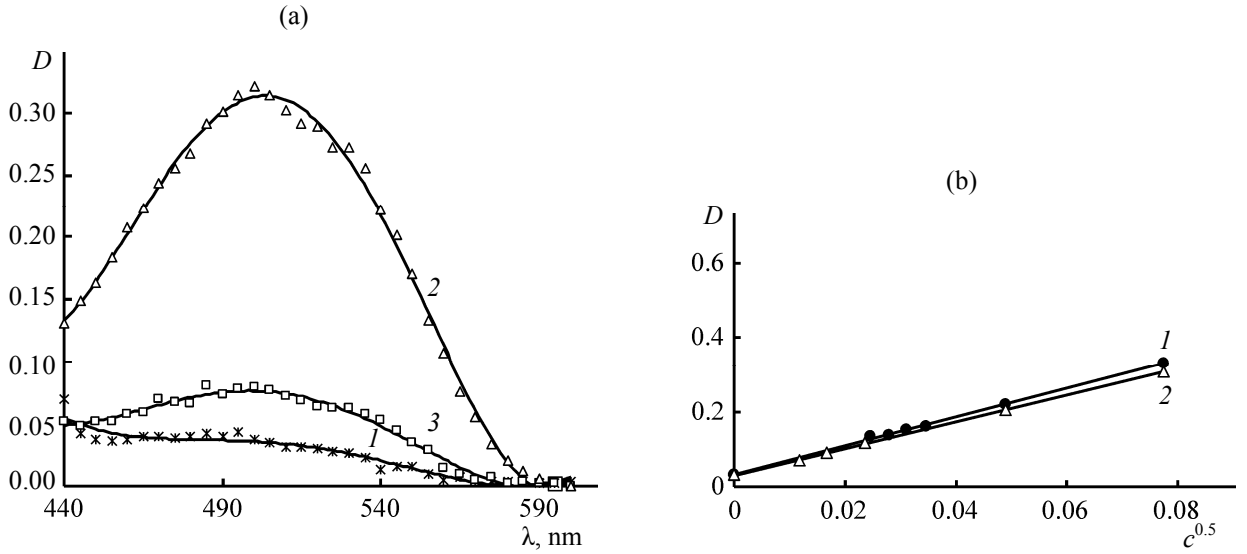


Fig. 2. (a) Electron absorption spectrum of anthrone (5×10^{-4} mol/L) in (*1*) DMSO, in (*2*) saturated KOH solution in DMSO, and (*3*) in DMSO in presence of Et_3N (0.029 mol/L) at 298 K and (b) dependence of optical density of (*1*) anthrone/deuteroanthrone solution (0.025 mol/L) in 1 : 1 DMSO–acetonitrile with (*2*) the addition of H_2O/D_2O on the concentration of Et_3N (λ 490 nm, 298 K).

Analogous influence of isotope substitution was observed previously [11] for the process of ionization of 4,4'-disubstituted benzhydrols [Eq. (9)] where the value of secondary isotope effect varied in the range 1.1–1.3.

$$Ar_2CHOH + H^+ = Ar_2CH^+ + H_2O,$$
$$Ar_2CDOH + H^+ = Ar_2CD^+ + H_2O. \quad (9)$$

Hence, the obtained data permit to suggest that isotope effect in the reaction of anthrone oxidation and deuteroanthrone is secondary one. It is connected with isotope substitution in the reaction center of molecule where insertion of oxygen takes place.

EXPERIMENTAL

NMR spectra were taken on a Bruker Avance II 400 (400 MHz) spectrometer. Visible electron absorption spectra were recorded on a Genesys 10 S UV-Vis (Thermo Electron Corp.) spectrophotometer. All the experiments were carried out at 298 K. Kinetics of oxidation was controlled by gas volumetry under the constant partial pressure of molecular oxygen.

Anthrone ("Aldrich," 97%), acetonitrile ("Merk," ≥ 99.5%) DMSO-d_6 ("Aldrich," ≥ 99.8%) and D_2O ("Aldrich," ≥ 99.9%) were used without additional purification. DMSO was purified by vacuum distillation, its purity was controlled by chromatography.

Isopropoxypropylamine and triethylamine were purified by distillation at atmospheric pressure. Their purity was controlled by refraction index value.

Anthrone deuterated in the position 10 was obtained by non-catalytic isotope exchange in DMSO–D_2O system. Choice of just this approach was due to some complications arising at the use of catalysts: Firstly, the presence of even insignificant residual amounts of base might influence the rate of oxidation [4]; secondly, at the use of acidic catalyst might change the position of deuteration (instead of the position 10 duteration might occur in positions 2(7)

Effective rate constants of oxygen absorption of with the solutions of anthrone and deuteroanthrone (0.05 mol/L) in the presence of isopropoxypropylamine (0.005 mol/L) in DMSO–H_2O (D_2O) mixture and deuterium isotope effect at 760 mm and 307 K

$(k_{ef}^H \pm 0.04) \times 10^3$, s^{-1}	$(k_{ef}^D \pm 0.04) \times 10^3$, s^{-1}	k_{ef}^H/k_{ef}^D	k_{ef}^H/k_{ef}^D [a]	Mean deuterium isotope effect
0.95	0.60	1.58	1.75	1.59–1.8
0.98	0.61	1.60	1.81	

[a] Considering the deuteration degree of anthrone (χ).

and 4(5) [12]; finally, in the case of using of basic catalyst the intensification of oxidation might lead to significant consumption of substrate [4].

In the preliminary experiments it was shown that heating favors the increase in deuteration degree. Optimum temperature is 323–328 K. We failed to isolate fully deuterated product evidently because of its oxidation in the course of the process. In this connection the optimum solution of this problem was the direct application of reaction solutions containing deuterated derivative together with non-deuterated anthrone.

These solutions were prepared as follows. Anthrone, 0.08 g, was dissolved in 7 mL of DMSO and treated with 1 mL of D_2O. Obtained mixture was stirred, with argon bubbled through the solution, and maintained at 298 K for 96 h and 4 h at 328 K. After that a sample for NMR analysis was taken, and from the spectrum obtained the content of deuterated product was evaluated (Fig. 1).

The rate of oxidation process was measured by gas volumetry. Amount of absorbed oxygen was measured at 307 K. In the course of evaluation of deuterium isotope effect in the amine-catalyzed reaction of anthrone oxidation with oxygen and in the investigation of process of carbanion formation the samples containing water instead of D_2O were used as reference solutions. They were prepared and treated analogously to the above-described deuterium-containing solutions.

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