INVESTIGATION OF THE REACTION OF 1,2,3-TRIMETHYL-2-PHENYLBENZIMIDAZOLINE WITH DEHYDROGENATING REAGENTS BY EPR SPECTROSCOPY

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The reaction of 1,2,3-trimethyl-2-phenylbenzimidazoline with a number of reagents that manifest dehydrogenating properties with respect to benzimidazolines was studied by EPR spectroscopy. These reagents convert 1,2,3-trimethyl-2-phenylbenzimidazoline to a relatively stable cation radical. The mechanism of the dehydrogenation of benzimidazolines is discussed taking into account the established facts.

A characteristic chemical property of 2,3-dihydrobenzimidazoles (benzimidazolines) is their pronounced tendency to undergo aromatization with the formation of benzimidazole derivatives [1-5]. In particular, under the influence of even weak dehydrogenating agents such as the silver cation, organic cations, and halogens, 1,3-disubstituted benzimidazolines are readily converted to benzimidazolium salts [2-5]. According to [2-5], the formation of these salts occurs as a result of hydride-ion transfer from the substrate to the dehydrogenating agent. However, at present the realization of hydride transfer in many dehydrogenation reactions seems unlikely [6]. On the other hand, there is no doubt that such reactions often have an ion-radical mechanism in which dehydrogenation of the substrate is a consequence of its initial oxidation by the reagent to a highly reactive cation radical. The subsequent transformations of the cation radical usually commence with its deprotonation [6, 7]; however, a scheme involving aromatization of the cation radical due to loss of a hydrogen atom by it has been proposed for some hydro derivatives of heteroaromatic compounds, particularly for benzimidazolines [8].

An ion-radical mechanism for the dehydrogenation of benzimidazolines is extremely likely inasmuch as these compounds are extremely inclined to donation of one electron,* and the dehydrogenating agents are simultaneously also oxidizing agents. The relationship between the redox potentials of the substrate and the reagent in this case is often such that electron transfer between them proves to be an exoergic process. In the present paper we present the results of a study by EPR spectroscopy of the reaction of 1,2,3-trimethyl-2-phenylbenzimidazoline (I) with a number of dehydrogenating reagents that confirm the realization of electron transfer in benzimidazoline—dehydrogenating reagent systems. Although I is known to be incapable of either donation of a hydride ion or dehydrogenation, it nevertheless reacts with the silver cation just as readily as benzimidazolines that have a hydrogen atom in the 2 position. The reaction products are a benzimidazoline cation radical and metallic silver, which develop as a result of electron transfer:

I

X=ClO$_4$, NO$_3$

I$^{+\cdot}$

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*This is confirmed by their low electrochemical oxidation potentials [9].

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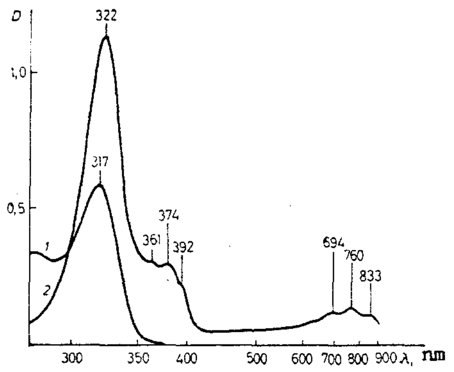


Fig. 1

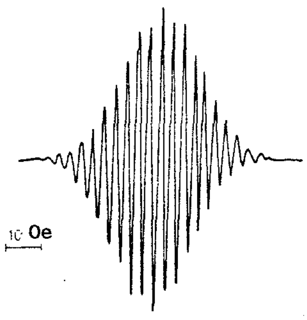


Fig. 2

Fig. 1. Electronic absorption spectra: 1) 1,2,3-trimethyl-2-phenylbenzimidazoline (I) in acetonitrile ($c_I = 8.5 \cdot 10^{-5}$ M; $\ell = 1$ cm); 2) reaction mixture in the oxidation of imidazoline I in acetonitrile with silver perchlorate ($c_I = 8.5 \cdot 10^{-5}$ M, $c_{AgClO_4} = 9.1 \cdot 10^{-2}$ M; $\ell = 1$ cm).

Fig. 2. EPR spectrum of cation radical $I^{+\cdot}$ formed in the reaction of imidazoline I with silver perchlorate in acetonitrile.

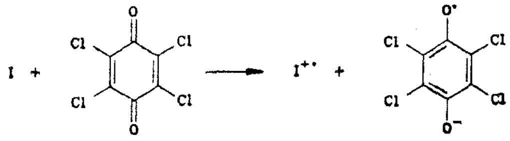
The oxidation process is clearly reversible: even when a large excess of the reagent is present, the addition of more of it leads to an increase in the intensities of the absorption bands of the cation radical in the electronic absorption spectrum of the reaction mixture (Fig. 1).

The EPR spectrum of the cation radical (Fig. 2) consists of 23 equidistant lines with a splitting of 3.2 Oe between them. It is due to coupling of the unpaired electron with two equivalent nitrogen atoms ($a_N = 6.4$ Oe), as well as with the protons of the N-methyl groups ($a_H^{CH_3} = 6.4$ Oe) and the 5 and 6 positions of the aromatic ring ($a_H^{5,6} = 3.2$ Oe). The observed ratio of the intensities of the lines is close to the theoretical value 1:2:9:16:36:60:100:140:180:224:264:224:180:140:100:60:36:16:9:2:1. Because of their low intensities, the two lines at the edges of the spectrum (Fig. 2) can be observed only when the edges of the spectrum are recorded with high amplification. The values of the hyperfine coupling (HFC) constants provide evidence that the highest occupied molecular orbital (HOMO) of the cation radical is similar in character to the antisymmetric e_1 orbital of benzene; the nodal points are the 4 and 7 positions of the benzimidazoline, in which the density of the unpaired electron is equal or close to zero. The HOMO of the unoxidized form is undoubtedly characterized by similar properties. The spectrum of radical $I^{+\cdot}$ is basically similar to the spectrum of the cation radical of 1,3-dimethyl-2-phenylbenzimidazoline (II) [8] — the only previously described cation radical of the benzimidazoline series. The difference consists in the absence of doublet splitting by the hydrogen atom in the 2 position.

In contrast to cation radical $II^{+\cdot}$, cation radical $I^{+\cdot}$ cannot undergo aromatization with splitting out of hydrogen; this is the reason for its relatively high stability. Whereas radical $II^{+\cdot}$ in solution in acetonitrile undergoes complete decomposition in fractions of a second [8], blue solutions of $I^{+\cdot}ClO_4^-$ obtained by oxidation of benzimidazoline I with silver perchlorate decompose appreciably under the same conditions only when they are stored for days. Thus the low stability of cation radical $II^{+\cdot}$ is associated with its ability to undergo facile aromatization with the formation of a benzimidazolium salt.

Divalent copper and trivalent iron cations react like the silver cation with imidazoline I. When this compound is treated with copper(II) tetrafluoroborate or iron(III) perchlorate in acetonitrile, the spectrum of cation radical $I^{+\cdot}$ is readily recorded by EPR spectroscopy. If imidazoline II is used in place of imidazoline I, the former undergoes rapid dehydrogenation with the formation of the corresponding benzimidazolium salts. These results, in combination with the results previously obtained for II [8], constitute evidence that in the dehydrogenation of benzimidazolines with metal cations the latter act as one-electron oxidizing agents rather than as hydride-ion acceptors.

Chloranil, halogens, and the nitrosonium cation behave like metal cations with respect to I. Both electron-transfer products — the cation radical of the substrate and the anion radical of the reagent — can be recorded in the reaction of imidazoline I with chloranil in acetonitrile. The EPR spectrum of the reaction mixture (Fig. 3) in this case is the superimposition of the multiplet signal of cation radical $I^{+\cdot}$ and the singlet signal of the quinone anion radical. Only the EPR spectrum of the $I^{+\cdot}$ cation radical alone with splitting constants close to those presented above is recorded in the reaction of I with bromine and iodine in acetonitrile.



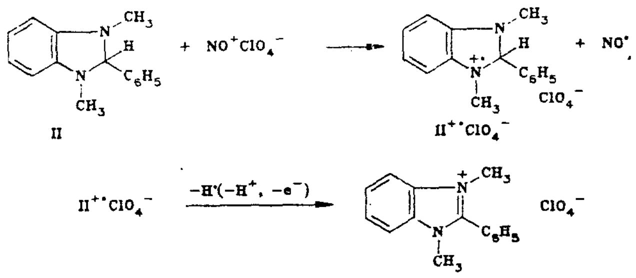
$$I + X_2 \longrightarrow I^{+\cdot} + X_2^{-\cdot}$$

X=Br, I

Taking into account the latter fact, the dehydrogenating effect of halogens with respect to benzimidazolines [3] should be linked with the ability of these reagents to act as acceptors of one electron.

In addition to the formation of cation radical $I^{+\cdot}$, which is readily observed by EPR spectroscopy, the vigorous evolution of nitric oxide — the product of one-electron reduction of NO^+ — is noted in the reaction of imidazoline I with nitrosonium perchlorate. It is not surprising that the nitrosonium cation readily hydrogenates benzimidazolines. For example, treatment of II with nitrosonium perchlorate leads to 1,3-dimethyl-2-phenylbenzimidazolium perchlorate and nitric oxide in good yield.

$$I + NO^+ClO_4^- \longrightarrow I^{+\cdot}ClO_4^- + NO^{\cdot}$$



The facile transfer of an electron from benzimidazolines to NO^+ is promoted by its considerable exoergic character. Theoretical estimates [10] show that exoergic electron transfer from aromatic and heterocyclic compounds to the nitrosonium cation should occur at high rates. For benzimidazoline II the change in free energy ΔG_0 in the transfer of an electron to the nitrosonium cation can be estimated by a value on the order of −85 kJ/mole (starting from the redox potentials of $NO^{\cdot}/NO^+$ and $II/II^{+\cdot}$ half cells, which are, respectively, 1.25 V [10] and ∿0.3 V [8] relative to a saturated calomel electrode).

EXPERIMENTAL

The EPR spectra were recorded with an RÉ-1301 spectrometer at 20°C under degassing conditions. The IR spectra (of mineral oil suspensions), the PMR spectra, and the electronic absorption spectra, respectively, were recorded with Specord IR-71, Tesla BS-487C (80 MHz), and Specord M-40 spectrometers.

1,2,3-Trimethyl-2-phenylbenzimidazoline (I). A suspension of 12 g (0.03 mole) of 1,3-dimethyl-2-phenylbenzimidazolium iodide [3] in 20 ml of ether was added with stirring to a solution of methylmagnesium iodide, obtained from 23 g (0.16 mole) of methyl iodide and 4 g (0.16 mole) of magnesium in 70 ml of ether, after which the mixture was maintained at 25°C for 1 h, refluxed for 30 min, and hydrolyzed cautiously with 25 ml of water. The ether layer was separated, the solvent was removed by distillation, and the residue was dissolved in the minimum amount of benzene. The solution was passed through a column packed with aluminum oxide with collection of the first fraction [elution with benzene—hexane

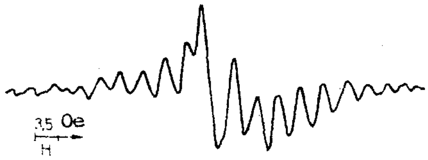


Fig. 3. EPR spectrum of a mixture of cation radical $I^{+\cdot}$ and the chloranil anion radical in the I–chloranil system in acetonitrile.

(1:3)] to give 1.2 g (15%) of a product with mp 56-57°C (from aqueous alcohol). Found: C 80.4; H 8.0; N 11.6%. $C_{16}H_{18}N_2$. Calculated: C 80.6; H 7.6; N 11.8%. PMR spectrum (C_6D_6): 6.8-7.4 (m, 5H, C_6H_5), 6.60-6.75 (m, 2H, 5,6-H_2), 5.92-6.15 (m, 2H, 4,7-H_2), 2.11 (s, 6H, N–CH_3), 1.21 ppm (s, 3H, C–CH_3).

Dehydrogenation of 1,3-Dimethyl-2-phenylbenzimidazoline (II). A) A 0.5-g (2.2 mmole) sample of imidazoline II in 10 ml of acetonitrile was added with stirring in the course of 1 min to a solution of 1.6 g (4.6 mmole) of copper(II) tetrafluoroborate hexahydrate in 5 ml of acetonitrile, after which the mixture was evaporated to dryness, and the residue was extracted with 25 ml of boiling alcohol. Crystals of 1,3-dimethyl-2-phenylbenzimidazolium tetrafluoroborate contaminated with admixed copper salts precipitated when the extract was cooled. The salt was purified by recrystallization from water and then from alcohol to give 0.3 g (43%) of a product with mp 204-205°C. The IR spectrum was similar to the spectrum of 1,3-dimethyl-2-phenylbenzimidazolium perchlorate (see below): 705, 718, 758, 825, 869, 950, 1078 (BF_4^-), 1172, 1275, 1281, 1357, 1413, 1476, 1525, 1543, 1579, 1608 cm^{-1}.

B) An aqueous solution of 0.6 g (2.6 mmole) of II in 12 ml of acetonitrile was added with stirring and cooling to a solution of 3.1 g (6 mmole) of iron(III) perchlorate nonahydrate in 10 ml of acetonitrile. A rapidly vanishing blue coloration, which belongs, in all likelihood, to cation radical $II^{+\cdot}$, was observed at the instant that the reagents were mixed. The reaction mixture was diluted with 100 ml of ether, and the lower layer was separated and maintained at 0°C until precipitation of 1,3-dimethyl-2-phenylbenzimidazolium perchlorate was complete. Alcohol (10 ml) was then added, and the salt was removed by filtration, washed with a small amount of alcohol, and dried to give 0.7 g (81%) of a product with mp 216-217°C (from alcohol) [3]. IR spectrum: 705, 719, 760, 825, 870, 940, 952, 1090 (ClO_4^-), 1171, 1273, 1287, 1358, 1407, 1462, 1517, 1546, 1579, 1609 cm^{-1}. Found: C 56.2; H 4.8; Cl 11.2%. $C_{15}H_{15}ClN_2O_4$. Calculated: C 55.8; H 4.7; Cl 11.0%.

C) A 1.5-g (6.7 mmole) sample of imidazoline II in 10 ml of acetonitrile was added with stirring in a nitrogen atmosphere in the course of 15 min to a suspension of 2 g (15.4 mmole) of nitrosonium perchlorate* [11] in 15 ml of dry acetonitrile. The reaction was accompanied by the vigorous evolution of nitric oxide (in 56% yield; determined by the method in [12]). Five minutes after the reagents had been mixed, the reaction mixture was treated with 3 ml of alcohol (to decompose the possibly unchanged nitrosonium salt), the mixture was evaporated to 10 ml, and the reaction product – 1,3-dimethyl-2-phenylbenzimidazolium perchlorate – was precipitated with 80 ml of ether to give 1.9 g (86%) of a product with mp 214-215°C (from alcohol). No melting-point depression was observed for a mixture of this product with a sample of the salt obtained by the method described above.

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*Dangerously explosive! Precautionary measures must be observed; do not allow contact with solvents of the ether type and aliphatic ketones.

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PREPARATION OF 2-ARYL-SUBSTITUTED IMIDAZO[4,5-b]PYRIDINES AND IMIDAZO[4,5-c]PYRIDINES

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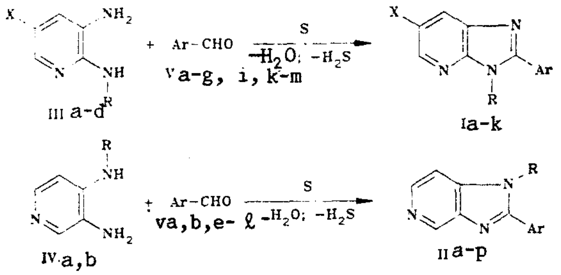
It is proposed that sulfur be used as the oxidizing agent in the synthesis of 2-arylimidazopyridines from o-diaminopyridines and aromatic (heteroaromatic) aldehydes. Benzyl alcohols and benzylpyridinium salts can be used in place of aldehydes. 2-Phenylimidazopyridines are also formed in the thermal oxidation with sulfur of o-diaminopyridines with a benzyl substituent attached to the ring or exocyclic nitrogen atoms.

It is known that o-diamines of the benzene series readily undergo cyclization to the corresponding benzimidazoles on heating with carboxylic acids or their anhydrides [1, 2]. However, imidazopyridines cannot be obtained by this method, since, with rare exceptions [3, 4], N-acylation products are formed from o-diaminopyridines [5-7]. The cyclization of o-diaminopyridines with aromatic acids proceeds only in strong dehydrating agents [polyphosphoric acid (PPA), $POCl_3$] [7, 8]. In this connection, the synthesis of imidazopyridines from o-diaminopyridines and aldehydes in the presence of oxidizing agents such as air oxygen, nitrobenzene [9], or a copper(II) salt [5, 10] is of particular interest.



I a–e, i–k X=H, f, g X=Cl, h X=Br; a–j R=H, k $R=CH_3$; a $Ar=C_6H_5$, b $Ar=4\text{-}ClC_6H_4$, c $Ar=4\text{-}FC_6H_4$, d $Ar=4\text{-}HOC_6H_4$, e $Ar=4\text{-}CH_3OC_6H_4$, f $Ar=4\text{-}(CH_3)_2NC_6H_4$, g $Ar=2\text{-}(HO)\text{-}3\text{-}(CH_3O)C_6H_3$, h $Ar=2,5\text{-}(CH_3O)_2C_6H_3$, i Ar=2-thienyl, Ar=3-pyridyl, k Ar=1-methyl-3-indolyl; IIa, c–e, h, j, ℓ, n, p R=H; b, f, g, i, k, m, o $R=CH_3$; a, b $Ar=C_6H_5$, c $Ar=4\text{-}ClC_6H_4$, d $Ar=4\text{-}CH_3OC_6H_4$, e, f $Ar=4\text{-}(CH_3)_2NC_6H_4$, g $Ar=2\text{-}(HO)\text{-}3\text{-}(CH_3O)C_6H_3$, h $Ar=4\text{-}(HO)\text{-}3\text{-}(CH_3O)C_6H_3$, i $Ar=4\text{-}(HO)\text{-}3\text{-}(CH_3O)C_6H_3$, j, k $Ar=3,4\text{-}(CH_3O)_2C_6H_3$, ℓ, m $Ar=2,5\text{-}(CH_3O)_2C_6H_3$, n, o Ar=2-thienyl p Ar=3-pyridyl; IIIa, b X=H, c X=Cl, d X=Br; a, c, d R=H, b $R=CH_3$; IVa R=H; b $R=CH_3$; V a $Ar=C_6H_5$; b $Ar=4\text{-}ClC_6H_4$; c $Ar=4\text{-}FC_6H_4$; d $Ar=4\text{-}HOC_6H_4$; e $Ar=4\text{-}CH_3OC_6H_4$; f $Ar=4\text{-}(CH_3)_2NC_6H_4$; g $Ar=2\text{-}(HO)\text{-}3\text{-}(CH_3O)C_6H_3$; h $Ar=4\text{-}(HO)\text{-}3\text{-}(CH_3O)C_6H_3$; i $Ar=2,5\text{-}(CH_3O)_2C_6H_3$; j $Ar=3,4\text{-}(CH_3O)_2C_6H_3$; k Ar=2-thienyl, ℓ Ar=3-pyridyl; m Ar=1-methyl-3-indolyl.

We have found [11] that the simplest and most convenient modification of the last of the methods cited above for the synthesis of 2-arylimidazo[4,5-b]pyridines Ia, f and 2-aryl-

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