

# Nucleophilic Replacement of Hydrogen in *para*-Substituted Nitrobenzenes by Phenylacetonitrile Carbanion

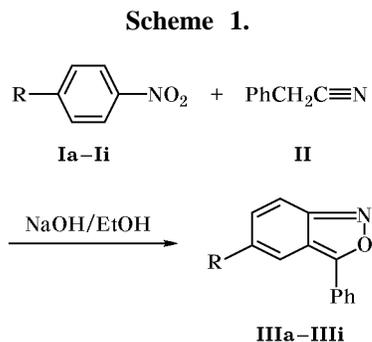
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Received August 2, 2000

**Abstract**—The kinetic relations holding in nucleophilic replacement of hydrogen in *para*-substituted nitrobenzenes by phenylacetonitrile carbanion suggest a complex reaction mechanism involving two alternative pathways. The direction of the process is determined by the structure of intermediate  $\sigma$ -complex.

Nucleophilic replacement of hydrogen in *para*-substituted nitrobenzenes **Ia–Ii** by carbanion generated *in situ* (ethanolic alkali) from phenylacetonitrile (**II**) leads to formation of the corresponding 2,1-benzisoxazoles **IIIa–IIIi** (Scheme 1).

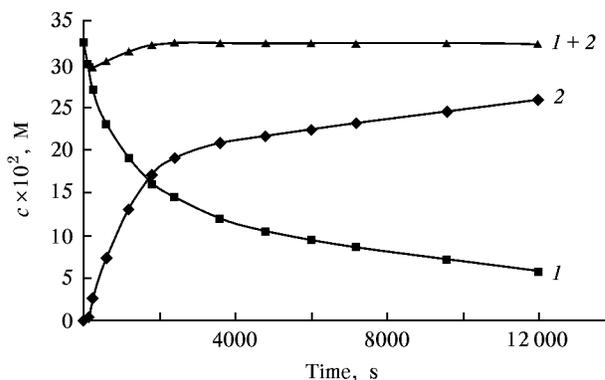


**I, III**, R = Cl (**a**), Br (**b**), I (**c**), 1-methyl-1,3-dioxolan-2-yl (**d**), 1,3-dioxolan-2-yl (**e**), Ph (**f**), OPh (**g**), 2,4-Cl<sub>2</sub>C<sub>6</sub>H<sub>3</sub>O (**h**), 4-PhC<sub>6</sub>H<sub>4</sub>O (**i**).

The synthetic aspect of nucleophilic substitution of hydrogen has been extensively studied [1, 2]; however, very limited published data are available on quantitative, in particular kinetic relations holding in this process. The lack of such information makes it difficult to formulate a general concept of the reaction mechanism. Therefore, the present communication reports the results of our study on the kinetics of the reaction outlined in Scheme 1.

The progress of the reaction was monitored following the concentrations of initial nitro compounds **I** and final 2,1-benzisoxazoles **III**. The concentrations of **I** and **III** were determined by polarography. The

yields of the products were almost quantitative, and neither accumulation of intermediate products nor formation of by-products was observed (Fig. 1). The kinetic measurements were performed under pseudo-first-order conditions using the isolation technique [3], i.e., all reactants, except for the nitroaromatic substrate, were taken in a large excess. The order of the reaction and its rate constant were determined from the kinetic curves by the van't Hoff method and by integration [4]. The results obtained by the two methods almost coincided. It should be noted that the reaction rate does not depend on the order of mixing of the reactants and that the kinetic parameters determined from variation of the concentrations of 4-nitrochlorobenzene (**Ia**) and benzisoxazole **IIIa** were similar. These findings indicate a high reactivity of intermediates. The reaction order with respect to the substrate and reagent is equal to unity.



**Fig. 1.** Kinetic curves for (1) consumption of *p*-nitrochlorobenzene (**Ia**) and (2) appearance of 5-chloro-3-phenyl-2,1-benzisoxazole (**IIIa**) in the reaction of **Ia** with phenylacetonitrile carbanion.

Apparent activation parameters of the reaction of substituted nitrobenzenes **Ia**, **Ie**, and **Ih** with carbanion generated from phenylacetonitrile (**II**)

Comp. no.	Temperature range, K	$E_a$ , kJ/mol	$\Delta H$ , kJ/mol	$\Delta S$ , J mol <sup>-1</sup> K <sup>-1</sup>	$\Delta G$ , kJ/mol	lnA
<b>Ia</b>	303–314	29.2±1.5	26.6±1.3	-252.0±13	104.3±1.3	2.41±0.02
	314–328	91.4±3.9	88.7±4.0	-57.7±2.5	107.2±4.0	25.9±0.1
<b>Ie</b>	303–328	42.6±1.8	40.0±1.3	-192.7±12	100.8±1.3	6.3±0.05
<b>Ih</b>	303–314	5.8±1.3	3.2±1.1	-310.8±15	99.1±1.1	1.8±0.1
	314–328	31.2±3.7	28.6±3.8	-230.9±3.5	102.7±3.8	7.9±0.1

Preliminary study of the temperature dependence of the reaction rate in the range from 303 to 328 K gave unexpected results. The  $\ln k_{ap} - 1/T$  dependences for nitrochlorobenzene **Ia** and ether **Ih** have an inflection point (Fig. 2). Such shape of the Arrhenius plot suggests that the process takes two pathways. It should be noted that within both temperature intervals (before and after inflection point) the same product is formed, 5-substituted 3-phenyl-2,1-benzisoxazole. Therefore, change of the reaction pathway with rise in temperature does not result in formation of another final product but involves variation of intermediate stages. The  $\ln k_{ap} - 1/T$  plot for nitro compound **Ie** has no inflection. Presumably, this is explained by suppression of one of the alternative pathway or by location of the inflection point beyond the examined temperature range. The thermodynamic parameters of the reactions with nitro compounds **Ia**, **Ie**, and **Ih** are given in table.

Taking into account the existence of two alternative pathways for formation of 2,1-benzisoxazoles, the subsequent kinetic measurements were performed at 303 K (the first branch of the Arrhenius plot) and 320 K (the second branch of the Arrhenius plot).

Figure 3 shows the effect of alkali concentration on the rate of the reaction of chloronitrobenzene **Ia** with phenylacetonitrile. The plots of  $k_{ap}$  versus alkali concentration at 303 and 320 K are similar. The corresponding curves are described by the equations

$$k_{ap} = 3 \times 10^{-4} c_{\text{NaOH}}^3 - 0.0001 \quad (303 \text{ K})$$

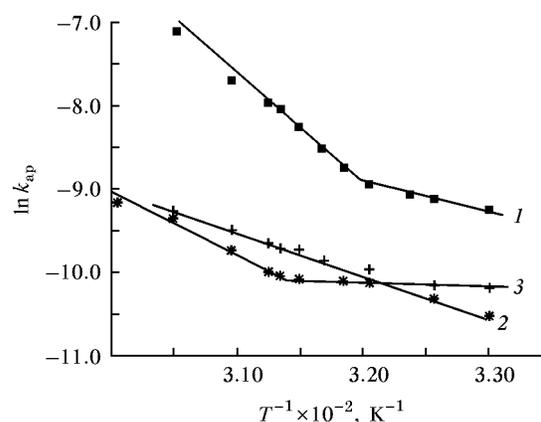
and

$$k_{ap} = 5 \times 10^{-6} c_{\text{NaOH}}^3 + 0.0007 \quad (320 \text{ K}).$$

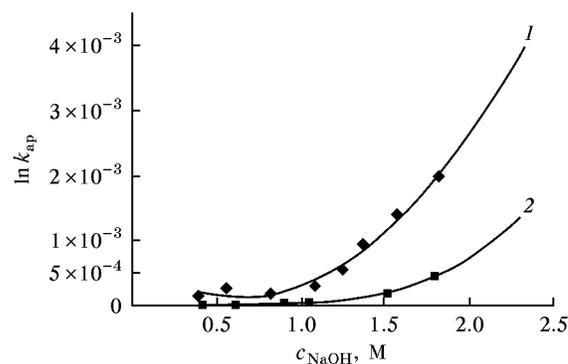
The nonlinear character of these dependences suggests a complex mechanism of participation of alkali in the process.

We also examined the kinetic parameters of the reactions carried out in aliphatic alcohols as solvents.

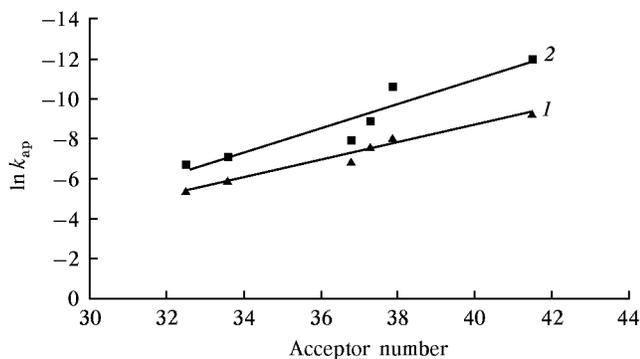
The results are shown in Fig. 4. The plots obtained in both temperature ranges have similar shapes. We tried to interpret them with the aid of acceptor number



**Fig. 2.** Plots of  $\ln k_{ap}$  versus  $1/T$  for the reactions of (1) 4-chloronitrobenzene (**Ia**), (2) 2,4-dichloro-4'-nitrodiphenyl ether (**Ih**), and (3) 4-(1,3-dioxolan-2-yl)nitrobenzene (**Ie**) with phenylacetonitrile (**II**);  $c_{\text{I}} = 0.03 \text{ M}$ ,  $c_{\text{II}} = 0.435 \text{ M}$ ,  $c_{\text{NaOH}} = 1.25 \text{ M}$ .



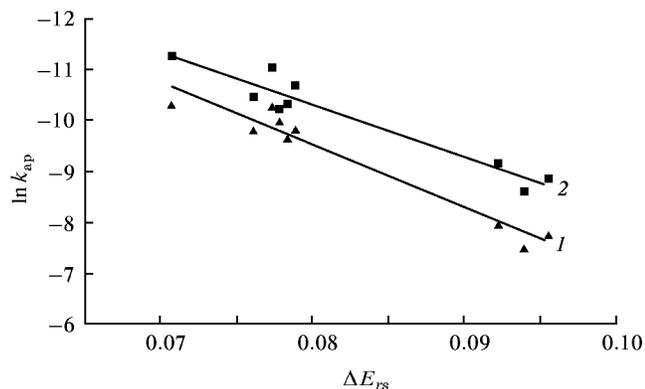
**Fig. 3.** Plots of  $k_{ap}$  versus alkali concentration  $c_{\text{NaOH}}$  for the reaction of 4-chloronitrobenzene (**Ia**) with phenylacetonitrile (**II**) at (1) 320 K ( $y = 0.000005x^3 + 0.0007$ ;  $R^2 = 0.9839$ ) and (2) 303 K ( $y = 0.0003x^3 - 0.0001$ ;  $R^2 = 0.9991$ );  $c_{\text{Ia}} = 0.020 \text{ M}$ ,  $c_{\text{II}} = 0.435 \text{ M}$ .



**Fig. 4.** Plots of  $\ln k_{\text{ap}}$  versus acceptor number of the solvent for the reaction of 4-chloronitrobenzene (**Ia**) with phenylacetonitrile (**II**) at (1) 320 K ( $y = 0.4457x + 9.1235$ ,  $R^2 = 0.9703$ ) and (2) 303 K ( $y = 0.6114x + 13.485$ ,  $R^2 = 0.8937$ );  $c_{\text{Ia}} = 0.020$  M,  $c_{\text{II}} = 0.435$  M,  $c_{\text{NaOH}} = 0.750$  M.

(AN), i.e., the parameter characterizing electrophilic properties of a solvent [5]. Figure 4 shows that the reaction slows down as AN increases at both 303 and 320 K. This is explained by stronger solvation of phenylacetonitrile carbanion than of intermediate  $\sigma$ -complex; as a result, the activation barrier increases. Our data indicate that in the two temperature ranges the rate-determining stage is formation of intermediate  $\sigma$ -complex.

In order to interpret the dependence of the reaction rate on the substrate structure we invoked an approach based on simulation of orbital interactions, namely between the highest occupied molecular orbital (HOMO) of the substrate and the lowest unoccupied molecular orbital (LUMO) of the reagent. We previously found [6] that in the formation of 2,1-benzisoxazoles from *para*-substituted nitroarenes the



**Fig. 5.** Plots of  $\ln k_{\text{ap}}$  versus  $\Delta E_{rs}$  for the reaction of substituted nitrobenzenes **I** with phenylacetonitrile (**II**) at (1) 320 K ( $y = 124.07x - 19.449$ ,  $R^2 = 0.048$ ) and (2) 303 K ( $y = 103.55x - 18.607$ ,  $R^2 = 0.9228$ );  $c_{\text{I}} = 0.0104$  M,  $c_{\text{II}} = 0.435$  M,  $c_{\text{NaOH}} = 1.250$  M.

position of the reaction center is determined by the frontier orbital structure. Rusakov *et al.* [7, 8] demonstrated the applicability of the Klopman combined reactivity index ( $\Delta E_{rs}$ ) [9] to some nucleophilic substitution reactions:

$$\Delta E_{rs} = -\frac{q_r q_s r}{\varepsilon} + \Delta_{\text{solv}} + \sum_m \sum_n \frac{2(C_{rm} C_{sn} \beta)^2}{E_n^* - E_m^*}.$$

Here,  $r$  and  $s$  are the indices of the reaction centers,  $\varepsilon$  is the dielectric constant of the solvent,  $r$  is a term characterizing Coulomb repulsion between the  $r$  and  $s$  atoms,  $m$  is the occupied orbital of the donor,  $n$  is the vacant orbital of the acceptor,  $c$  is the electron density on the frontier orbitals of the reaction center, and  $\beta$  is the resonance integral.

Taking into account that the substrate reaction center is characterized by the LUMO structure and that the contribution of the reagent is constant, the parameter  $\Delta E_{rs}$  is expressed by the equation

$$\Delta E_{rs} = C_{pz}^2 / \Delta E,$$

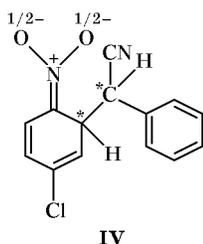
where  $C_{pz}^2$  is the orbital coefficient of the carbon atom neighboring to the nitro group and  $\Delta E$  is the energy difference between the LUMO of the substrate and HOMO of the reagent.

The  $\Delta E_{rs}$  values of the substrates were derived from the results of AM1 quantum-chemical calculations. Figure 5 shows the dependences of  $\ln k_{\text{ap}}$  versus  $\Delta E_{rs}$ . The linear character of the  $\ln k_{\text{ap}} - \Delta E_{rs}$  plots ( $r_2 = 0.95$  and  $r_1 = 0.92$ ) leads us to presume that the rate-determining stage is formation of new C–C bond. It is notable that analogous relations were obtained for both temperature intervals.

As stated above, the  $\ln k_{\text{ap}} - 1/T$  dependences for different 4-substituted nitroaromatic substrates are similar. However, the activation parameters for the reaction with ether **Ih**, calculated from the  $\ln k_{\text{ap}} - 1/T$  dependence, turned out to be anomalously low. The low activation energy implies a weak temperature effect on the reaction rate. In some cases this may be due to formation of contact ion pairs, specifically between sodium cation and phenylacetonitrile anion. However, the formation of such ion pairs in the reaction under study is hardly probable, for aliphatic alcohols solvate well both cations and anions. The dependence of  $k_{\text{ap}}$  on the solvent acceptor numbers also indicates that contact ion pairs are not formed. Furthermore, replacement of sodium hydroxide by potassium hydroxide and addition of a crown ether did not affect the reaction rate. Presumably, the low

energy of activation is explained by the fact that the reaction occurs under isoparametric conditions [10].

On the basis of the temperature dependence of the apparent rate constant we concluded that 2,1-benzisoxazoles are formed via two concurrent pathways with different activation barriers. The kinetic studies performed at 303 and 320 K showed that both pathways involve the same rate-determining stage and are characterized by analogous dependences of the apparent rate constant on the concentration of alkali, solvent nature, and substituent in the substrate. We presume that the two pathways involve formation of isomeric  $\sigma$ -complexes. Some examples of formation of such isomers have been reported [11]. Addition of phenylacetonitrile carbanion to chloronitrobenzene **Ia** gives  $\sigma$ -complex **IV** possessing two asymmetric carbon atoms. Therefore, formation of four isomeric  $\sigma$ -complexes could be expected. Their structure was simulated by quantum-chemical calculations.



The calculated energy parameters (such as heats of formation, total energies, etc.) were different for different isomers. This means that there is the possibility for predominant formation of particular  $\sigma$ -complexes at different temperatures, which does not contradict the results of kinetic measurements.

## EXPERIMENTAL

The reactions of nitroarenes **Ia–Ii** with phenylacetonitrile (**II**) in the presence of sodium hydroxide were carried out under stirring in an inert atmosphere with protection from moisture, maintaining the temperature with an accuracy of  $\pm 0.5^\circ\text{C}$ . Samples of the

reaction mixture were withdrawn when necessary and were immediately analyzed by polarography. The polarographic measurements were performed with the aid of an LP-7 instrument (CzSSR); a 0.1 M solution of sulfuric acid containing 50% of DMF was used as supporting electrolyte. Quantum-chemical calculations were performed using MOPAC 7.0 software package.

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