Synthesis of Aryl Ethers by Nonactivated Aromatic Nucleophilic Substitution Reactions

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Abstract—The results of a kinetic study of model reactions between substituted phenols and bromobenzene in the presence of potassium carbonate and the copper(I) chloride–8-hydroxyquinoline catalytic complex in *N,N*-dimethylformamide are presented. The reactions were found to obey a first-order rate law. Both orbital and charge interactions should be taken into account in a consideration of the effect of the structural characteristics of reactants on the rate of reaction. The kinetics of substitution of the phenoxide anion for an aromatically bound halogen atom in activated and nonactivated systems with the formation of practically valuable aryl ethers were comparatively studied. The results presented provide an opportunity to distinguish the common features and regularities of activated and nonactivated aromatic substitution in the test systems.

INTRODUCTION

Substitution for halogen atoms in nonactivated aromatic systems presents a problem in the synthesis of practically valuable products. This problem can potentially be minimized based on a kinetic study of this reaction. We developed a process for the synthesis of *meta*-phenoxyphenol by condensation of bromobenzene with resorcinol in the presence of potassium carbonate and the copper(I) chloride–8-hydroxyquinoline catalytic complex [1]. In this work, we present the results of a kinetic study of the model reaction of substituted phenols (R–PhOH) with bromobenzene in the presence of potassium carbonate in an *N,N*-dimethylformamide (DMF) solution. These results were compared with previously published kinetic data [2, 3] for the replacement of a halogen atom in activated systems (substrate: 4-nitrochlorobenzene (4-NCB)) by the phenoxy anion.

EXPERIMENTAL

The kinetics of the reactions of bromobenzene with substituted phenols in the presence of potassium carbonate and a complex catalyst (copper(I) chloride–8-hydroxyquinoline) was studied in a thermostatted flask (at $T = 145°C$) equipped with a stirrer, a backflow condenser, a nitrogen inlet capillary, a thermostatically controlled dropping funnel, and a Dean–Stark trap. The initial reactant concentrations were an 1.0 mol/l, and the concentration of the catalytic complex was 0.08 mol/l; DMF was used as a solvent. Toluene was used as an agent for the removal of water from the reaction zone. The flask was thermostatted and purged with nitrogen; the solvent, the reactants, potassium carbonate, copper(I) chloride, and 8-hydroxyquinoline were loaded in the flask. In the course of reaction, samples were taken, cooled, and analyzed for bromobenzene by gas–liquid chromatography (GLC) (Chrom-4 chromatograph with a flame-ionization detector; carrier gas, nitrogen; column length, 3 m; column diameter, 3 mm; stationary phase, polyethylene glycol adipate; solid support, NAW; column and injector temperatures, 170 and 280°C, respectively; internal standard, *meta*-toluidine).

Solvents of reagent grade were additionally dried with alkali metal hydroxides and calcium chloride and distilled in a vacuum.

Quantum-chemical calculations were performed using the AM1 (Moras 7.0 software) and INDO1 (ARGUS 1.1 software) methods.

RESULTS AND DISCUSSION

The synthesis of substituted diphenyl oxides by the condensation of bromobenzene with substituted phenols in the presence of potassium carbonate and the copper(I) chloride–8-hydroxyquinoline can be represented by the following reaction scheme:
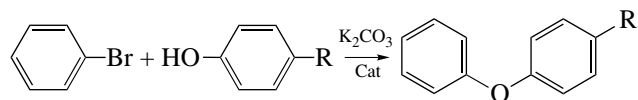

where R = $-NH_2$, $-CH_3$, $-H$, $-Cl$, or $-NO_2$ and Cat = Cu_2Cl_2 + 8-hydroxyquinoline.

Scheme 1.

The reaction was performed at 145°C; the yields of target products were higher than 90%.

Because potassium carbonate is almost insoluble in DMF, we found reaction conditions under which the conversion of reactants is independent of the stirring rate (n), the molar ratio between potassium carbonate and phenol (MR), and the carbonate particle size d with the use of the previously developed procedure [3]. The
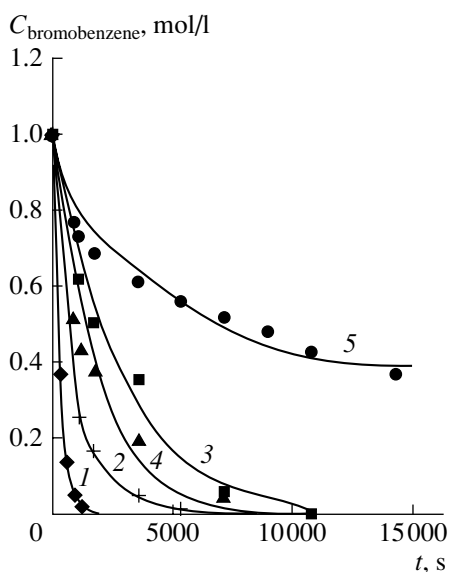
Fig. 1. Kinetic curves for reactions of bromobenzene with substituted phenols in the presence of potassium carbonate (DMF; 145°C; [R–PhOH] = [bromobenzene] = 1 mol/l; bromobenzene/K_2CO_3 = 1 : 2; [Cu_2Cl_2] + [8-hydroxyquinoline] = 0.08 mol/l: (*1*) 4-NH_2–PhOH, (*2*) 4-CH_3–PhOH, (*3*) PhOH, (*4*) 4-Cl–PhOH, and (*5*) 4-NO_2–PhOH.
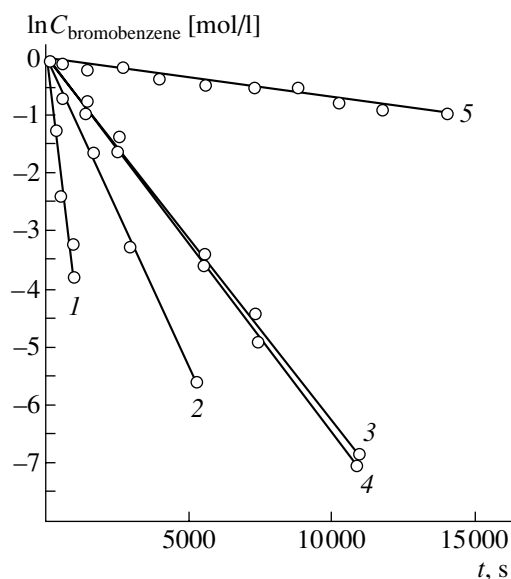
Fig. 2. Anamorphoses of kinetic curves on the ln *C*–*t* coordinates for reactions of bromobenzene with substituted phenols in the presence of potassium carbonate (DMF; 145°C; bromobenzene/K_2CO_3 = 1 : 2; [Cu_2Cl_2] + [8-hydroxyquinoline] = 0.08 mol/l: (*1*) 4-NH_2–PhOH, (*2*) 4-CH_3–PhOH, (*3*) PhOH, (*4*) 4-Cl–PhOH, and (*5*) 4-NO_2–PhOH.

following values of the above parameters were obtained: $n \geq 1000$ rpm, $d \leq 0.5$ mm, and MR ≥ 1.0.

Figure 1 demonstrates the time dependence of current concentrations at an equimolecular ratio between the substrate and reagents.

We found that the semilogarithmic anamorphoses of the kinetic curves (ln *C* – *t*) are linear for all of the substituted phenols (Fig. 2); this fact is indicative of the first order of the reaction.

The pseudo-first order of the reactions of bromobenzene with substituted phenols in the presence of the copper(I) chloride–8-hydroxyquinoline catalytic complex can be explained by the fact that bromobenzene participates in the reaction act as a species bound to the catalytic complex (Fig. 3), and its concentration is constant.

Table 1 summarizes the apparent rate constants for various pairs of reactants.

Substituted phenols are arranged in the following order with respect to reactivity: 4-NH_2 > 4-CH_3 > H, 4-Cl > 4-NO_2.

The rate constants of the test reaction changed symbatically with the nucleophilicity of the corresponding phenolates. This suggests that the nucleophilic substitution of a phenoxy anion for the bromine atom of the substrate is the rate-limiting step of the process. Note that previously prepared potassium phenolate reacted with bromobenzene in the specified reaction medium (in the absence of potassium carbonate) at 145°C at a

rate comparable to the rate of the test reaction of phenol with bromobenzene; this fact supports the above assumption.

A correlation between the rate constants obtained and the Hammett σ constants ($r = 0.86$) allowed us to consider only a symbatic relationship.

The logarithms of the rate constants of bromobenzene reactions with substituted phenols were compared to various reactivity indices (RIs). We used a simplified variant of RIs according to Klopman, which took into
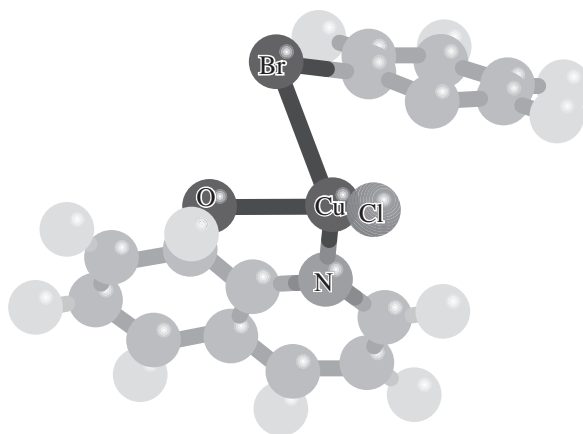
Fig. 3. Structure of the copper(I) chloride–8-hydroxyquinoline–bromobenzene reaction complex (the results of INDO1 calculations).

account only the orbital interaction of reaction centers and had the form

$$RI(1) = Cp_z^2/E_{HOMO},$$

where E_{HOMO} is the energy of the phenolate highest occupied molecular orbital (HOMO), and Cp_z is the contribution of the oxygen atom as a reaction center to the HOMO of the reagent.

However, the correlation was not quite satisfactory for the process under consideration ($r = 0.83$). Therefore, we used the following RI, which also took into account charge interaction:

$$RI(2) = |q_O|/\varepsilon r + Cp_z^2/E_{HOMO},$$

where q_O is the charge at the oxygen atom in the corresponding substituted phenolate, ε is the permittivity of the solvent, and r is the distance between the phenolate oxygen atom and the carbon reaction center in bromobenzene.

We found (Fig. 4) a more satisfactory correlation between RI(2) and the logarithm of the rate constant of the test reaction ($r = 0.93$). This fact indicates that both orbital and charge interactions of the phenolate reaction center with bromobenzene should be taken into account. Thus, the activation of bromobenzene is significantly different from the activation of the reaction center in 4-NCB [2] because of not only a decrease in the energy of the lowest unoccupied molecular orbital (LUMO) of bromobenzene upon conjugation with the electron system of the catalytic complex but also the polarization of the C–Br bond on the formation of a strongly polarized bromobenzene complex with the catalytic system. Complex activation of this kind significantly facilitates C–Br bond cleavage in bromobenzene and makes it possible to explain mild conditions of the test reaction: temperature of 145°C and a reaction time of 1 h or less.

Table 1. Apparent rate constants for various pairs of reactants in the reaction of bromobenzene with substituted phenols R–PhOH

Parameter	Substituent R				
	4-NH$_2$	4-CH$_3$	H	4-Cl	4-NO$_2$
k, s^{-1}	3.2×10^{-3}	8×10^{-4}	6×10^{-4}	6×10^{-4}	5×10^{-6}
σ [4]	−0.660	−0.170	0	0.227	0.778
RI(1)	0.0716	0.0724	0.078	0.0637	0.0387
RI(2)	0.0854	0.0861	0.085	0.0771	0.0505

Table 2. Rate constants of the reactions of 4-NCB and bromobenzene with substituted phenols in the presence of potassium carbonate

Parameter	Substituent R				
	4-NH$_2$	4-CH$_3$	H	4-Cl	4-NO$_2$
$k \times 10^4$, s^{-1} (4-NCB) [3]	5.2	7.5	11.4	15.0	16.6
$k \times 10^4$, s^{-1} (bromobenzene)	32.0	8.0	6.0	6.0	0.05

Taking into account the fact that kinetic data for the reactions of substituted phenols with 4-NCB [3] and bromobenzene were obtained at close temperatures (140 and 145°C, respectively) and the reactions exhibited a pseudo-first order, the reaction rate constants can be compared (Table 2).

The interaction of bromobenzene with substituted phenols can be represented similarly to the reaction of 4-NCB with phenols [3]:

$$\text{where R} = -NH_2, -CH_3, -H, -Cl, \text{ or } -NO_2.$$
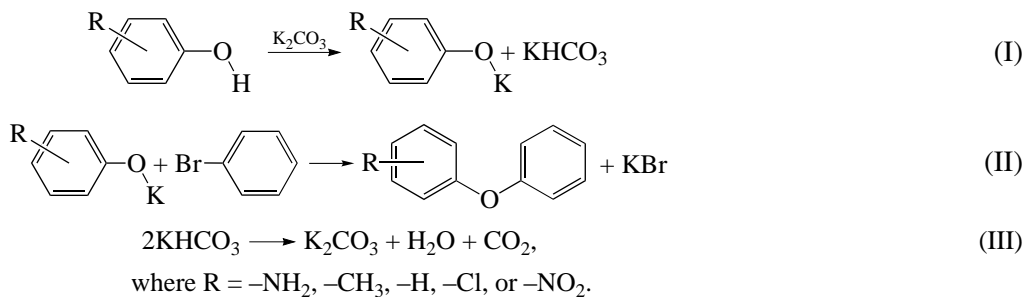
Scheme 2.

Here, reaction (I) is the deprotonation of phenols, and reaction (II) is nucleophilic substitution. Under the test reaction conditions, these steps can compete with each other as the rate-limiting step depending on the nature of the substituent in the reagent. If nucleophilic substitution is the rate-limiting step, the phenolate

HOMO structure is a controlling factor. However, if the deprotonation of phenols is the rate-limiting step of the process, the value of pK_a is a controlling parameter.

An analysis of data given in Table 2 allowed us to draw the following conclusion: In the interaction with bromobenzene, donor substituents in the phenol mole-
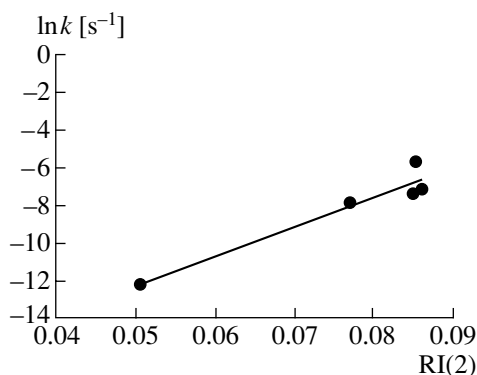
Fig. 4. Dependence of ln k on the reactivity index for the reactions of bromobenzene with substituted phenols in the presence of potassium carbonate and the copper(I) chloride–8-hydroxyquinoline catalytic complex.

cule (–NH$_2$ and –CH$_3$) increase the reactivity of the resulting phenolates so that the deprotonation of phenols can be a rate-limiting step of the process. The rate of bromobenzene reaction with phenolates containing acceptor substituents (–Cl and –NO$_2$) is lower than the rate of deprotonation; in this case, step (II) is responsible for the overall reaction rate.

In general, the data reported allowed us to recognize common features and regularities of activated and non-activated aromatic nucleophilic substitution for the test systems, and to refine particular aspects of the reaction mechanisms.

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