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Influence of β-Cyclodextrin on Coupling Reactions of *o*-Nitrobenzenediazonium Salt with Pyrrole

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The influence of β-cyclodextrin on *o*-nitrobenzenediazonium salt coupling with pyrrole has been studied analyzing the yield and products distribution.

Key words: pyrrole, diazonium salts, coupling reaction, β-cyclodextrin

Cyclodextrins found wide application in contemporary chemistry. Complexation of lipophilic molecules by cyclodextrins caused significant increase of their solubility in polar solvents, *e.g.*, in water [1] which is important for preparation of drug formulations leading to their better accessibility from alimentary canal [2]. Cyclodextrins affect stability of complexed molecules; in some cases they delay their chemical changes, *e.g.* increase photofading resistance of free azo dyes and dyes anchored to cotton fibers [3]. On the other hand cyclodextrins show catalytic activity in some reactions, for example, increasing hydrolysis rate of *m-tert*-butylphenol acetate [4,5]. Analogously, complexation of anisole by α-cyclodextrin changes availability of *p*-position of the aromatic nuclei for chlorination dramatically changing the ratio of *o*- and *p*-substitution [6]. Cyclodextrins affect stereoselectivity of Diels-Alder reaction [7] or bromine addition to double carbon–carbon bonds [8]. Such reactions are interpreted as specific enzyme mimicking action of cyclodextrin that mediates transfer of reacting species, *c.f.* [9].

Some papers pay attention on steric hindrance caused by cyclodextrin encapsulated substrates of enzymatic reactions. For example, the catalytic activity of tyrosine phenol-lyase is reduced when tyrosine is complexed with methylated cyclodextrin [10]. By steric effects, cyclodextrins reduce accessibility of complexed indicators to protonation [11] or prevent opening phenolphthalein lactone ring under basic conditions [12].

Cyclodextrins form catenanes and rotaxanes with azo compounds [13]. The inclusion reaction of azo dyes into cyclodextrins to form pseudorotaxanes [14] takes milliseconds or less for azobenzene with ordinary substituents while typical formation constants for α-cyclodextrin inclusion complexes with azobenzene derivatives

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are in the range of 10^3 to 10^4 $mol^{-1} \cdot dm^3$ [15]. The orientation of azo compounds inside the cyclodextrin cavity depends on polarity of substituents and on the degree of steric hindrance [16]. Some factors controlling the complexation mechanism [17] and orientation of guest molecules with azo unit included in cyclodextrins were studied [18]. Theoretical calculations of azobenzene complexation [19] gave data comparable with experiments. Recently, the chemistry of cyclodextrin combinations with azo-compounds has been reviewed [20].

Diazonium salts, the starting materials for azo-dyes are complexed by cyclodextrins [21]. It was also found that, in particular, α- and β-CD show catalytic effect on coupling reaction of (*p*-substituted)benzenediazonium salts with phenol [22].

The aim of this work was study of β-cyclodextrin influence on the reaction course of *o*-nitrobenzenediazonium salt coupling with pyrrole. It is known that ordinary coupling reactions of diazonium salts proceed preferentially in positions 2 and 5 of pyrrole [23–25]. Preliminary experiments showed that coupling of isomeric *p*-nitrobenzenediazonium salt (2 mmol) with pyrrole (1 mmol) produces large variety of compounds; composition of the products was not significantly influenced by β-cyclodextrin. Contrary to this result, composition of coupling products of *o*-nitrobenzenediazonium salt with pyrrole showed significant differences that depend on β-cyclodextrin concentration in the reaction medium. On first sight the influence of cyclodextrin is easy to assess because the colors of reaction mixtures are different.

EXPERIMENTAL

General: All materials and solvents used for syntheses were of analytical reagent grade. For products separation column chromatography (Silica gel 60, Merck) and/or preparative TLC glass plates covered with Silica gel 60 F_{254} (Merck) was applied. ^{1}H NMR spectra, all in $CDCl_3$, were taken on Varian instruments at 500 MHz. Mass spectra were recorded on AMD-604 apparatus. The m.p. are uncorrected.

Solution A. *o*-Nitroaniline (2 mmol) was dissolved in ice-cold water (20 ml) acidified with 0.5 ml conc. hydrochloric acid. The cold solution was diazotized with sodium nitrite (0.14 g; 2.1 mmol) dissolved in 2 ml cold water.

Solutions B. Five separate solutions of pyrrole (0.06 ml; 1 mmol) and sodium hydroxide (0.2 g; 5 mmol) dissolved in 40 ml water were prepared. To the consecutive solutions β-cyclodextrin (0, 1, 2, 3 or 4 mmol; *i.e.* 0, 1.135, 2.27, 3.405, and 4.54 g, respectively) was added.

Both solutions were ice-cooled and stirred. Solution **A** was dropped with the same speed to the successive solutions **B** under vigorous stirring. The temperature of the reaction mixtures was maintained at around 10°C for 1 h and then the mixtures were continuously stirred at room temp. for 12 h. Then the mixtures were ice-cooled, pH was adjusted to 6–7 with acetic acid to deposit the reaction products. The products were exhaustively extracted with chloroform/toluene (10/1) mixture until the aqueous layer was nearly colorless. The products were separated using column chromatography and identified by spectroscopic methods. The yields are shown in Table 1.

Compound 1: 2-[2-nitrophenylazo]-pyrrole. Deep grey solid, dirty yellow CH_2Cl_2 solution, R_F (hexane:ethyl acetate 3:1 = 0.98). M.p. 108–110°C. ^{1}H NMR; δ_H (d-acetone); 11.2 (1H, s, N-H); 7.85 (1H, d, J = 7.8 Hz, ArH); 7.80–7.66 (2H, m, ArH); 7.61–7.59 (1H, m, ArH); 7.22 (1H, s, Ar); 7.05 (1H, s, Ar); 6.43 (1H, s, Ar). HRMS (EI): found M^+ = 216.06561; $C_{10}H_8N_4O_2$ requires 216.06473.

Compound 2: 5-(2-nitrophenylazo)-2,2′-bipyrryl. Deep red solid, red CH_2Cl_2 solution, R_F (hexane:ethyl acetate 3:1 = 0.9). M.p. 165–167°C. ^{1}H NMR; δ_H (d-acetone); 12.4 (1H, s, N-H); 11.4 (1H, s, N-H); 8.18 (1H, d, *J* = 8.8 Hz, ArH); 8.06–8.00 (1H, m, ArH); 7.76 (1H, t, *J* = 7.2 Hz, ArH); 7.40–7.26 (2H, m, ArH); 7.24–7.10 (3H, m, ArH); 6.40 (1H, s, ArH). HRMS (EI): found M^+ = 281.09092; $C_{14}H_{11}N_5O_2$ requires 281.09127.

Compound 3: 2-(2-nitrophenylazo)-5-(2-nitrophenyl)-pyrrole. Dark orange solid, orange CH_2Cl_2 solution, R_F (hexane:ethyl acetate 3:1 = 0.75). M.p. 147–150°C. ^{1}H NMR; δ_H (d-acetone); 11.6 (1H, s, N-H); 8.2 (1H, d, *J* = 8.3 Hz, ArH); 7.88–7.94 (1H, m, ArH); 7.84–7.72 (4H, m, ArH); 7.72–7.58 (2H, m, ArH); 7.16 (1H, s, ArH); 6.59 (1H, s, ArH). HRMS (EI): found M^+ = 339.08129; $C_{16}H_{11}N_5O_4$ requires 337.08110.

Compound 4: 2,5-bis(2-nitrophenylazo)-pyrrole. Grey solid, deep red CH_2Cl_2 solution, R_F (hexane:ethyl acetate 3:1 = 0.45). M.p. 185–188°C. ^{1}H NMR; δ_H ($CDCl_3$); 10.55 (1H, s, N-H); 8.18 (2H, d, *J* = 8.3 Hz, ArH); 7.85 (2H, d, *J* = 8.8 Hz, ArH); 7.67 (2H, t, *J* = 7.8 Hz, ArH); 6.95 (2H, t, *J* = 7.8 Hz, ArH); 6.92 (2H, s, ArH). HRMS (EI): found M^+ = 365.08859; $C_{16}H_{11}N_7O_4$ requires 365.08725.

Compound 5: 2,3-bis(2-nitrophenylazo)-pyrrole. Dark red solid, red CH_2Cl_2 solution, R_F (hexane:ethyl acetate 3:1 = 0.35). M.p. 165–168°C. ^{1}H NMR; δ_H (d-acetone); 12.2 (1H, s, N-H); 7.95 (2H, d, *J* = 8.3 Hz; ArH); 7.84–7.78 (4H, m, ArH); 7.76–7.70 (2H, m, ArH); 7.24 (2H, s, ArH). HRMS (EI): found M^+ = 365.08768; $C_{16}H_{11}N_7O_4$ requires 365.08725.

RESULTS AND DISCUSSION

The molar ratio of *o*-benzenediazonium salt to pyrrole in all experiments was 2:1. The purpose of such ratio was preparation of disubstituted pyrrole **2**, and/or isomer **3**, *c.f.* [24]. Coupling reactions were performed under standardized conditions (concentration of reacting species, pH, temperature, stirring, isolation). Contrary to expectation, the most abundant product is compound **1** although in the reaction mixture there is an excess of diazonium salt. Less abundant are compounds **2–5** (Figure 1), accompanied by large amount of high-molecular side products. Compounds **1–5** were isolated by column chromatography or preparative thin layer chromatography. Structures of these products were solved by spectral methods.

Considering the discussed above complexing properties of cyclodextrins, it could be expected that compounds **1–5** and the starting materials (pyrrole and diazonium salt) form complexes with β-CD in the reaction medium. Thus, the influence of β-CD on the coupling reaction course was expected. In subsequent experiments the changes of products yield and ratio in relation to the increasing amount of β-cyclodextrin (1–4 molar ratio) added to the reaction mixture at coupling stage was investigated (Table 1).

Reaction performed in the absence of β-CD mainly produces water insoluble compound **1** that ends the synthesis. Evidently, **1** is an intermediate in reactions producing compounds **2** and **3**, and most likely leading to compounds **4** and **5**. One molar equivalent of β-CD added to the reaction mixture causes dramatic yield decrease of compounds **1** meaning its successive coupling owing to interaction with β-CD. At four molar excess of CD, compound **1** was not found in the reaction mixture. Correspondingly, the yield of compound **2** increases slightly and remains practically unchanged with higher excess of β-CD. Compounds **4** and **5** were likely produced as a

result of homolytic cleavage of diazonium salts promoted by cyclodextrins [26]. The highest yield of these compounds was obtained at 2 moles of CD per 1 mole of pyrrole and decreased with further increase of β-CD excess. Compound **3**, an isomer of **2**, is formed in substantially higher yield in the absence of cyclodextrin. Assuming the overall yield of compounds **1–5**, β-CD reduces formation of low-molecular products in favor of high-molecular by-products. However, significant decrease of compound **1** formation in the presence of some CD concentration facilitates isolation of the remaining coupling products.

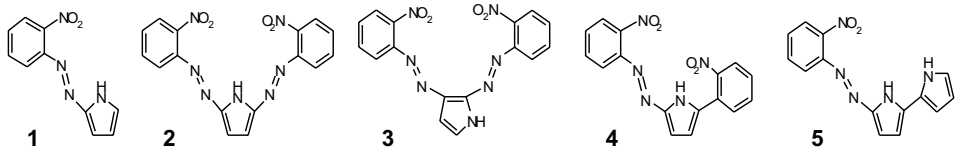

Figure 1. Coupling products of *o*-nitrobenzenediazonium salt (2 mmol) with pyrrole (1 mmol).

Table 1. Yield of main low-molecular coupling products **1–5** in reaction of *o*-nitrobenzenediazonium salt (2 mmol) and pyrrole (1 mmol) in the presence of various amounts of β-CD.

Amount of β-CD [mmol]	Yield of product %				
	1	**2**	**3**	**4**	**5**
0	33	6	7	3	2
1	5	11	0	3	2
2	3	12	0	9	8
3	3	14	3	3	3
4	0	14	2	0	1

Compound **2** should be the main product considering the ratio of substrates and higher reactivity of positions 1 and 5 of pyrrole [23–25]. Probably, CD causes selective steric hindrance that shields part of mono-substituted pyrrole (Figure 2). In both complexes pyrrole positions 3 or 5, respectively, are exposed to substitution. The orientation A of intermediate **1** explains better the synthetic results than does orientation B.

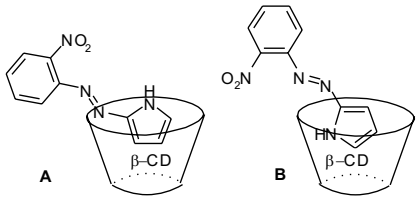

Figure 2. Considered orientations of monosubstituted pyrrole in β-CD complex. Complexation of benzene residue by cyclodextrin is omitted for clarity.

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