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Effect of Cyclodextrins on Coupling of *o*-Ethoxybenzenediazonium Salt with Pyrrole, Imidazole and 2-Methylimidazole

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Abstract

The effect of β-cyclodextrin on *o*-ethoxybenzenediazonium salt coupling with pyrrole, imidazole and 2-methylimidazole has been studied. The differences in the reaction course, the overall yield and products distribution have been analyzed. Experiments without cyclodextrins and selected reactions with α- and γ-cyclodextrins have been performed for comparison. The results are discussed in terms of co-conformation of azole molecules embedded in cyclodextrin cavity.

Introduction

Cyclodextrins (CDs) are very frequently used in contemporary chemistry and technology. Complexation of lipophilic compounds by CDs usually increase their solubility in water [1]. This behavior is important for preparation of better accessible drug formulations [2]. Molecules encapsulated by CDs are protected against oxidation or chemical changes that increase e.g. photofading resistance of azo-dyes [3, 4]. In some reactions CDs show catalytic activity, significantly increasing, for example, hydrolysis rate of *m*-tert.-butylphenol esters [5, 6]. Hydrolysis of DNA in the presence of cerium complexes of α-, β-, and γ-CD proceeds faster by many orders of magnitude [1]. CDs affect regio- and stereoselectivity of substitution or addition reactions. Anisole embedded in α-CD undergoes almost exclusively chlorination in *p*-position while free form of this substrate is chlorinated in *o*- and *p*-position to the same degree [7]. CDs affect stereoselectivity of Diels–Alder reaction [8] or bromine addition to non-symmetric double carbon–carbon bonds [9]. Such reactions are interpreted as specific enzyme mimicking action of CD [10], in which the CD takes part in transfer of the reacting species or shields particular fragments of substrate molecule against reaction. The shielding caused by CD (and derivatives) towards substrates of enzymatic reaction was also observed. For example, the catalytic activity of tyrosine phenol-lyase is reduced when tyrosine is complexed with methylated CDs [11].

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The shielding ability of CDs is also manifested by the reduction of proton receptiveness of complexed indicators. It concerns for example amino-β-CD acylated with methyl red. This compound changes color upon competing guest complexation that expunges the methyl red residue from the cavity and exposes it to pH of the bulk solution [12]. In a similar way CD prevents opening phenolphthalein lactone ring under basic conditions [13].

CDs form inclusion complexes with azo-compounds. Accordingly, CDs spontaneously form pseudorotaxanes of different stoichiometry with azo dyes [14]. Typical formation constants for α-CD inclusion complexes with azobenzene derivatives are in the range of 10^3–10^4 mol^{-1} dm^3. The inclusion process takes milliseconds or less for azobenzene with ordinary substituents [15]. The orientation of azo compounds inside the CD 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 bearing azo unit included in CDs were studied [18, 19]. Theoretical calculations of azobenzene complexation [20] gave data comparable with experiments. Diazonium salts, the starting materials for azo-dyes, are also complexed by CDs [21]. It was also found that α- and β-CD increases the rate of diazonium salts coupling reaction with phenol; in the case of β-CD the reaction rate is increased almost six times [22]. Bravo-Diaz *et al.* [23] found, however, that CD does not affect coupling reactions of 2-, 3-, and 4-methylbenzenediazonium salt with typical aromatics.

Finally, it was observed that β-CD promotes homolytic dediazoniation of diazonium salts [24]. For

current reviews on macrocyclic compounds with azo unit and on azo dye complexes with CDs see [25, 26].

Preliminary experiments have shown that β-CD affects the coupling reaction of *o*-nitrobenzenediazonium salt with pyrrole changing the yield and ratio of formed azo compounds [27]. The aim of the present work is to check whether the CD effect on coupling reaction is general. The reaction course of *o*-ethoxybenzenediazonium salt is exemplified on coupling with pyrrole, imidazole and 2-methylimidazole.

Experimental

General. All solvents were of analytical reagent grade. The reagents from Aldrich were used without further purification. Silica gel 60 (63–200 μm) was used for column chromatography (Merck). Preparative chromatographic isolation of products was performed on glass plates covered with silica gel (60 F_{254} MERCK). ^{1}H-NMR spectra were recorded on a Varian apparatus at 500 MHz working frequency. Mass spectra were taken on AMD-604 spectrometer. FTIR spectra were recorded on Mattson Genesis II instrument.

Pyrrole derivatives 1–3

Five solutions A were prepared
o-Ethoxyaniline (0.26 ml; 2 mmol) was dissolved in 20 ml ice-cold water acidified with 1 ml conc. hydrochloric acid. To this solution sodium nitrite (0.14 g, 2.1 mmol) solution in 2 ml cold water was added.

Five solutions: B1–B5 were prepared. B1: Pyrrole (0.06 ml, 1 mmol) and sodium hydroxide 0.2 g, 5 mmol) was dissolved in 150 ml water. To the remaining solutions B2–B5 1, 2, 3 or 4 mmol β-CD (1.135, 2.27, 3.405, or 4.54 g) was added, respectively.

Both solutions were cooled (4 °C). Then solution A was added drop-wise to vigorously stirred solution B (B1, B2 ... etc.). The temperature was maintained below 10 °C for 1 h and then at room temperature for additional 12 h. The reaction mixture was adjusted to pH 6–7 with acetic acid and the products were extracted three times with chloroform–acetic acid–toluene mixture (6:1:1) (until the aqueous phase nearly decolorizes). The desired products were separated using toluene–ethyl acetate (9:2) system on preparative TLC plates. The silica gel containing particular spots was collected and washed out with methanol. The amounts of compounds were determined gravimetrically.

Experiments with α- or γ-CD were performed analogously.

2-(2-Ethoxybenzeneazo)-pyrrole 1
Yellow oil, rapidly darkening on air, R_F 0.46 (toluene–ethyl acetate 9:2). ^{1}H-NMR (*d*-acetone); δ 10.82 (1H, s, NH); 7.58 (1H, d, J = 7.8 Hz, ArH); 7.34 (1H, t, J = 7.3 Hz, ArH); 7.15 (1H, d, J = 8.3 Hz, ArH); 7.05 (1H, s, ArH); 6.99 (1H, t, J = 7.3 Hz, ArH); 6.90–6.88 (1H, m, ArH); 6.56–6.52 (1H, m, ArH); 4.20 (2H, q, J = 6.8 Hz, $ArOCH_2$); 1.40 (3H, t, J = 6.8 Hz, $ArOCH_2CH_3$). IR (film, ν_{max}) 2979, 2925, 1588, 1485, 1471, 1362, 1294, 1279, 1256, 1237, 1158, 1118, 1028, 874, 747 cm^{-1}. HRMS (EI): M^+ found 215.10676; $C_{12}H_{13}N_3O$ requires 215.10586.

2,5-Bis(2-ethoxybenzeneazo)-pyrrole 2
Deep red solid described elsewhere [28]. Mp 150–155 °C, R_F 0.63 (toluene–ethyl acetate 9:2).

5-(2-Ethoxybenzeneazo)-2-hydroxypyrrole 3
Yellowish brown solid, rapidly darkening on air, mp 211–216 °C, R_F 0.10 (toluene–ethyl acetate 9:2); R_F 0.83 (methylene chloride–acetone 4:1). ^{1}H-NMR (*d*-acetone); δ 10.1 (~1H, s, NH); 8.57 (1H, s, ArOH); 7.47 (1H, dd, J_1 = 7.81; J_2 = 1.46, ArH); 7.17 (1H, d, J = 5.62, ArH); 6.91–6.97 (2H, m, ArH); 6.84–6.87 (1H, m, ArH); 6.22 (1H, d, J = 5.62 ArH); 4.15 (2H, q, J = 6.84, $ArOCH_2$); 1.4 (3H, t, J = 7.08, $ArOCH_2CH_3$). IR (ν_{max}) (nujol) 3284; 3138; 1695; 1663; 1593; 1521; 1259; 1195; 1144; 1044; 923; 802; 731; 680 cm^{-1}. (MS (EI): M^+ = 231; $C_{12}H_{13}N_3O_2$ requires 231.

Imidazole derivatives 4–6

Analogous set of reactions as with pyrrole was performed with imidazole using solutions A, and solutions B, that contained imidazole instead of pyrrole. The reaction conditions were exactly the same. The final separation was completed using preparative TLC in methylene chloride–acetone (2:1) system.

Experiments with α- or γ-CD were performed analogously.

2-(2-Ethoxybenzeneazo)-imidazole 4
Orange solid, mp 176–179 °C; R_F 0.55 (methylene chloride–acetone 2:1). ^{1}H-NMR (*d*-acetone); δ 11.8 (1H, s, NH); 7.67 (1H, d, J = 7.8 Hz, ArH); 7.49 (1H, t, J = 7.3 Hz, ArH); 7.32 (2H, d, J = 5.4 Hz, ArH); 7.23 (1H, d, J = 8.3 Hz, ArH); 7.04 (1H, t, J = 7.8 Hz, ArH); 4.26 (2H, q, J = 6.8 Hz, $ArOCH_2$); 1.42 (3H, t, J = 6.8 Hz, $ArOCH_2CH_3$). FTIR, (nujol) 2982, 2926, 1590, 1486, 1471, 1435, 1364, 1280, 1234, 1158, 1114, 1038, 922, 899, 758 cm^{-1}. MS (EI): M^+ = 216; $C_{11}H_{12}N_4O$ requires 216. HRMS (EI): M^+ found 216.10228; $C_{11}H_{12}N_4O$ requires 216.10111.

2,4(5)-Bis(2-ethoxybenzeneazo)-imidazole 5
Dark solid, magenta solution in methylene chloride, mp 137–142 °C, R_F 0.84 (methylene chloride–acetone 2:1). ^{1}H-NMR ($CDCl_3$); δ NH (out of sight); 8,08 (1H, s, ArH); 7.94 (1H, d, J = 8.3 Hz, ArH); 7.78 (1H, d, J = 7.8 Hz, ArH); 7.49 (1H, t, J = 7.3, ArH); 7.43 (1H, t, J = 7.3, ArH); 7,09 (2H, t, J = 6.3 Hz, ArH); 7.02 (2H, t, J = 7.8, ArH); 4.24 (4H, q, J = 6.8 Hz, $ArOCH_2$); 1.56 (6H, t, J = 6.8 Hz, $ArOCH_2CH_3$). MS (EI): M^+ = 364. HRMS (EI): M^+ found 364.16444; $C_{19}H_{20}N_6O_2$ requires 364.16477.

4-(2-Ethoxybenzeneazo)-2-(2-ethoxyphenyl)-imidazole 6
Deep yellowish orange solid, yellow solution in methylene chloride. Mp 195–199 °C, R_F 0.92 (methylene chloride–acetone 2:1). ^{1}H-NMR ($CDCl_3$); δ 11.2 (1H, bs, NH); 7.94 (1H, d, J = 7.8 Hz, ArH); 7.84 (1H, s, ArH); 7.44 (1H, t, J = 7.3 Hz, ArH); 7.31 (1H, t, J = 7.8 Hz, ArH); 7.10–7.04 (5H, m, ArH); 4.32–4.20 (4H, m, $ArOCH_2$); 1.65 (3H, t, J = 7.3 Hz, $ArOCH_2CH_3$); 1.54 (6H, t, J = 6.8 Hz, $ArOCH_2CH_3$). FTIR, (nujol): 2980, 2928, 1590, 1486, 1471, 1435, 1395, 1364, 1281, 1234, 1158, 1116, 1078, 921, 900, 754 cm^{-1}. MS (EI): M^+ = 336. HRMS (EI): M^+ found 336.15775; $C_{19}H_{20}N_4O_2$ requires 336.15863.

2-Methylimidazole derivatives 7–9

Similar solutions A and B were prepared containing equivalent amounts of 2-methylimidazole. In this case the amount of β-CD was limited to three equivalents per one equivalent of 2-methylimidazole. The coupling reactions were performed as above. The final separation of products was achieved on preparative TLC plates in ethyl acetate–toluene–methanol–acetic acid 5:25:4:2 system. The following main compounds were isolated:

4(5)-(2-Ethoxyphenyl)-5(4)-(2-ethoxyphenylazo)-2-methylimidazole 7
Yellow very thick oil, R_F 0.38 (ethyl acetate–toluene–methanol–acetic acid 5:25:4:2). ^{1}H-NMR (*d*-acetone); δ 8.15 (1H, d, J = 7.3 Hz, ArH); 7.56 (1H, d, J = 7.8 Hz, ArH); 7.39–7.36 (2H, m, ArH); 7.21–7.16 (2H, m, ArH); 7.10–7.08 (1H, m, ArH); 7.01–6.96 (1H, m, ArH); 4.31–4.24 (4H, m, $ArOCH_2$); 2.43 (3H, s, $ArCH_3$); 1.40 (3H, m, $ArOCH_2CH_3$). ^{1}H-NMR (DMSO); δ 12.25 (1H, s, NH); 7.66 (1H, d, J = 7.3 Hz, ArH); 7.38 (1H, t, J = 7.3 Hz, ArH); 7.34–7.30 (2H, m, ArH); 7.17–7.14 (2H, m, ArH); 7.04 (1H, t, J = 7.3, ArH); 6.93 (1H, t, J = 7.8 Hz, ArH); 4.20 (2H, Q, J = 6.8 Hz, $ArOCH_2$); 4.11 (2H, q, J = 6.8 Hz, $ArOCH_2$); 2.38 (3H, s, $ArCH_3$); 1.38 (3H, t, J = 6.8 Hz, $ArOCH_2CH_3$); 1.33 (3H, t, J = 6.8 Hz, $ArOCH_2CH_3$). FTIR, (film): 3407, 3212, 3066, 2924, 2858, 1590, 1444, 1386, 1242, 1164, 1115, 1039, 922, 747 cm^{-1}. HRMS (EI): M^+ found 350.17495; $C_{20}H_{22}O_2N_4$ requires 350.17428.

4,5-bis-(2-Ethoxyphenylazo)-2-methylimidazole 8
Deep red very thick oil, R_F 0.46 (ethyl acetate–toluene–methanol–acetic acid 5:25:4:2). ^{1}H-NMR (*d*-acetone); δ NH out of sight; 7.77 (2H, d, J = 7.8 Hz, ArH); 7.48 (2H, t, J = 7.8 Hz, ArH); 7.25 (2H, t, J = 8.3 Hz, ArH); 7.05 (2H, t, J = 7.8 Hz, ArH); 4.32 (4H, m, $ArOCH_2$); 2.48 (3H, s, $ArCH_3$); 1.46 (6H, m, $ArOCH_2CH_3$). ^{1}H-NMR (DMSO); δ 12.91 (1H, s, NH); 7.57 (1H, d, J = 7.8 Hz, ArH); 7.47 (2H, t, J = 7.8 Hz, ArH); 7.28–7.24 (2H, m, ArH); 7.06–7.00 (2H, m, ArH); 4.31–4.25 (4H, m, $ArOCH_2$); 2.44 (3H, s, $ArCH_3$); 1.45–1.40 (6H, 2q, J = 6.8, $ArOCH_2CH_3$). FTIR, (film): 3389, 2929, 2861, 1584, 1456, 1276, 1233, 1150, 1107, 1089, 1037, 930, 800, 753 cm^{-1}. HRMS (ESI): ($M + H^+$) found 379.1895; $C_{20}H_{23}N_6O_2$ requires 379.18947.

Compound 9
Deep yellow very thick oil, R_F 0.56 (ethyl acetate–toluene–methanol–acetic acid 5:25:4:2), that spontaneously converts into compound **8**. ^{1}H-NMR (*d*-acetone) identified signals taken from spectrum of a mixture with **8**; δ 7.69 (1H, d, J = 7.8 Hz, ArH); 7.41 (1H, d, J = 7.8 Hz, ArH); 7.03–6.99 (4H, m, ArH); 6.90 (1H, t, J = 7.3 Hz, ArH); 6.83 (1H, t, J = 7.8 Hz, ArH); 6.79 (1H, t, J = 7.8 Hz, ArH); 4.43 (2H, q, J = 6.8 Hz, $ArOCH_2$); 4.22 (2H, q, J = 6.8 Hz, $ArOCH_2$); 2,37 (3H, s, $ArCH_3$).

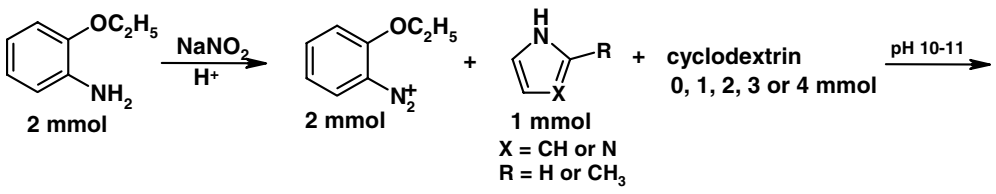
Results and discussion

Synthesis

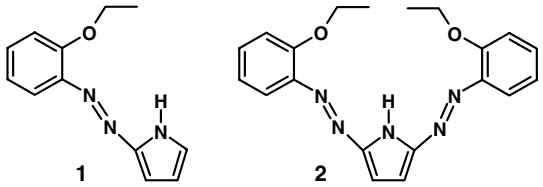
All coupling reactions were performed under standardized conditions (2:1 molar ratio of diazonium salt to azole, overall concentration, temperature, stirring) and different molar ratios (0, 1, 2, 3 or 4) of β-CD added to pyrrole, imidazole or 2-methylimidazole solutions in water. In the case of 2-methylimidazole coupling the amount of β-CD was limited to 3 mol equivalents. At the coupling stage pH 10–11 was maintained (Scheme 1). On first sight the influence of β-CD on the reaction course is easy to assess as colors of the respective reaction mixtures differ. The yield and ratio of formed products was examined. Selected reactions were repeated using α- or γ-CD. Blank experiments (without CD) were performed for comparison. The performed reactions are shown in Scheme 1.

Coupling reactions with pyrrole

Preliminary experiments on coupling reactions of *o*-, or *p*-nitrobenzenediazonium salts with pyrrole have shown



Scheme 1. Coupling of *o*-ethoxybenzenediazonium salt with pyrrole, imidazole and 2-methylimidazole in the presence of different ratios of β-CD.



Scheme 2. Main low-molecular products isolated from the coupling products of *o*-ethoxybenzenediazonium salt with pyrrole in the absence and in the presence of β-CD.

that β-CD significantly affects the reaction course in the case of the first reagent [27]. Similarly, differences in the reaction course were observed when *o*-ethoxybenzenediazonium salt was coupled with pyrrole. Ordinary coupling of diazonium salts proceeded preferentially in positions 2 and 5 of pyrrole [29, 30, cf. 31]. Accordingly, two main low-molecular reaction products with pyrrole were isolated from the reaction mixtures: 2-mono-, and 2,5-disubstituted pyrrole **1** and **2**, Scheme 2. ^{1}H-NMR spectrum of compound **1** is shown in Figure 1.

The influence of the ratio of β-CD added to the reaction mixtures on the yield of products **1** and **2** is presented in Figure 2.

Considering literature data it may be assumed that β-CD instantly inserts both substrates, i.e., *o*-ethoxybenzenediazonium salt and pyrrole. The same concerns reaction intermediates and final coupling products. In the absence of CD a mixture of compound **1** (42%) and **2** (52%) is formed. Compound **2** is expected to be the main reaction product considering the ratio of used reagents and higher reactivity of pyrrole positions 2 and 5. The yield of product **1** decreases with increased concentration of β-CD; **1** was not detected when the ratio of β-CD to pyrrole exceeds 3. The yield of simultaneously formed compound **2** decreases to 22% (at 2 mmol CD per 1 mmol pyrrole) and then increases up to 44% at higher concentration of CD. As product **1** evidently is an intermediate in the synthesis of **2**, its yield decrease may be attributed to reorientation of **1** inside CD cavity compared to co-conformation of unsubstituted pyrrole complex.

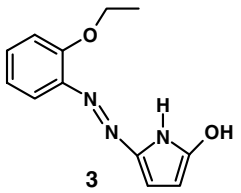
The isolated and characterized product **1** is not very stable; it quickly decomposes to form dark products. Under appropriate concentration of β-CD, formation of compound **1** is highly reduced improving isolation of disubstituted pyrrole **2** from the reaction mixture.

Few coupling experiments were repeated with the use of α-, or γ-CD. In the case of four molar excess of α-CD to pyrrole apart from compounds **1** and **2**, hydroxypyrrole derivative **3** (Scheme 3) is formed in significant yield. This compound decomposes rapidly to form dark products. Formation of **3** with ArOH group is attributed to free radical decomposition of diazonium salt promoted by CD [cf. 21, 24]. The influence of excess of α-, β- or γ-CD on coupling of *o*-ethoxybenzenediazonium salt with pyrrole is shown in Figure 3.

Coupling reactions with imidazole

Identical set of coupling reactions of *o*-ethoxybenzenediazonium salt was performed with imidazole (cf. Scheme 1). Imidazole undergoes preferentially substitution in positions 2 and 4 under ordinary conditions [29, 30, cf. 31]. In our case, three main low-molecular products were isolated and identified, Scheme 4. The yield of isolated products is shown in Figure 4.

In the case of imidazole the coupling reaction performed without CD yielded large variety of



Scheme 3. Compound formed on coupling of *o*-ethoxybenzenediazonium salt with pyrrole in the presence of α-CD excess.

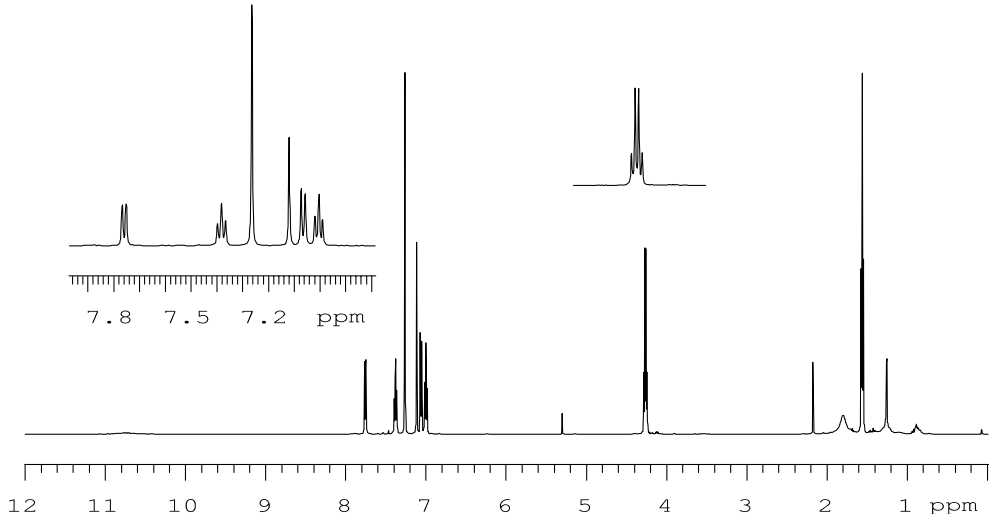


Figure 1. ^{1}H-NMR spectrum of pyrrole derivative **1** in $CDCl_3$.

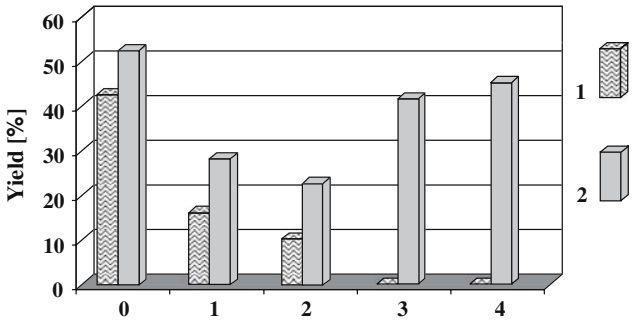


Figure 2. Yield of products **1** and **2** formed on coupling of *o*-ethoxybenzenediazonium salt with pyrrole in the presence of different concentrations of β-CD.

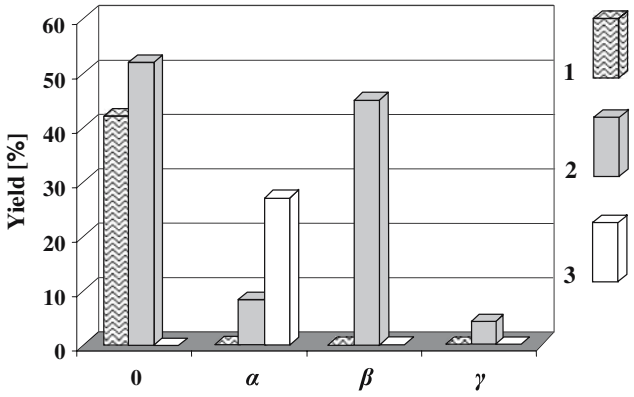


Figure 3. Influence of α-, β- and γ-CDs (4 mmol) on coupling yield of *o*-ethoxybenzenediazonium salt (2 mmol) with pyrrole (1 mmol).

low-molecular products, amongst which the 2-monosubstituted imidazole **4** dominates. The yield of **4** drastically drops down in the presence of 1 mmol of β-CD in favor of higher-molecular products, and remains almost constant at larger excess of host molecules. Considering the ratio of reactants the yield of disubstituted imidazole **5** is surprisingly low. The yield of rather unexpected, free radical reaction product **6** (^{1}H-NMR spectrum shown in Figure 5) is quite high when β-CD is absent, and decreases with increasing concentration of host compound. It somehow opposes previous observations on CD promoted homolytic cleavage of diazonium salt [24].

Both α- or γ-CD applied in four molar excess decrease formation of compound **4** to 6% and 5%, respectively.

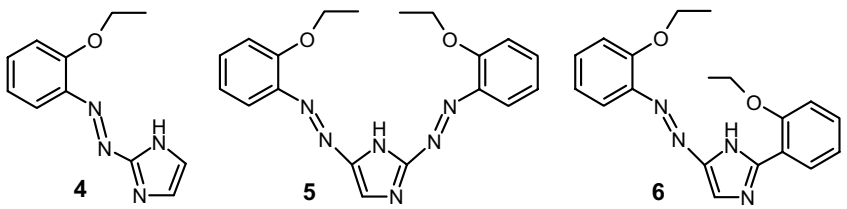
Generally the yield decrease in the presence of β-CD is more evident for imidazole than for pyrrole reactions. However, in the case of pyrrole the side reactions are to a greater degree retarded with except of that leading to disubstitution product **2**. The imidazole case is opposite; the yield decrease is the smallest for monosubstitution product **4**. These observations point to an assumption that the above reaction courses are moderated by different co-conformations of pyrrole or imidazole CD complexes. The same concerns co-conformations of the respective complexes of monosubstituted pyrrole and monosubstituted imidazole.

Orientations "a", "b" and "c" (Figure 6) may be considered for CD complexed pyrrole, and orientations "d", "e" and "f" for imidazole. Arrangements "a" and "d" are very similar to the orientation of cyclopentadienyl residue in ferrocene complex with two α-CD molecules [32]. Pyrrole and imidazole in such orientation are probably unreactive towards the incoming diazonium cation. Orientation "b" is unfavorable assuming negligible yield of 3- or 3,4-substituted pyrrole. Orientation "c" much better rationalizes the yield and structures of pyrrole derivatives formed under applied experimental conditions. First of all it explains rather small influence of β-CD on the yield of disubstituted pyrrole **2**.

The experimental results also support crucial role of co-conformation "f" of imidazole embedded in β-CD, as the host to a minor extent decreases the yield of 2-substituted imidazole **4**. On the other hand, it explains well drastic drop of second substitution step that leads to imidazole derivatives **5** or **6** (the differences in reactivity of positions 2 and 4 of imidazole are neglected here).

Coupling reactions with 2-methylimidazole

To assess whether these above assumptions are correct, experiments on coupling *o*-ethoxybenzenediazonium salt with 2-methylimidazole were performed under standardized conditions. The lipophilic methyl substituent should reduce the number of possible coupling products and reorient the imidazole residue leading to co-conformation "g" in a manner similar to that found for 2,3-diazabicyclo[2.2.2]oct-2-ene and its 1-isopropyl-4-methyl derivative [cf. 18, 19]. In co-conformation "g" (Figure 6) positions 4 and 5 of 2-methylimidazole are exposed to substitution.



Scheme 4. Low-molecular coupling products of *o*-ethoxybenzenediazonium salt with imidazole.

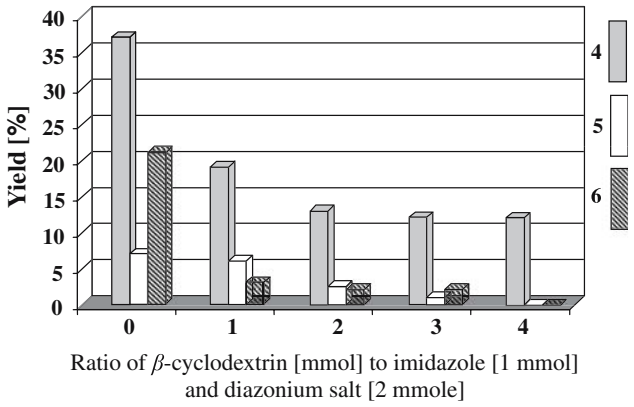


Figure 4. Yield of coupling products **4**–**6** of *o*-ethoxybenzenediazonium salt with imidazole in the presence and in the absence of β-CD.

In this case the most interesting result is connected with the yield of extractable matter from the reaction mixture. Without β-CD the yield of extractable products is 200 mg accompanied by a large amount of insoluble material. The reaction mixture is very dark; the insoluble component is black. In the presence of CD the yield of extractable components exceeds that obtained in plain experiment and was around 300, 250 and 210 mg if 1, 2 or 3 mol equivalents of CD were used, respectively. In the presence of CD only traces of black insoluble matter is formed. More, the extracts are bright. On evaporation and standing the colors deepen and finally part of the matter deposited in solid insoluble form.

Chromatographic inspection shows that each reaction mixture was composed of many individual compounds. For quantitative determinations only those were taken into account, which are colored and their abundance is relatively high. It concerns four components with R_F 0.82, 0.56, 0.46 and 0.38 in ethyl acetate–toluene–methanol–acetic acid 5:25:4:2 system. A lot of red-violet compound with high R_F (0.82) is produced in the absence of CD while in experiments with β-CD its presence is negligible. This compound, freshly isolated by preparative TLC, very rapidly decomposes even on NMR examination ($CDCl_3$, *d*-acetone) producing black insoluble matter. In the registered spectrum methyl residue of 2-methylimidazole and aromatic protons were identified. High concentration of this compound rationalizes formation of large quantity of insoluble material in plain experiment. Due to fast decomposition, structure of this compound was not established. Most likely, free radical substitution(s) plays an important role as the plain reaction is accompanied by release of a huge amount of nitrogen.

Identified compounds formed on coupling *o*-ethoxybenzenediazonium salt with 2-methylimidazole are shown in Scheme 5; the yield and distribution of products in plain experiment and in the presence of different concentrations of β-CD are collected in Figure 7.

Compound **9** (R_F 0.56), is characteristic for couplings conducted in the presence of β-CD, while its concentration in plain experiment is very low. The yield of this compound enlarges with the increase of CD

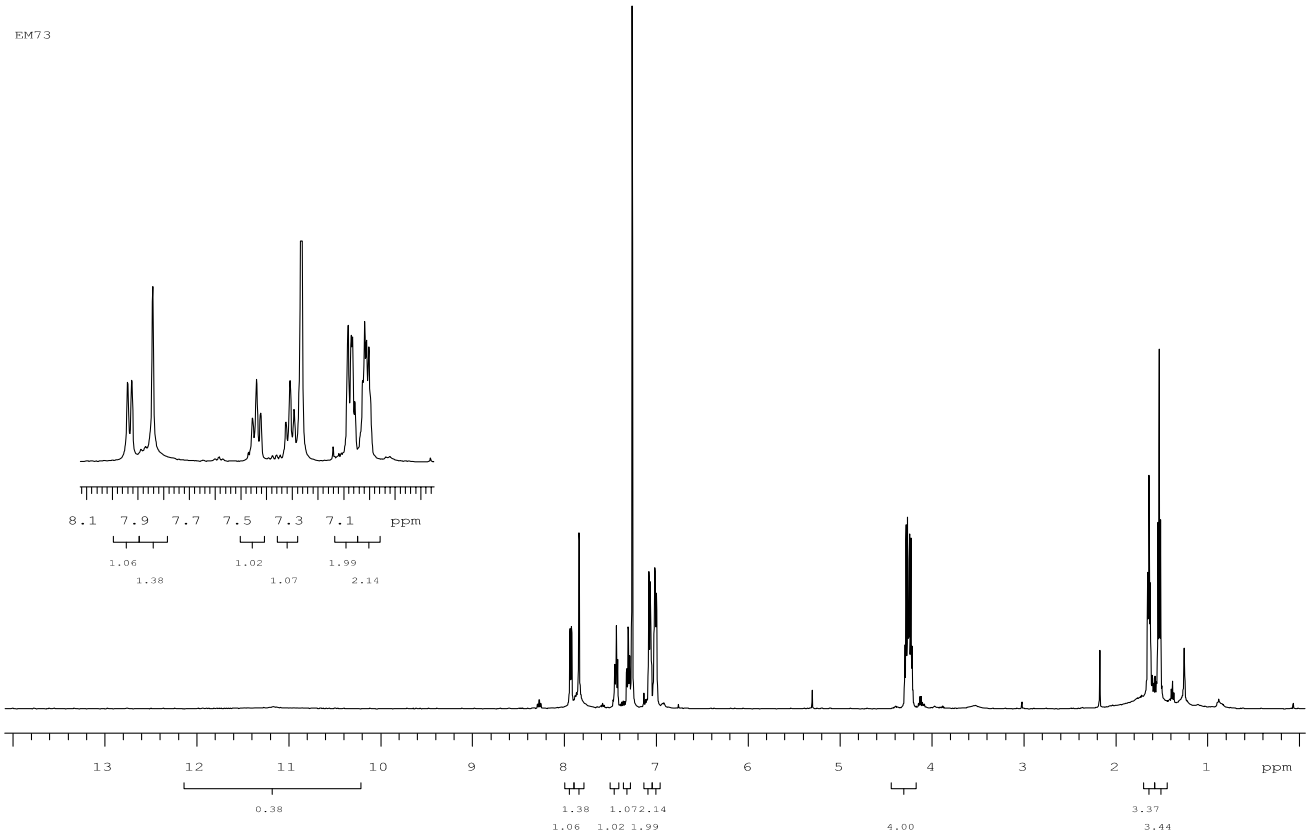


Figure 5. ^{1}H-NMR spectrum of 4-(2-ethoxybenzeneazo)-2-(2-ethoxyphenyl)-imidazole **6** in $CDCl_3$.

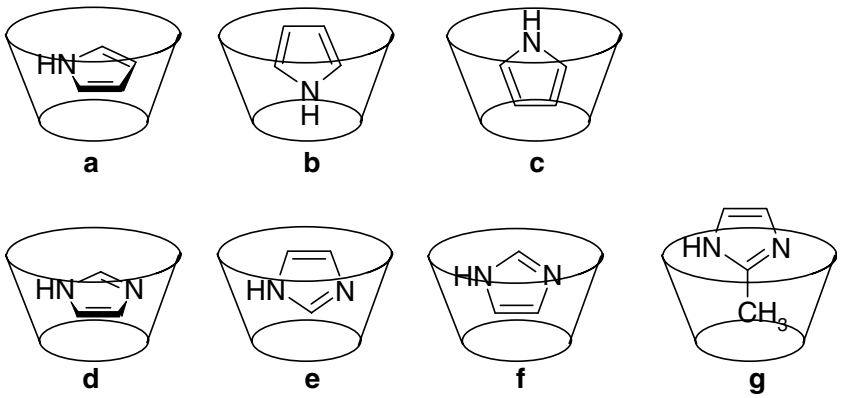
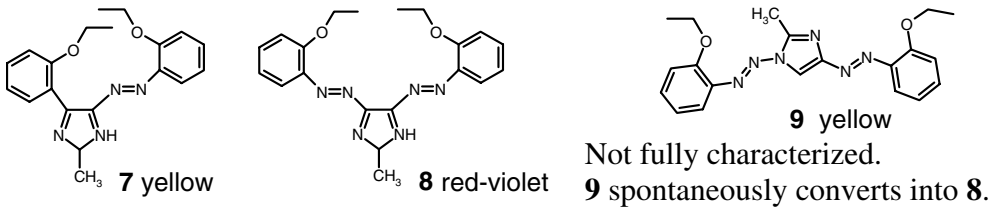


Figure 6. Considered co-conformations of azole molecules embedded in CDs.



Scheme 5. Low-molecular coupling products of *o*-ethoxybenzenediazonium salt with 2-methylimidazole.

concentration. Compound **9** is yellow; on chromatograms it very quickly changes color to deep red/violet indicating conversion into 4,5-disubstituted 2-methylimidazole **8** (R_F 0.46).

Compounds **7** (R_F 0.38) and **8** were found amongst products of each coupling reaction. The yield of compound **7** substantially increases with the increase of β-CD concentration; it is however slightly lower at 1 mol equivalent of CD compared with plain experiment. It also indicates increased contribution of free radical reaction to the total reaction course. Contrary to **7**, the yield of **8** decreases with the increase of β-CD concentration in favor of compound **9**. ^{1}H-NMR spectrum of **8** is shown in Figure 8.

At this point it is interesting, why high concentration of CD limits formation of compound **8** in favor of compound **9**. Co-conformation "g" (Figure 6) rationalizes to some extent the experimental data. The coupling reaction of azoles with diazonium salt may proceed directly, or indirectly by diazonium group solvated with the secondary hydroxyl groups of β-CD. The last case favors further coupling reaction *via* a "*Z*-diazo ether" [33], which in turn transfers the azo-residue onto nitrogen atom or position 5 of 2-methylimidazole to produce **9**. Stabilization of **9** in form of a CD complex by an excess of host molecules was considered as another factor explaining the yield increase. After decomplexation **9** spontaneously converts into **8** (Scheme 5).

Conclusions

CDs generally retard coupling reactions of *o*-ethoxybenzenediazonium salt with pyrrole or imidazole leading to yield decrease of low-molecular products. CDs control also the yield ratio of the most abundant products. Thus, β-CD reduces to a greater extent formation of monosubstituted pyrrole in favor of disubstituted pyrrole whereas the influence of host molecules is opposite for imidazole. Most likely the influence of host molecules may be rationalized by assuming different co-conformations of complexed azoles. Experiments on coupling of 2-methylimidazole support the above assumption as in this case CD causes increased yield of coupling products.

Free radical reactions are also stimulated by CDs. It concerns formation of imidazole derivative **6** and 2-methylimidazole derivative **7**. In the case of imidazole the most significant yield decrease was observed for free radical reaction product **6**. More, in the presence of CD products are formed, that were not found when the coupling reaction proceeds in the absence of host

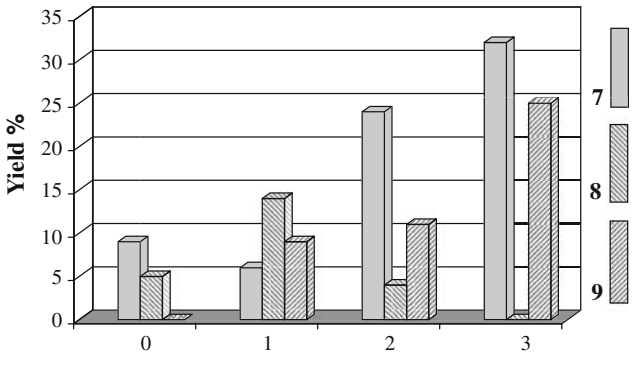


Figure 7. Yield dependence of **7**–**9** on β-CD concentration found for coupling *o*-ethoxybenzenediazonium salt with 2-methylimidazole.

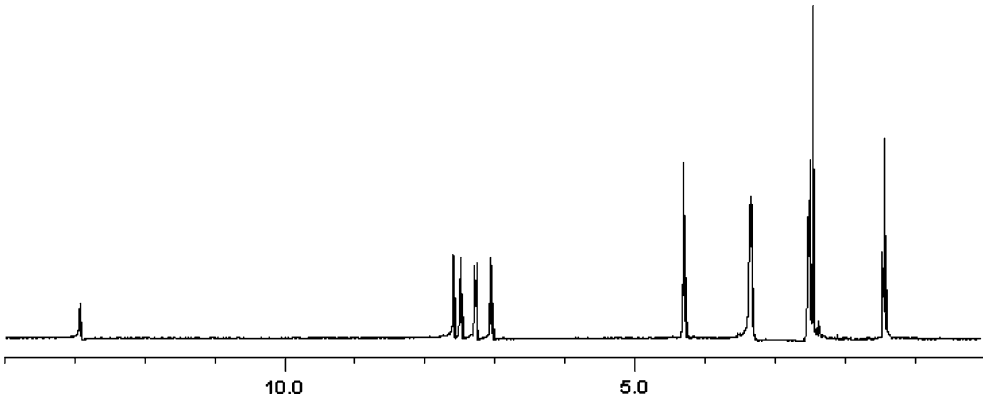


Figure 8. ^{1}H-NMR spectrum of compound **8** in DMSO.

molecules. It concerns e.g. α-CD promoted formation of hydroxypyrrole derivative **3** or β-CD stimulated formation of 2-methylimidazole derivative **9**.

The results on azole couplings with diazonium salts present additional evidence for a concept of molecular reactors [34]. CD may serve as useful tool for specific change of the ratio of formed products, thus facilitating isolation of particular products.

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