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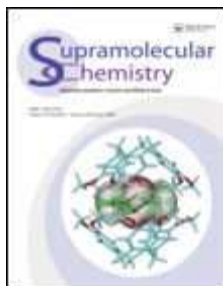
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Stimulated by cyclodextrins high yield synthesis of azocrown analogues comprising pyrrole or imidazole residues

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<p>Note: The following files were submitted by the author for peer review, but cannot be converted to PDF. You must view these files (e.g. movies) online.</p> <p>scheme1.cdx scheme2.cdx scheme3.cdx scheme4.cdx scheme5.cdx</p>	



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4 **Stimulated by cyclodextrins high yield synthesis of azocrown analogues**
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7 **comprising pyrrole or imidazole residues**
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11 **KAMILA SADOWSKA, MARZENA JAMRÓGIEWICZ[◇] and JAN F. BIERNAT***
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24 *Keywords:* cyclodextrin, bis-diazonium salts, azoles, macrocyclic compounds
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31 The influence of cyclodextrins on formation of azocrown ethers comprising pyrrole,
32 imidazole and substituted imidazole has been studied. Pyrrole, imidazole, 2-methyl-, 4-
33 methyl- and 4-phenylimidazole were coupled with bis-diazonium salts derived from bis-
34 1,5-(2-aminophenoxy)-3-oxapentane or bis-1,8-(2-aminophenoxy)-3,6-dioxaoctane to
35 form macrocyclic compounds with two azo units. **The syntheses were performed under**
36 **standard conditions in the presence of α -, β -, or γ -cyclodextrin (CDs) and the yield of**
37 **the reaction products was compared with the results of plain experiments, i.e. without**
38 **CDs.** The results are discussed in terms of co-conformation of azole molecules
39 embedded in cyclodextrin cavity.
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1. Introduction

Cyclodextrins found wide application in contemporary chemistry due to their ability to form host-guest complexes [1]. Molecules encapsulated inside CDs are at least partially protected against reactions [2,3], e.g. CDs complexed azo-dyes show increased photofading resistance [4].

On the other hand, cyclodextrins or their derivatives show catalytic activity, significantly increasing, for example hydrolysis rate of *m-tert*-butylphenol esters or DNA [5]. Cyclodextrins affect regio- and stereoselectivity of substitution or addition reactions [6-8]. Such behaviour is interpreted as enzyme mimicking action of cyclodextrin [9], in which the macrocyclic component serves as a mediator, taking part in a transfer of the reacting species. Due to these properties CDs are also called molecular reactors [10]. Our preliminary studies revealed, that the yield and the ratio of coupling products of *o*-nitrobenzene-diazonium salt with pyrrole significantly depends on the concentration of β -cyclodextrin, purposely added to the reaction mixture [11]. Coupling reactions of *o*-ethoxybenzene-diazonium salt with pyrrole, imidazole and 2-methylimidazole are affected by α -, β -, or γ -cyclodextrin so that, not only the yield and the ratio of products is changed, but also formation of additional compounds is promoted [12]. Co-conformation of azole complexes with CDs was assumed to be a key factor, which controls the coupling reaction course [11,12].

The aim of this paper is to demonstrate how CDs influence the overall yield of macrocyclic products formed on coupling of pyrrole, imidazole or substituted imidazoles with bis-diazonium salts.

2. Results

Coupling reactions with pyrrole

Coupling reactions of bis-diazonium salts, derived from bis-1,5-(2-aminophenoxy)-3-oxapentane or bis-1,8-(2-aminophenoxy)-3,6-dioxaoctane [13,14], with pyrrole were performed as shown in Scheme 1.

[Insert SCHEME 1 about here]

Addition of 0.25 mmol of α -, β -, or γ -cyclodextrin per 2 mmol of bis-diazonium salt and 2 mmol of pyrrole changed the total yield and the ratio of products. In case of α -CD, yield of compound **1p** increased slightly, whereas yield of compound **2p** was almost doubled. When β -CD was used, the ratio was inverted; product **1p** was isolated with yield more than double as compared to plane reaction, whereas amount of product **2p** was only a little bit higher. The overall yield of the two macrocyclic compounds formed simultaneously reached 87%. The influence of γ -cyclodextrin was noted as **1p** yield increase and **2p** slight decrease. Comparison of the yield of macrocycles obtained from pyrrole in the presence and in the absence of cyclodextrins is presented in Figure 1.

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4 Interestingly, the 18-membered compound **1p** is accompanied by its isomer **2p**, however
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6 the respective isomer of **3p** of larger cavity was not found.
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11 [Insert **FIGURE 1** about here]
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14 15 16 17 18 *Coupling reactions with imidazole and its derivatives* 19

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22 To establish how general the influence of cyclodextrins on macrocyclic products
23 formation is, coupling reactions of bis-diazonium salts with imidazole and its methyl or
24 phenyl derivatives were carried out. The syntheses were performed as shown in
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31 **S**cheme 2.
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35 [Insert **SCHEME 2** about here]
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40 Coupling of bis-diazonium salt [derived from bis-1,5-(2-aminophenoxy)-3-oxapentane]
41 with imidazole, and 2- and 4-methylimidazole was performed in the presence of α -, β -,
42 or γ -cyclodextrin. The most spectacular results were obtained for γ -CD in the case of 2-
43 and 4-methylimidazole (**F**igure 2). Yield of product **3i** and **7i** was as high as 75 and
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49 89%, respectively.
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54 [Insert **FIGURE 2** about here]
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Coupling reactions of bis-diazonium salts derived from bis-1,5-(2-aminophenoxy)-3-dioxapentane or bis-1,8-(2-aminophenoxy)-3,6-dioxaoctane with imidazole in the presence of α -, β -, or γ -cyclodextrin show the influence of the ether chain length on the yield of products. The yield of 18- and 21-membered azocrowns **1i** and **2i** with regard to the ether chain length is presented in Figure 3. Product **1i** formation is inhibited in the presence of β - or γ -CD, whereas addition of α -CD has no distinct influence. In case of reaction leading to compound **2i** the influence of β -CD is not substantial, while presence of α - or γ -CD decreases product **2i** yield drastically; only traces of compound were found when the latter one was added to the reaction mixture.

[Insert FIGURE 3 about here]

More coupling experiments with substituted imidazoles and bis-diazonium salts of different oxyethylene chain length were performed in the presence of β -CD. Results are summarized in Figure 4.

[Insert FIGURE 4 about here]

The highest yield increase in the presence of β -CD was found for macrocycles **7i** and **8i**. The yield of 17-membered and 20-membered chromogenic, macrocyclic derivatives of 2-methylimidazole is almost two times higher as compared with plain experiment. The yield increase observed for compounds **2i** – **6i** with β -CD is less prominent, whereas formation of compound **1i** is retarded in the presence of β -CD.

3. Discussion

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7 Previously, very similar coupling reactions of *o*-ethoxybenzenediazonium salt
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9 with pyrrole, or imidazole, or 2-methylimidazole [12] were carried out in the presence
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11 of α -, β - or γ -cyclodextrin. For comparison, blank experiments were performed under
12
13 exactly the same experimental conditions (ratio of substrates, concentration,
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15 temperature, pH and isolation procedure). The yield and ratio of the desired compounds
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17 (Scheme 3), intermediates, isomers and products of free radical side reactions, were
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19 discussed with regard to the applied concentration of CDs.
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26 [Insert SCHEME 3 about here]
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31 Syntheses of these compounds served as model reactions for the analogous syntheses of
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33 azocrown ethers considered in this paper. The previously obtained data [12] led to the
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35 conclusion that high concentration of CDs (up to 4 mmol per 1 mmol of azole)
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37 generally decreases the total yield of coupling and changes the percentage of free
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39 radical reaction products. Reaction of *o*-ethoxybenzenediazonium salt with 2-
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41 methylimidazole at high cyclodextrin concentrations leads mainly to free radical
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43 reaction product.
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47 The observed influence of cyclodextrins on model reactions with *o*-
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49 ethoxybenzenediazonium salts suggests that reactions leading to azomacrocycles may
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51 also be affected by CDs. As high concentration of CDs were unfavourable, only small
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53 amounts of CDs were added to the reaction mixtures. At small concentrations of CDs
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55 the difference between the blank and CDs promoted reaction should be emphasized, if
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57 all conditions are exactly the same as in model reactions.
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4 The model coupling reactions leading to products shown in Scheme 3 are
5 intermolecular. In case of coupling leading to the macrocyclic compounds, the reaction
6 proceeds in two stages: the first consists in intermolecular coupling of bis-diazonium
7 salt with azole molecule to form first –N=N– bond; and the second, intramolecular
8 coupling that closes the macrocyclic unit. Under the applied conditions the CDs
9 influence mainly the second stage.
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18 It is known that diazonium salts [15] and their coupling products form spontaneously
19 complexes with CDs with the typical formation constants in the range of 10^3 to 10^4
20 $\text{mol}^{-1}\cdot\text{dm}^3$ [16,17]. It is also known that the inclusion process takes milliseconds or less
21 [18]; for a recent review see [19,20].
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28 Considering the above literature data and the results of model reactions it seems that
29 CDs favour complexation of azoles over benzene residues. In the syntheses of
30 macrocycles the intermediate product formed at the first coupling stage, could also be
31 complexed by CDs.
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40 As shown previously [12], the differences in the yield of the macrocyclic products led to
41 assumption, that the reaction course is stimulated by relative orientation of azole
42 molecule and/or the intermediate inside CDs cavity. The included molecules are
43 normally oriented in the host in such way, that the hydrophobic part of the guest enters
44 the cavity as deep as possible.
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54 *Pyrrole macrocycles*
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4 Under standardized conditions, for 18-membered pyrrole azocrown ether **1p** the
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6 yield increases in the presence of CDs in the order β , γ and α as compared with the
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8 plain experiment. Surprisingly, for the 17-membered isomer **2p** the highest yield
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10 increase is caused by α -CD, whereas for other CDs the yield is comparable with plain
11
12 experiment. Looking at the relative yield and the ratio of positional isomers of pyrrole
13
14 azocrown ether it could be assumed that orientation of the first stage coupling products
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16 in CDs cavities is as shown in Scheme 4. Co-conformation “a” is favoured over “b”
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18 because in the latter one the pyrrole NH group occupies the most lipophilic part of CD
19
20 cavity. Hence the yield of compound **2p** is generally lower than **1p**. Taking into account
21
22 that the position 2 and 5 of pyrrole is more reactive, formation of compound **1p** seems
23
24 to be more favoured than formation of compound **2p**. These assumptions, however, do
25
26 not explain tremendous yield increase of **1p**, and smaller yield increase of **2p** in the
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28 reactions carried out in the presence of β -cyclodextrin. It may be supposed that CD
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30 somehow favours intramolecular coupling of intermediate “a”.
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40 [Insert SCHEME 4 about here]
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45 For the synthesis of 21-membered pyrrole azocrown **3p** addition of CDs causes yield
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47 decrease. It is worth noting that in this case the isomeric 20-membered crown ether,
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49 analogous to **2p**, is not formed in plain experiment as well as in the presence of CDs.
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Imidazole macrocycles

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5 For 18-membered imidazole derivative **1i** the influence of all CDs on yield is not
6 substantial. The influence of CDs on the synthesis of 4-methylimidazole derivative **3i** is
7 better pronounced: α -CD reduces the yield, whereas γ -CD enhances macrocycle
8 formation more than double. In case of coupling of 2-methylimidazole, α - and β -CD
9 demonstrate small desired influence while γ -CD increases the yield of **7i** from 25% to
10 89% as compared with plain synthesis.
11

12 Coupling leading to imidazole derivative **1i** is specially sensitive to the presence of β -
13 CD; the yield is reduced probably because deeply embedded the imidazole moiety is
14 sterically hindered by the host, see scheme 5, “c”. In case of 2- or 4-methylimidazole
15 co-conformation “d” and “e” for intermediate CDs complexes are the most probable
16 (Scheme 5). Analysing the experimental data (Figure 2) a steric hindrance was observed
17 only for α -cyclodextrin. More, CDs stimulate macrocyclization with the highest effect
18 observed for γ -CD. It may be interpreted with respect to the CDs cavity size. Probably,
19 the azole–N=N–benzene fragment includes into γ -CD cavity enhancing the
20 intramolecular coupling, c.f. *cis* \rightleftharpoons *trans* isomerization of azobenzene derivative of γ -
21 CD [21].
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46 [Insert SCHEME 5 about here]
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53 In case of 4-phenylimidazole coupling β -CD also influences the yield of compounds **5i**
54 and **6i**, although the effect is less pronounced; side reactions involving benzene residue
55 or partial expulsion of imidazole residue from CD cavity could be the reason.
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Considering the influence of oxyethylene chain length it could be stated that β -CD promotes to a greater extent formation of macrocycles; contrary to this α -CD and γ -CD strongly decrease yield of compound **2i**.

Interestingly, the free radical reactions, which are significant in syntheses leading to open-chained products [11,12], play negligible role in case of syntheses of macrocycles.

None free radical reaction product was identified. It suggests that coupling of the diazonium salt with azoles proceeds faster than homolysis.

4. Conclusions

As suggested in the literature, under the applied conditions CDs form complexes with organic components of the reaction mixture. The embedded parts of molecules are shielded from the bulk. It may ultimately protect them against side reactions or improve intramolecular reaction. Cyclodextrins have an influence on the formation of macrocyclic compounds comprising pyrrole, imidazole and substituted imidazole. Experiments on coupling bis-diazonium salt(s) with imidazoles in the presence of CDs revealed important influence of lipophilic methyl or phenyl residues on the yield of macrocycles .

Co-conformation of substrates or reaction intermediates hosted in the cyclodextrin cavity is a key factor determining the reaction course. Intramolecular coupling of the intermediate is probably favoured by CDs, and as a result the by-products formation is decreased. Although, cyclodextrins are reported to facilitate homolytic decomposition of diazonium salts and stabilize radical species [15], here we have not observed substantial yield of free radical reaction products.

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4 The results of enhancement of macrocycle synthesis may be described in terms of
5 templating from the outside inwards [22]; otherwise the CDs molecules may be treated
6 as molecular reactors [9].
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11 As far as we are concerned, the implementation of cyclodextrins to macrocycle yield
12 stimulation has not been announced in the literature yet.
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15 16 17 18 19 **5. Experimental**

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22 All materials and solvents were of analytical reagent grade. α -CD (TCI), β -CD (Fluka)
23 and γ -CD (TCI) were used as purchased. Isolation of macrocyclic products was
24 performed on silica gel filled chromatographic column or on preparative
25 chromatographic plates (Silica gel 60 F₂₅₄, Merck). The yield was determined
26 gravimetrically.
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35 Compounds **1p** – **3p** and **1i**, including X-ray structure of compound **2p** [23], and
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Compounds **2i** – **8i**, including X-ray structure of **4i** [24] were fully characterized
previously and served as reference materials in this study.

5.1 Syntheses

Two solutions were prepared:

Solution A. To a suspension of bis-1,5-(2-aminophenoxy)-3-oxapentane or bis-1,8-(2-aminophenoxy)-3,6-dioxaoctane [13,14] (2 mmol) in 40 cm³ water 1 cm³ conc.

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4 hydrochloric acid was added. The clear solution was diazotized with sodium nitrite
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6 (0.28 g, 4 mmol) dissolved in 2 cm³ cold water.
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11 *Solution B.* Pyrrole, or imidazole, or 2-methyl-, or 4-methyl- or 4-phenylimidazole (2
12 mmol) and sodium hydroxide (0.2 g, 5 mmol) were dissolved in 40 cm³ water. To
13 solutions containing pyrrole or 4-phenylimidazole 2 cm³ of ethanol was added. In the
14 case of syntheses with cyclodextrins, 0.25 mmol of CD was added to each solution B.
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20 Ice-cold solutions A and B were added dropwise with the same rate during 45 min to a
21 vigorously stirred cold (10°C) water (600 cm³) alkalized with NaOH to pH ~ 10. Then
22 stirring was continued overnight. During the first three hours the temperature was
23 maintained at 10°C, and then at 20°C. Finally, the reaction mixture was cooled to 5°C
24 and adjusted to pH ~ 6 with acetic acid. The precipitate was collected and the filtrate
25 was extracted with chloroform – toluene – acetic acid (30:1:1) mixture until the aqueous
26 phase decolorizes. Then the extracts were evaporated under reduced pressure. The
27 macrocyclic compounds were isolated and characterized as described in [23,24].
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54 **7. References**

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SCHEMES

SCHEME 1. Syntheses of azocrown ethers with pyrrole units in the presence of cyclodextrins

SCHEME 2. Syntheses of azocrown ethers with imidazole or imidazole derivative units

SCHEME 3. Products of double coupling of *o*-ethoxybenzenediazonium salt with azoles

SCHEME 4. Considered co-conformations of pyrrole molecules embedded in CDs

SCHEME 5. Considered co-conformations of imidazole molecules embedded in CDs

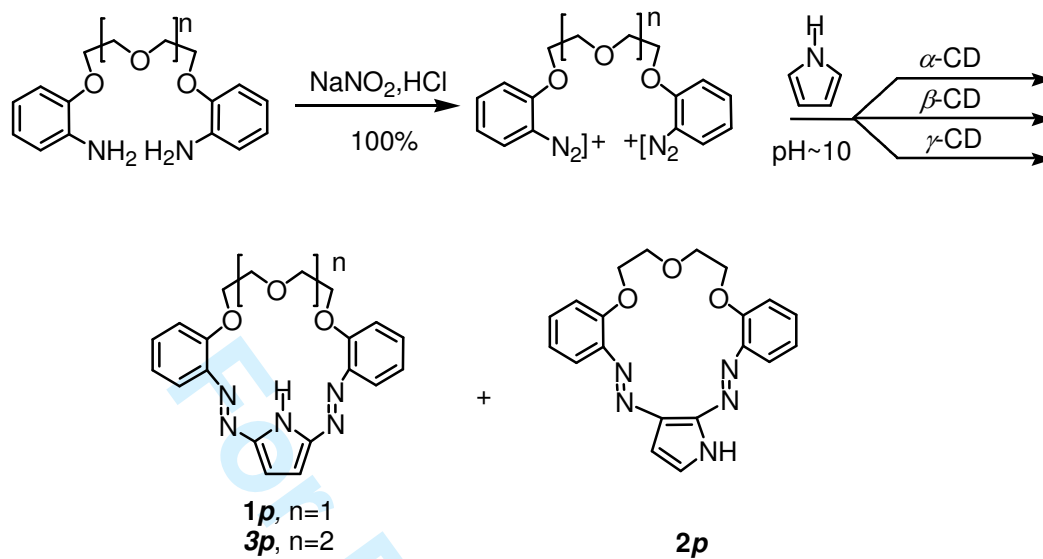
FIGURES

FIGURE 1. Yield of macrocyclic products obtained from pyrrole and bis-diazonium salts in the presence and in the absence of cyclodextrins.

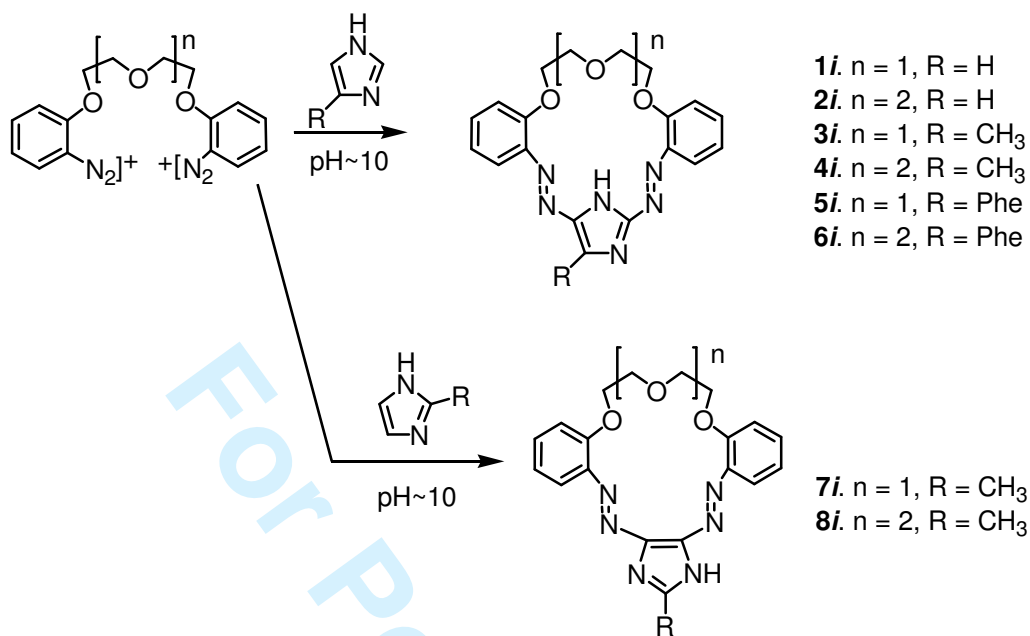
FIGURE 2. Yield of macrocyclic products, obtained from bis-diazonium salt and imidazole or its derivatives in the presence and in the absence of cyclodextrins

FIGURE 3. Yield of 18- and 21-membered macrocycles with imidazole units in the presence and in the absence of cyclodextrins

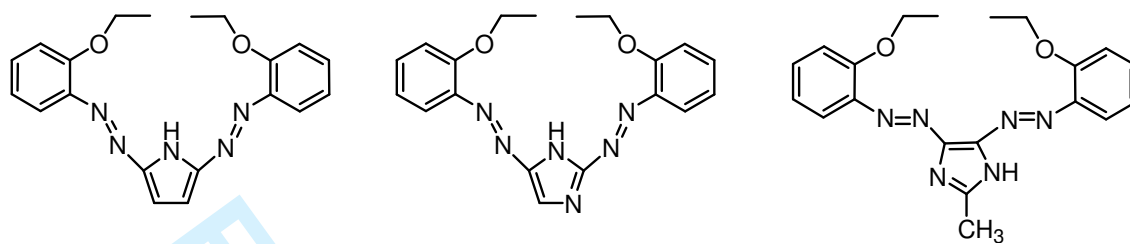
FIGURE 4. Yield of macrocyclic products obtained from bis-diazonium salts and imidazole or its derivatives in the presence and in the absence of β -cyclodextrin



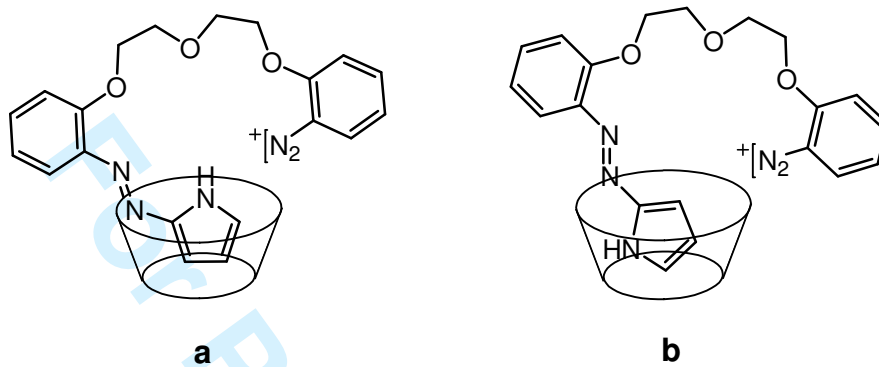
SCHEME 1



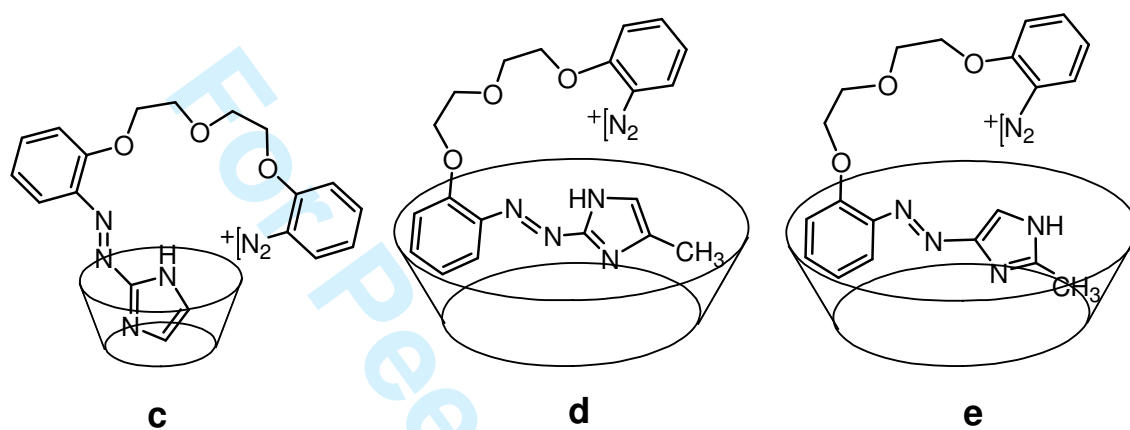
SCHEME 2



SCHEME 3



SCHEME 4



SCHEME 5

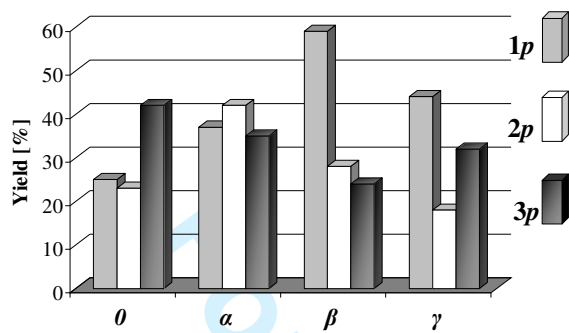
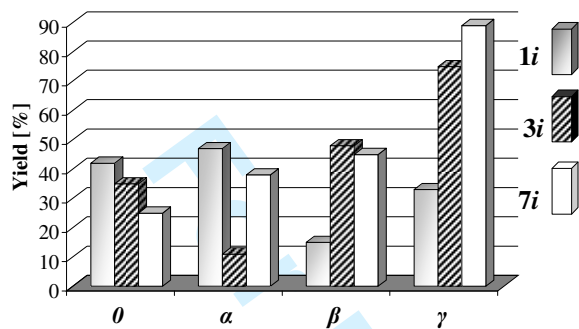
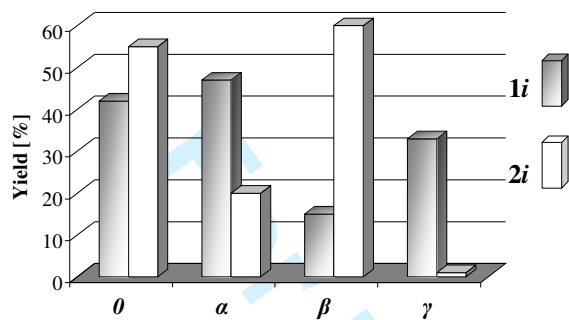
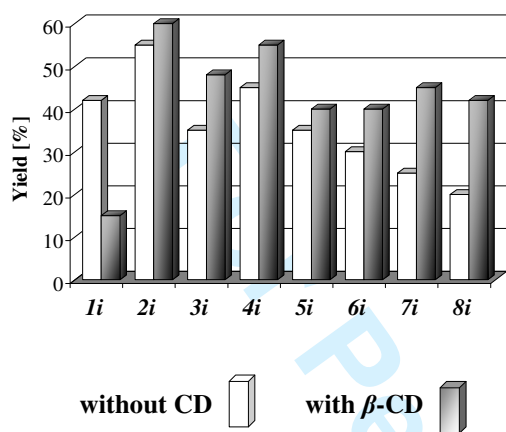


FIGURE 1

**FIGURE 2**

**FIGURE 3**

**FIGURE 4**

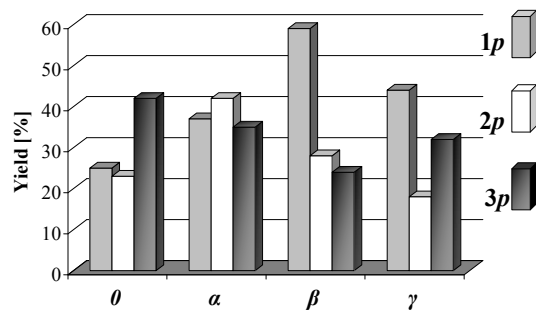


figure 1

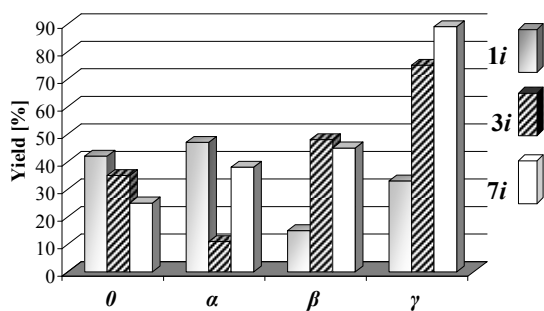


figure 2

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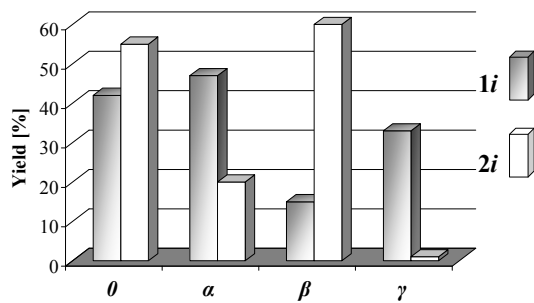


figure 3

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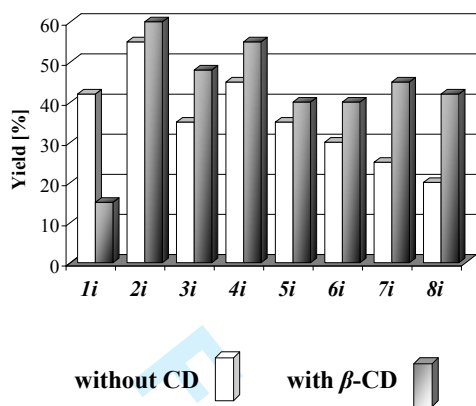


figure 4