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

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The influence of cyclodextrins (CDs) on the formation of azocrown ethers comprising pyrrole, imidazole and substituted imidazole has been studied. Pyrrole, imidazole, 2-methyl-, 4-methyl- and 4-phenylimidazole were coupled with bis-diazonium salts derived from bis-1,5-(2-aminophenoxy)-3-oxapentane or bis-1,8-(2-aminophenoxy)-3,6-dioxaoctane to form macrocyclic compounds with two azo units. The syntheses were performed under standard conditions in the presence of α-, β- or γ-CDs and the yield of the reaction products was compared with the results of plain experiments, i.e. without CDs. The results are discussed in terms of co-conformation of azole molecules embedded in CD cavity.

Keywords: cyclodextrin; bis-diazonium salts; azoles; macrocyclic compounds

1. Introduction

Cyclodextrins (CDs) 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, CDs or their derivatives show catalytic activity, significantly increasing, for example hydrolysis rate of *m-tert*-butylphenol esters or DNA (*5*). CDs affect the regio- and stereoselectivity of substitution or addition reactions (*6–8*). Such behaviour is interpreted as an enzyme mimicking action of CD (*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-CD, 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-CD so that not only the yield and the ratio of products are changed, but the formation of additional compounds is also 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 the coupling of pyrrole, imidazole or substituted imidazoles with bis-diazonium salts.

2. Results

2.1 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.

The addition of 0.25 mmol of α-, β- or γ-CD 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, the yield of compound **1p** increased slightly, whereas that of compound **2p** was almost doubled. When β-CD was used, the ratio was inverted; product **1p** was isolated with an yield more than twice as compared with the plane reaction, whereas the amount of product **2p** was only a little bit higher. The overall yield of the two macrocyclic compounds formed simultaneously reached 87%. γ-CD increases the yield of **1p** and slightly decreases the yield of **2p**. A comparison of the yield of macrocycles obtained from pyrrole in the presence and in the absence of CDs is presented in Figure 1. Interestingly, the 18-membered compound **1p** is accompanied by its isomer **2p**; however, the respective isomer of **3p** of larger cavity was not found.

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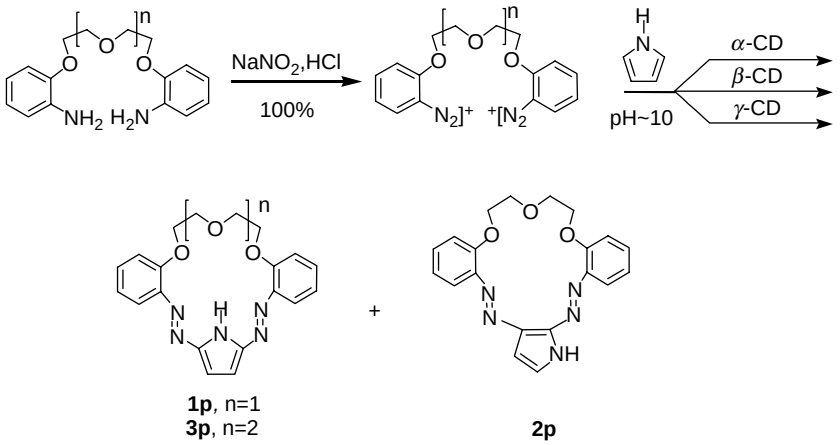


Scheme 1. Syntheses of azocrown ethers with pyrrole units in the presence of CDs.

2.2 Coupling reactions with imidazole and its derivatives

To establish how general the influence of CDs on macrocyclic products formation is, coupling reactions of bis-diazonium salts with imidazole and its methyl or phenyl derivatives were carried out. The syntheses were performed as shown in Scheme 2.

Coupling of bis-diazonium salt [derived from bis-1,5-(2-aminophenoxy)-3-oxapentane] with imidazole, and 2- and 4-methylimidazole was performed in the presence of α-, β- or γ-CD. The most spectacular results were obtained for γ-CD in the case of 2- and 4-methylimidazole (Figure 2). The yield of product **3i** and **7i** was as high as 75 and 89%, respectively.

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-CD 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. The formation of product **1i** is inhibited by the presence of β- or γ-CD, whereas addition of α-CD has no distinct influence. In the case of a reaction leading to compound **2i** the influence of β-CD is not substantial, while the presence of α- or γ-CD decreases the yield of product **2i** drastically; only traces of the compound were found when the latter one was added to the reaction mixture.

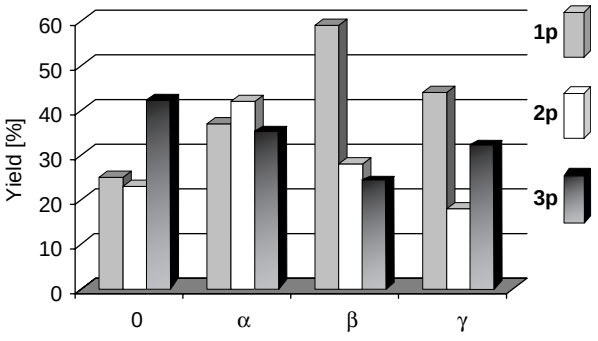


Figure 1. Yield of macrocyclic products obtained from pyrrole and bis-diazonium salts in the presence and in the absence of CDs.

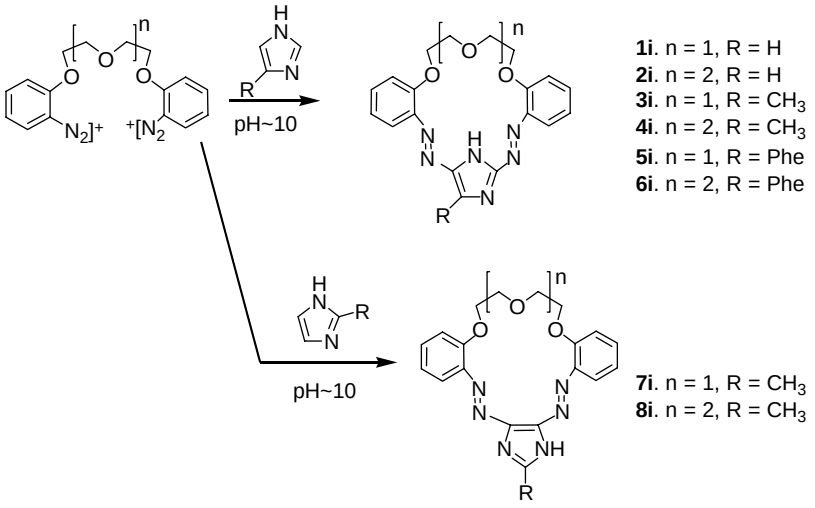
More coupling experiments with substituted imidazoles and bis-diazonium salts of different oxyethylene chain length were performed in the presence of β-CD. Results are summarised in Figure 4.

The highest increase in yield 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 the plain experiment. The increase in yield observed for compounds **2i**–**6i** with β-CD is less prominent, whereas the formation of compound **1i** is retarded in the presence of β-CD.

3. Discussion

Previously, very similar coupling reactions of *o*-ethoxybenzene-diazonium salt with pyrrole, imidazole or 2-methylimidazole (*12*) were carried out in the presence of α-, β- or γ-CD. For comparison, blank experiments were performed under exactly the same experimental conditions (ratio of substrates, concentration, temperature, pH and isolation procedure). The yield and ratio of the desired compounds (Scheme 3), intermediates, isomers and products of free radical side reactions, were discussed with regard to the applied concentration of CDs.

The syntheses of these compounds served as model reactions for the analogous syntheses of azocrown ethers considered in this paper. The previously obtained data (*12*) led to the conclusion that high concentration of CDs (up to 4 mmol per 1 mmol of azole) generally decreases



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

the total yield of coupling and changes the percentage of free radical reaction products. The reaction of *o*-ethoxybenzene-diazonium salt with 2-methylimidazole at high CD concentrations leads mainly to the free radical reaction product.

The observed influence of CDs on model reactions with *o*-ethoxybenzene-diazonium salts suggests that reactions leading to azomacrocycles may also be affected by CDs. As high concentrations of CDs were unfavourable, only small amounts of CDs were added to the reaction mixtures. At small concentrations of CDs, the difference between the blank and CDs promoted reaction should be emphasised, if all conditions are exactly the same as in model reactions.

The model coupling reactions leading to products shown in Scheme 3 are intermolecular. In the case of coupling leading to the macrocyclic compounds, the reaction proceeds in two stages: the first consists in intermolecular coupling of bis-diazonium salt with azole molecule to form first —N═N— bond and the second, intramolecular coupling that closes the macrocyclic unit. Under the applied conditions, the CDs influence mainly the second stage.

It is known that diazonium salts (*15*) and their coupling products spontaneously form complexes with CDs with the typical formation constants in the range of 10^3–10^4 mol^{-1} dm^3 (*16*, *17*). It is also known that the inclusion process takes milliseconds or less (*18*); for a recent review see Refs. (*19*, *20*).

Considering the above literature data and the results of model reactions it seems that CDs favour complexation of azoles over benzene residues. In the syntheses of macrocycles, the intermediate product formed at the first coupling stage, could also be complexed by CDs.

As shown previously (*12*), the differences in the yield of the macrocyclic products led to the assumption that the reaction course is stimulated by relative orientation of azole molecule and/or the intermediate inside the CD cavity. The included molecules are normally oriented in the host in such a way that the hydrophobic part of the guest enters the cavity as deep as possible.

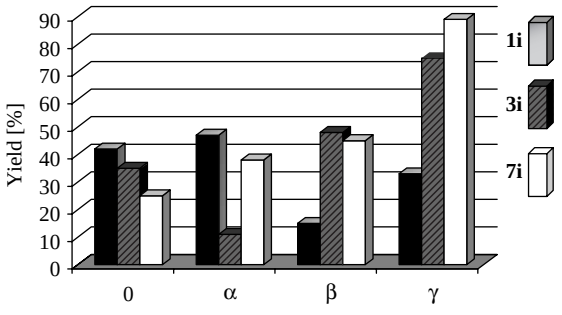


Figure 2. Yield of macrocyclic products, obtained from bis-diazonium salt and imidazole or its derivatives in the presence and in the absence of CDs.

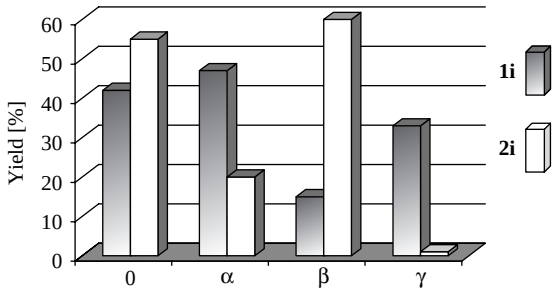


Figure 3. Yield of 18- and 21-membered macrocycles with imidazole units in the presence and in the absence of CDs.

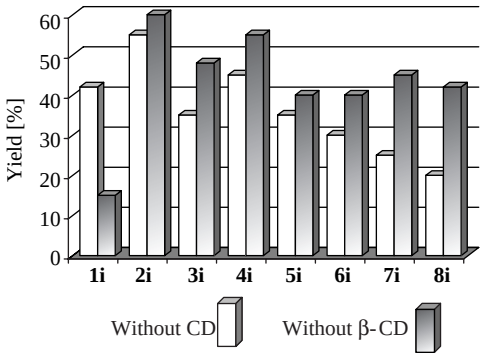
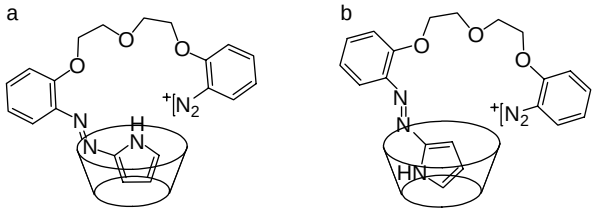


Figure 4. Yield of macrocyclic products obtained from bis-diazonium salts and imidazole or its derivatives in the presence and in the absence of β-CD.

3.1 Pyrrole macrocycles

Under standardised conditions, for 18-membered pyrrole azocrown ether **1p**, the yield increases in the presence of CDs in the order β, γ and α as compared with the plain experiment. Surprisingly, for the 17-membered isomer **2p**, the highest yield increase is caused by α-CD, whereas for other CDs the yield is comparable with the plain experiment. Looking at the relative yield and the ratio of positional isomers of pyrrole azocrown ether it could be assumed that the orientation of the first-stage coupling products in CD cavities is as shown in Scheme 4. Co-conformation 'a' is favoured over 'b' because in the latter one the pyrrole NH group occupies the most lipophilic part of the CD cavity. Hence, the yield of compound **2p** is generally lower than that of **1p**. Taking into account that the positions 2 and 5 of pyrrole are more reactive, formation of compound **1p** seems to be more favoured than the formation of compound **2p**. These assumptions, however, do not explain the tremendous increase in the yield of **1p** and smaller increase in the yield of **2p** in the reactions carried out in the presence of β-CD. It may be supposed that CD somehow favours the intramolecular coupling of intermediate 'a'.

For the synthesis of 21-membered pyrrole azocrown **3p**, the addition of CDs causes the yield to decrease. It is worth noting that in this case the isomeric 20-membered crown ether, analogous to **2p**, is not formed in the plain experiment as well as in the presence of CDs.



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

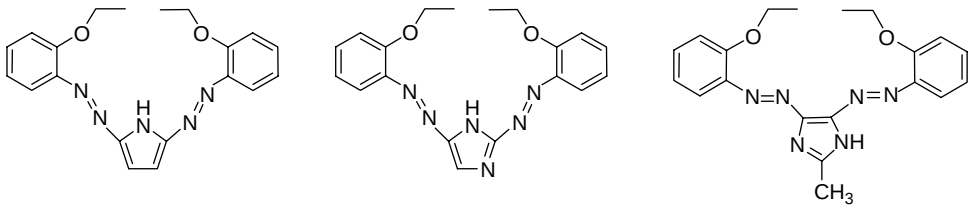
3.2 Imidazole macrocycles

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

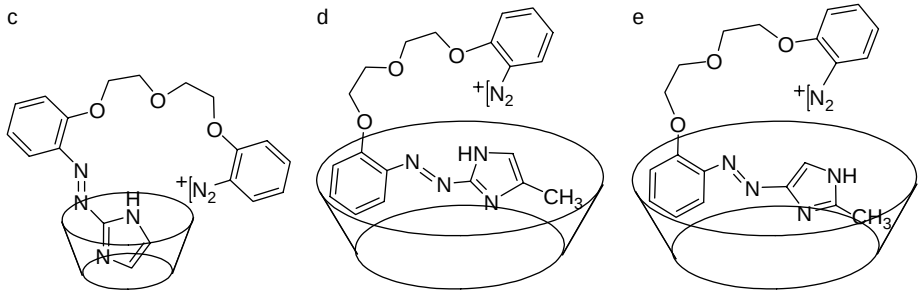
Coupling leading to imidazole derivative **1i** is especially sensitive to the presence of β-CD; the yield is reduced probably because the deeply embedded imidazole moiety is sterically hindered by the host, see Scheme 5, 'c'. In the case of 2- or 4-methylimidazole, co-conformation 'd' and 'e' for intermediate CDs complexes are the most probable (Scheme 5). Analysing the experimental data (Figure 2) a steric hindrance was observed only for α-CD. Furthermore, CDs stimulate macrocyclisation with the highest effect observed for γ-CD. It may be interpreted with respect to the cavity size of CDs. Probably, the azole—N═N—benzene fragment includes into γ-CD cavity enhancing the intramolecular coupling, cf. *cis* ⇌ *trans* isomerisation of azobenzene derivative of γ-CD (*21*).

In the case of 4-phenylimidazole coupling β-CD also influences the yield of compounds **5i** and **6i**, although the effect is less pronounced; side reactions involving benzene residue or partial expulsion of imidazole residue from the CD cavity could be the reason.

Considering the influence of oxyethylene chain length it could be stated that β-CD promotes the formation of macrocycles to a greater extent; contrary to



Scheme 3. Products of double coupling of *o*-ethoxybenzene-diazonium salt with azoles.



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

this, α-CD and γ-CD strongly decrease the yield of compound **2i**.

Interestingly, the free radical reactions, which are significant in the syntheses leading to open-chained products (*11*, *12*), play a negligible role in the case of syntheses of macrocycles. No free radical reaction product was identified in the last case. It suggests that the 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. CDs 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 an important influence of lipophilic methyl or phenyl residues on the yield of macrocycles.

Co-conformation of substrates or reaction intermediates hosted in the CD 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, CDs are reported to facilitate the homolytic decomposition of diazonium salts and stabilise radical species (*15*), here we have not observed a substantial yield of free radical reaction products.

The results of enhancement of macrocycle synthesis may be described in terms of templating from the outside inwards (*22*); otherwise, the CDs molecules may be treated as molecular reactors (*9*).

As far as we are concerned, the implementation of CDs to macrocycle yield stimulation has not been announced in the literature yet.

5. Experimental

All materials and solvents were of analytical reagent grade. α-CD (TCI Europe, Belgium), β-CD (Fluka, Sigma–Aldrich, Germany) and γ-CD (TCI) were used as purchased. The isolation of macrocyclic products was performed on silica gel filled chromatographic column or on preparative chromatographic plates (Silica gel 60 F_{254}, Merck). The yield was determined gravimetrically.

Compounds **1p**–**3p** and **1i**, including the X-ray structure of compound **2p** (*23*) and compounds **2i**–**8i**, including the X-ray structure of **4i** (*24*), were fully characterised 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 cm^3 water, 1 cm^3 conc. hydrochloric acid was added. The clear solution was diazotised with sodium nitrite (0.28 g, 4 mmol) dissolved in 2 cm^3 cold water.

Solution B. Pyrrole, imidazole, 2-methyl-, 4-methyl- or 4-phenylimidazole (2 mmol) and sodium hydroxide (0.2 g, 5 mmol) were dissolved in 40 cm^3 water. To the solution containing pyrrole or 4-phenylimidazole, 2 cm^3 of ethanol was added. In the case of syntheses with CDs, 0.25 mmol of CD was added to each solution B.

Ice-cold solutions A and B were added dropwise with the same rate during 45 min to a vigorously stirred cold (10°C) water (600 cm^3) alkalised with NaOH to pH ~ 10. Then stirring was continued overnight. During the first 3 h, the temperature was maintained at 10°C and then at 20°C. Finally, the reaction mixture was cooled to 5°C and the pH was adjusted to ~6 with acetic acid. The precipitate was collected and the filtrate was extracted with chloroform–toluene–acetic acid (30:1:1) mixture until the aqueous phase decolorised. The extracts were then evaporated under reduced pressure.

The macrocyclic compounds were isolated and characterised as described in Refs. (*23*, *24*).

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Note

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