Benzimidazolium-cyclodextrin Inclusion Complexes

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A series of benzimidazolium salts bearing a para-halogenophenyl end group in position 3 was subject to complexation with a- and b-cyclodextrins. Two out of the three studied compounds were leading to inclusion complexes with both cyclodextrins. For both cyclodextrins the strength of interaction with bezimidazolium ions increases in the order F<Cl<Br.

Keywords: benzimidazolium salts, benzimidazolines, cyclodextrins, inclusion complexes, NMR

1-Benzyl-3-[2-(aryl)-2-oxoethyl]-5,6-dimethyl-benzimidazolium salts and ylides have been extensively used by us as intermediates in the synthesis of various benzymidazole fused rings or other heterocycles resulting from the imidazole ring opening [1-6]. These syntheses are part of our wider interest in the study of chemistry and properties of various nitrogen containing heterocycles [7-18]. There is a wide interest in studying cyclodextrin inclusion complexes of a range compounds with various aims including changing the solubility, drug/compound delivery carriers, structural or theoretical studies, etc. [19-22], including of course compounds with benzimidazole moieties [23-26]. To our knowledge there is no study up to date involving cyclodextrin complexes with 1-benzyl-3-[2-(aryl)-2-oxoethyl]-benzimidazolium salts. The solubility in water of 1-benzyl-3-[2-(aryl)-2-oxoethyl]-5,6-dimethyl-benzimidazolium salts is quite low and the possible complexation with cyclodextrins would possibly change significantly this physical property. Moreover, it would be interesting to asses which moieties, i.e. 1-benzyl, 3-aryloxoethyl, or 5,6-benzo-fused ring are the preferred complexation sites of these compounds.

In this study we report on the synthesis of 1-benzyl-3-[2-(4-fluorophenyl)-2-oxoethyl]-5,6-dimethyl-benzimidazolium bromide (**1a**), 1-benzyl-3-[2-(4-chlorophenyl)-2-oxoethyl]-5,6-dimethylbenzimidazolium bromide (**1b**) and 1-benzyl-3-[2-(4-bromophenyl)-2-oxoethyl]-5,6-dimethylbenzimidazolium bromide (**1c**) and on their complexation with a-cyclodextrin (**αCD**) and b-cyclodextrins (**βCD**).

Experimental part

Melting points were determined on a Boetius apparatus and are uncorrected. The IR spectra were recorded on a Nicolet Impact 410 spectrometer, in KBr pellets. The NMR spectra have been recorded on Bruker Avance III 400 and Bruker DRX 400 instruments, equipped with a 5 mm multinuclear inverse detection z-gradient probe and a 5 mm direct detection z-gradient QNP probe, operating at 400.1 and 100.6 MHz for ^{1}H and ^{13}C nuclei. For the benzimidazolium bromides derivatives, the chemical shifts are reported in d units (ppm), for ^{1}H relative to internal TMS and for ^{13}C relative to the residual peak of the solvent (ref.: $CHCl_3$ 77.0 ppm). H,H-COSY, H,C-HSQC and H,C-HMBC experiments, were recorded using standard pulse sequences in the version with z-gradients, as delivered by Bruker with TopSpin 1.3 PL10 spectrometer control and processing software. For the benzimidazolium bromides-cyclodextrins mixtures, the chemical shifts are reported in δ units (ppm), and were electronically referred to the residual peak of the solvent (ref.: H_2O 4.8 ppm). The H,H-ROESY experiments were recorded using standard pulse sequence, with water suppression, as delivered by Bruker with TopSpin 2.1 PL6 spectrometer control and processing software.

Synthesis of benzimidazolium bromides derivatives.

To a solution of 5 mmole of 1-benzil-5,6-dimethyl-benzimidazoline in 30 mL acetone, 5 mmole of substituted phenacyl bromide was added. The reaction mixture was heated at reflux temperature for 3 h and left overnight at room temperature. The solid was filtered off, washed on the filter with 10 mL mixture of acetone-diethyl ether 1:1 and recrystallized from MeOH/Et_2O.

1-Benzyl-3-[2-(4-fluorophenyl)-2-oxoethyl]-5,6-dimethylbenzimidazolium bromide (1a): white crystals with m.p. 238-240 °C. Yield: 98 %. Anal. calcd. $C_{24}H_{22}BrFN_2O$ (453.35): C 63.58; H 4.89; N 6.18. Found: C 63.35; H 4.96; N 6.03. **IR** (KBr, cm^{-1}): 2998, 1694, 1595, 1557, 1488, 1453, 1361, 1230, 1187, 1159, 1137. **^{1}H NMR** (*$CDCl_3$*, 25°C), δ(ppm)**:** 2.35 (6H, s, CH_3-5, CH_3-6), 5.69 (2H, s, CH_2-Ph), 6.64 (2H, s, CH_2-CO), 7.15 (2H, t, 8.6 Hz, H-3"), 7.30 (1H, s, H-7), 7.33-7.43 (6H, m, H-2', H-3', H-4', H-4), 8.24 (2H, dd, 8.8, 5.2 Hz, H-2"), 10.89 (1H, s, H-2). **^{13}C-NMR** (*$CDCl_3$*, 25 °C), δ (ppm): 20.5 (CH_3-5 or CH_3-6), 20.6 (CH_3-5 or CH_3-6), 51.4 (CH_2-Ph), 53.7 (CH_2-CO), 113.0 (C-7), 113.2 (C-4), 116.3 (d, 22 Hz, C-3"), 127.9 (C-2'), 129.2 (C-4'), 129.23 (C-7a), 129.4 (C-3'), 129.9 (d, 2.8 Hz, C-1"), 130.9 (C-3a), 131.7 (d, 9.7 Hz, C-2"), 132.2 (C-1'), 137.4 (C-6), 137.7 (C-5), 166.6 (d, 257.6 Hz, C-4"), 188.9 (C=O).

1-Benzyl-3-[2-(4-chlorophenyl)-2-oxoethyl]-5,6-dimethylbenzimidazolium bromide (1b): white crystals with m.p. 235-237 °C. Yield: 93 %. Anal. calcd. $C_{24}H_{22}BrClN_2O$ (469.80): C 61.36; H 4.72; N 5.96. Found: C 61.21; H 4.59; N 6.05. **IR** (KBr, cm^{-1}): 3002,

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1687, 1589, 1547, 1487, 1451, 1429, 1400, 1362, 1328, 1225, 1181, 1087. **^{1}H-NMR** (*$CDCl_3$*, 25 °C), δ (ppm): 2.35 (6H, s, CH_3-5, CH_3-6), 5.68 (2H, s, CH_2-Ph), 6.66 (2H, s, CH_2-CO), 7.29 (1H, s, H-7), 7.35-7.43 (6H, m, H-2', H-3', H-4', H-4), 7.45 (2H, d, 8.6 Hz, H-3"), 8.14 (2H, d, 8.6 Hz, H-2"), 10.90 (1H, s, H-2). **^{13}C-NMR** (*$CDCl_3$*, 25 °C), δ (ppm): 20.5 (CH_3-5 or CH_3-6), 20.6 (CH_3-5 or CH_3-6), 51.4 (CH_2-Ph), 53.8 (CH_2-CO), 113.0 (C-7), 113.2 (C-4), 127.9 (C-2'), 129.3 (C-7a), 129.4 (C-4'), 129.5 (C-3" and C-3'), 130.2 (C-2"), 130.9 (C-3a), 131.8 (C-1"), 132.2 (C-1'), 137.5 (C-6), 137.8 (C-5), 141.3 (C-4"), 142.2 (C-2), 189.4 (C=O).

1-Benzyl-3-[2-(4-bromophenyl)-2-oxoethyl]-5,6-dimethylbenzimidazolium bromide (1c): white crystals with m.p. 242-244 °C. Yield: 96 %. Anal. calcd. $C_{24}H_{22}Br_2N_2O$ (514.25): C 56.05; H 4.31; N 5.45. Found: C 56.23; H 4.47; N 5.32. **IR** (KBr, cm^{-1}): 3002, 1687, 1585, 1547, 1485, 1451, 1430, 1396, 1362, 1329, 1223, 1181, 1066. **^{1}H-NMR** (*$CDCl_3$*, 25°C), δ (ppm): 2.37 (6H, s, CH_3-5, CH_3-6), 5.68 (2H, s, CH_2-Ph), 6.65 (2H, s, CH_2-CO), 7.29 (1H, s, H-7), 7.34 (1H, s, H-4), 7.38-7.42 (5H, m, H-2', H-3', H-4'), 7.65 (2H, d, 8.6 Hz, H-3"), 8.06 (2H, d, 8.6 Hz, H-2"), 10.94 (1H, s, H-2). **^{13}C-NMR** (*$CDCl_3$*, 25 °C), δ (ppm): 20.6 (CH_3-6), 20.7 (CH_3-5), 51.5 (CH_2-Ph), 53.7 (CH_2-CO), 113.0 (C-7), 113.1 (C-4), 127.9 (C-2'), 129.3 (C-7a), 129.4 (C-4'), 129.5, (C-3'), 130.2 (C-2"), 130.3 (C-4"), 130.9 (C-3a), 132.1 (C-1'), 132.2 (C-1"), 132.5 (C-3"), 137.5 (C-6), 137.8 (C-5), 142.2 (C-2), 189.6 (C=O).

α-cyclodextrin: ^{1}H-NMR (*D_2O*, 25 °C), α (ppm): 3.61 (6H, t, 9.2 Hz, H-4), 3.65 (6H, dd, 10, 3.4 Hz, H-2), 3.86-3.98 (18H, m, H-5, H-6), 4.00 (6H, t, 9.7 Hz, H-3), 5.07 (6H, d, 3.4 Hz, H-1).

β-cyclodextrin: ^{1}H-NMR (*D_2O*, 25 °C), α (ppm): 3.62 (7H, t, 9.2 Hz, H-4), 3.68 (7H, dd, 9.9, 3.6 Hz, H-2), 3.89-3.94 (21H, m, H-5, H-6), 3.99 (7H, t, 9.5 Hz, H-3), 5.10 (7H, d, 3.9 Hz, H-1).

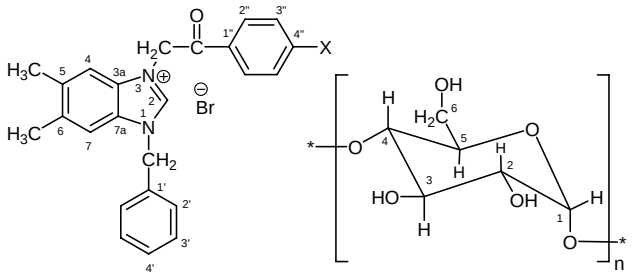
Preparation of the benzimidazolium bromides-cyclodextrins solutions

α-cyclodextrin (99.8% purity and 12% water) and b-cyclodextrin (98% purity and 15% water), were purchased from Sigma and were used without further purification. Stock solutions (in D_2O) of benzimidazolium bromides (10^{-3} M) and cyclodextrins (5 . 10^{-3} M) were used to prepare the benzimidazolium bromides-cyclodextrins mixtures. In each of the six mixtures the molar ratios bemzimidazolium derivative:cyclodextrin were 1:2. The final concentrations in the mixtures were 0.5 . 10^{-3} M (for benzimidazolium derivative) and 10^{-3} M (for cyclodextrin). 0.6 mL from these solutions were transferred into 5mm NMR tubes and subjected to the NMR analysis.

Results and discussions

The benzimidazolium bromides (**1a-c**) were obtained by the reaction of 1-benzil-5,6-dimethylbenzimidazole with corresponding phenacyl bromides in acetone according to a general synthesis method [27-30].

Due to their very poor water solubility, the initial NMR analyses for structures confirmation of the benzimidazolium bromides **1a-c** (**a**: X=F; **b**: X=Cl; **c**: X=Br) (scheme 1) were done in deuterated chloroform. The assignments for the ^{1}H and ^{13}C chemical shifts are based on 2D NMR homo- and heteronuclear correlations (H,H-COSY, H,C-HSQC, and H,C-HMBC).



Scheme 1. Chemical structures and numbering scheme for bezimidazolium bromides and cyclodextrins

The interactions between benzimidazolium bromides and cyclodextrins were followed in deuterated water (D_2O) as 1:2 molar ratios **1a-c**:**CD**.

When recorded in D_2O, the ^{1}H-NMR spectra of the benzimidazolium compounds exhibit a different pattern in comparison with the $CDCl_3$ solvent, due to deuteration of the protons from the groups H-2 and CH_2CO. As a consequence, the signals corresponding to these protons (aprox. 11 ppm and 6.7 ppm, fig. 1) no longer appear in the ^{1}H-NMR spectrum. For α- and β-cyclodextrins, recorded in D_2O, the characteristic signals resonate in the interval 3.4 – 5.2 ppm (the protons from the hydroxyl groups are also deuterated and no longer exhibit signals in the proton spectrum).

Comparing the ^{1}H-NMR spectra of guests and hosts compounds, recorded in D_2O, one can observed that there are no overlapping signals between the benzimidazolium derivatives and cyclodextrins (fig. 1). This is a favorable case which can be further exploited in interpreting the nuclear Overhauser (NOE) experiments. Thus the cross peaks between the guest and host will be due to their spatial proximity (intermolecular cross peaks) and cannot be confused with the intramolecular cross peaks, which also appear in 2D NOE experiments.

The host-guest interactions are usually followed in NMR through chemical shift variations for host and guest and/or appearance of NOE cross peaks between the two partners.

In the case of benzimidazolium salts (**1a-c**) there are very small chemical shifts variations (in the order of ±0.01 to ±0.02 ppm) in the ^{1}H-NMR spectra of the mixtures benzimidazolium bromides and cyclodextrins, as compared to the spectra of the individual compounds. These small variations were observed for the protons from the *para*-subtituted phenyl moiety of **1a-c** derivatives and for the protons H-3 and H-5 of cyclodextrins. The most significant modification of the cyclodextrins "spectral fingerprints" was obtained for the mixtures **1c-CD**. As an example, the ^{1}H-NMR spectra of the individual compounds and **1c-αCD** mixture are presented in figure 2. For this case we obtained a 0.05 ppm downfield shift for the protons from the *para*-subtituted phenyl, a 0.03 ppm upfield shift for the cyclodextrin's H-3 protons and visible "alteration" of the spectral region characteristic to H-5 and H-6 protons from cyclodextrin.

In the cases when the host-guest interactions cause very small alterations in the proton spectra a more reliable information can be obtained from the two-dimensional nuclear Overhauser effect spectroscopy.

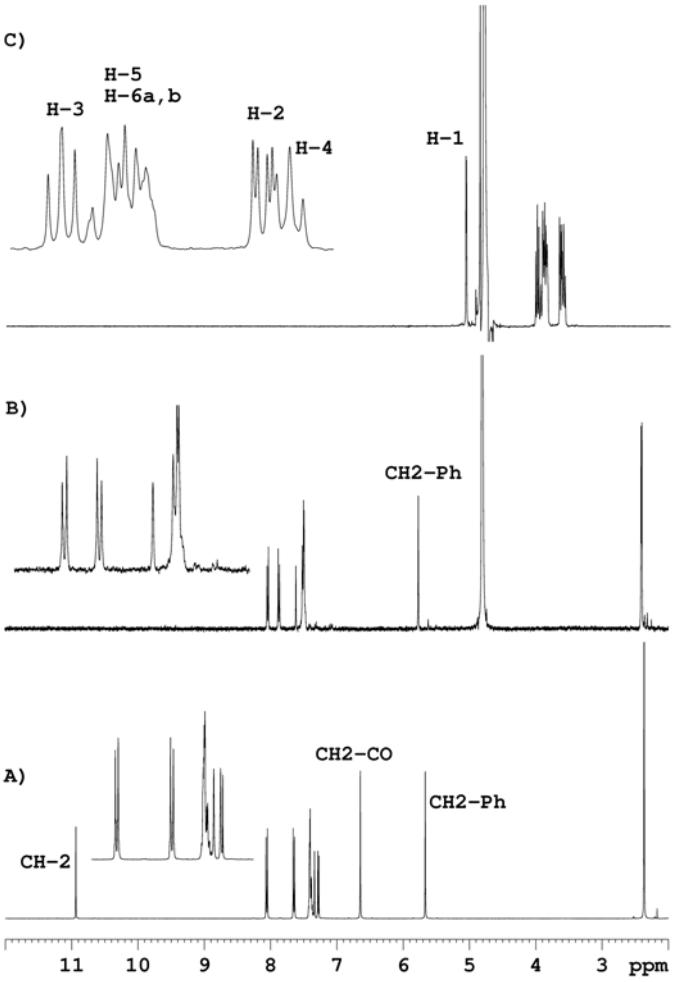


Fig. 1. ^{1}H-NMR spectra of: A) **1c** recorded in $CDCl_3$, B) **1c** recorded in D_2O and C) α-cyclodextrin recorded in D_2O

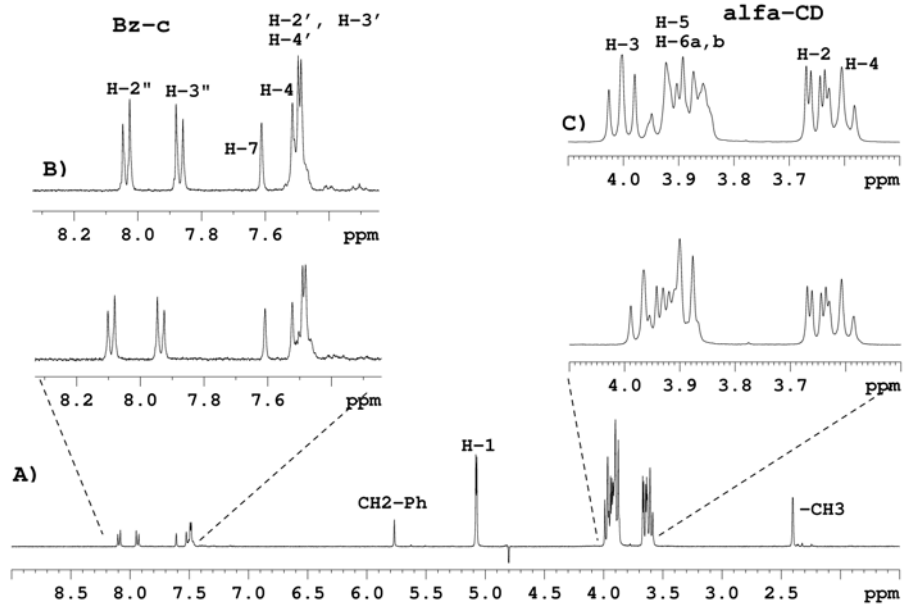


Fig. 2. **A)** ^{1}H-NMR spectrum of **1c-αCD** mixture (1:2). The expanded regions (3.5-4.1 ppm and 7.4-8.3 ppm) show the small chemical shifts variations of the **αCD** and **1c** signals caused by the host-guest interactions; **B)** Spectrum expansion showing the initial pattern of the aromatic region for **1c**; **C)** Spectrum expansion showing the initial pattern of the **αCD** signals

Two types of experiments are often used to prove the spatial proximity of the molecules in the inclusion complex: NOESY and/or the rotating frame NOE (ROESY).

In order to prove whether the studied compounds form indeed inclusion complexes, and to exclude outside the cavity interactions we performed ROESY experiments for all six benzimidazolium-cyclodextrin mixtures. The obtained spectra are presented in figure 3.

The compound **1a** presents no intermolecular NOE cross peaks with neither α- nor β-cyclodextrins. This indicates that there are no or very weak interactions between **1a** and cyclodextrins.

In the ROESY spectrum of the mixture **1b-αCD**, one signal of **1b** (H-3" at 7.6 ppm) has a weak intermolecular cross peak with H-3 protons of **αCD**, indicating their spatial proximity. Being the only visible cross peak we can conclude that the **1b** compound has the *para*-substituted phenyl, with the H-3" protons, closer to the wider rim of α-cyclodextrin. The same compound

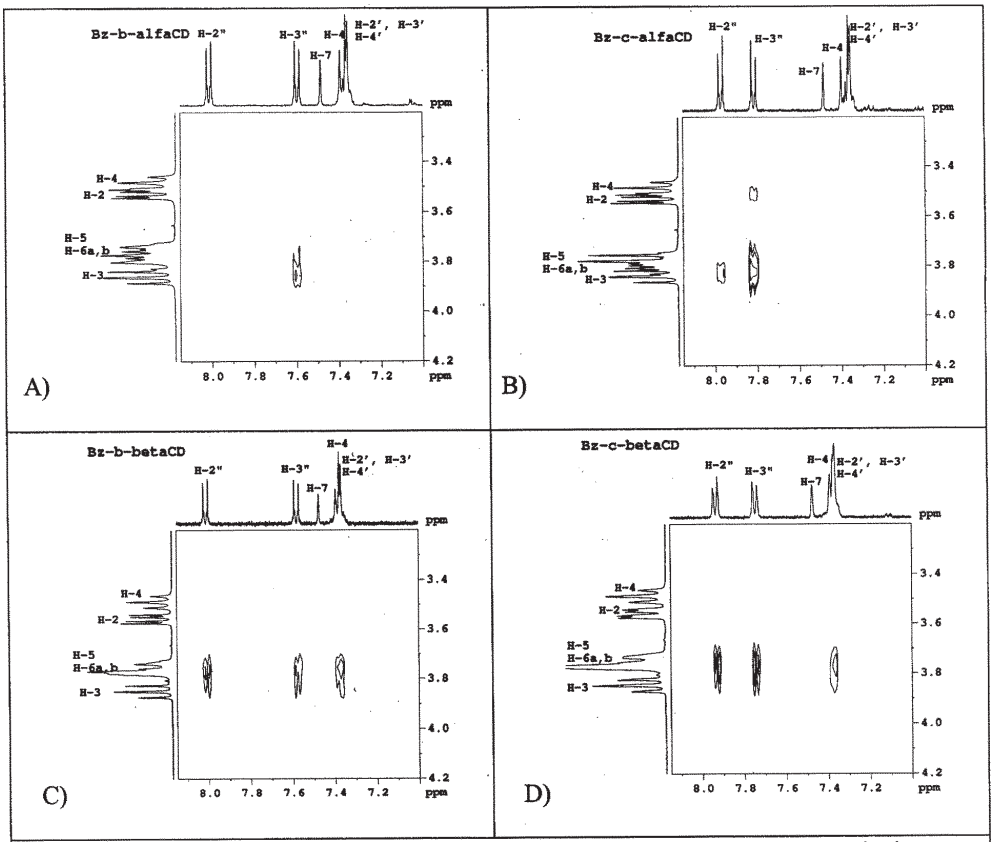


Fig. 3. The ROESY spectra showing only the intermolecular NOE cross peaks between guest and host molecules. A) **1b-αCD**; B) **1c-αCD**; C) **1b-βCD**; D) **1c-βCD**

in the presence of β-cyclodextrin behaves different. Thus in the ROESY spectrum of the **1b-βCD** mixture there are several intermolecular cross peaks between **1b** protons and H-3 and H-5 protons of β-cyclodextrin (fig. 3C). Both N-1 and N-3 aromatic substituents (H-2", H-3", H-2', H-3') give cross peaks with H-3 and H-5 protons of b-cyclodextrin, indicating spatial proximity between the two aromatic rings and the protons inside the β-cyclodextrin cavity. Based on these observations and considering the excess of CD used one can conclude that each aromatic ring enters a different cyclodextrin cavity leading to 1:2 complexes. The presence of the cross peak between the **1b** aromatic protons and H-5 protons of b-cyclodextrin indicates a deeper insertion of the aromatic rings inside the β-cyclodextrin (both H-2" and H-3") cavity as compared with a-cyclodextrin (only H-3").

A similar behaviour was observed for the compound **1c** in the presence of cyclodextrins. In the ROESY spectrum of the mixture **1c-αCD** there is only one intense intermolecular cross peak between H-3" protons (from the *para*-substituted phenyl ring) and H-3 and H-5 protons of α-cyclodextrin. The H-2" protons instead gave only one weak intermolecular cross peak with the H-3 protons of α-cyclodextrin. From this information we concluded that **1c** phenyl ring enters deeper in the α-cyclodextrin cavity as compared to the **1b** phenyl ring. The 4-bromo substituent is inside the α-cyclodextrin cavity, closer to the narrower rim, the rest of the skeleton pointing outside the cavity. The interaction of **1c** with **βCD** is similar with the case of **1b** compound. Both N-1 and N-3 aromatic rings are situated inside β-cyclodextrin cavities (fig. 3D).

The same influence of the halogen substituent that we reported for compounds **1a-c**, was previously reported for 4-substituted phenols [31]. This similarity is an additional argument for the preferred complexation of compounds **1b-c** with the N-3 aryloxoethyl moiety inside the cyclodextrin cavity, followed by the N-1 benzyl moiety when the 1:2 complex is formed.

Conclusions

Based on the information obtained from the ^{1}H-NMR spectra and ROESY spectra we shown that the strength of the interactions between benzimidazolium bromides derivatives and the inner cavities of α- and β-cyclodextrins depend on the *para*-phenyl substituent, increasing in the order F<Cl<Br. The β-cyclodextrin cavity is more receptive to the N-1 and N-3 aromatic rings than the α-cyclodextrin cavity, which can accommodate only part of the N-3 aromatic ring.

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