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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