# Selective mono- and bis-condensations of isophthalaldehyde derivative with 6-(*o*-aminoanilino)cyclodextrins

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COMMUNICATION

**Selective mono- and bis-condensations of an isophthalaldehyde derivative with a stoichiometric amount of 6-(*o*-aminoanilino)-α- (or β-) cyclodextrin to afford 2-(formylphenyl)benzimidazole-pendant α- (or β-) cyclodextrin and bisbenzimidazole-bridged homo- or hetero-dimers of cyclodextrins are described.**

Cyclodextrins and many of their derivatives can act as catalysts and induce selective reactions of bound substrates.[1] The regioselective functionalization of cyclodextrins themselves has also been well-developed,[1] in particular, regioselective sulfonylations with sulfonyl chlorides.[2] The fact that a cyclodextrin derivative reacts selectively with only one of the two or more identically active groups of a bi- or multi-functional reagent, however, has been less studied. The 1:1 reactions of properly activated cyclodextrin derivatives with symmetrical bifunctional reagents were frequently employed to prepare cyclodextrin derivatives bearing active moieties,[3,4] but they did not proceed in a selective manner in that a large excess of the reagents was usually required to suppress the further reaction of the products. Recently, we found the condensation of 6-(*o*-aminoanilino)-cyclodextrins **2** with isophthalaldehyde **1** proceeds in a highly selective manner. The exclusive mono- or bis-condensation can be achieved just by using the two reactants in the stoichiometric ratio. Here we describe this selective reaction.

A solution of the isophthalaldehyde **1** (36 mg, 0.22 mmol) and 6-(*o*-aminoanilino)-β-cyclodextrin **2b** (240 mg, 0.20 mmol) in methanol (40 $cm^3$) was stirred at room temperature for 20 h. After evaporation of the solvent, the residue was dissolved in 300 $cm^3$ of 15% aqueous methanol. The resultant solution was filtered and applied to reverse-phase column chromatography (Lobar Column LiChroprep Rp-18, size B, Merck) with a linear gradient elution from 15 to 45% aqueous methanol (each 1 $dm^3$), giving **3b** (200 mg, 75%). By a similar procedure, **3a** (89 mg, 65%) was obtained from **1** (20 mg, 0.12 mmol) and **2a** (120 mg, 0.11 mmol). Both **3a** and **3b** had the correct $^{13}C$ NMR and FAB-MS spectra.§ The $^1H$ NMR spectra of both **3a** and **3b** showed the basic pattern of cyclodextrins in the range of $\delta$ 3–6 and a series of largely shifted weak resonances which had a pattern quite similar to that of the benzimidazole-bearing glucoside and its neighbouring units in the bis(benzimidazole)-capped α-cyclodextrin.[5] The singlet at $\delta$ 10.2 can be assigned to the formyl proton and the set of resonances in the range between $\delta$ 6.9–8.0 correspond to the aromatic protons.

The formyl cyclodextrins can undergo further condensation if another molecule of an (*o*-aminoanilino)cyclodextrin exists. Thus heating **3a** with equimolar amount of **2a** in DMSO for 4 days at 40 °C afforded the homo-dimer of α-cyclodextrin **4a** in 28% yield, and the reaction of **3b** with **2a** in methanol for 3 days at room temperature gave the hetero-dimer **4c** in 36% yield. By reacting **1** directly with two equivalents of **2b** in methanol for 4 days at 40 °C and then one week at room temperature, the homo-dimer **4b** was constructed in 47% yield. All the cyclodextrin dimers were characterized with FAB-MS and NMR spectra.¶

Arenedialdehydes are known to react with aromatic *ortho*-diamines to form bis(benzimidazoles) and we[5] have succeeded in capping α-cyclodextrin by the bis(benzimidazole)-formation of bis(*o*-aminoanilino)-α-cyclodextrin with the isophthalaldehyde **1**. This dialdehyde, however, reacts with mono(*o*-aminoanilino)cyclodextrins **2** quite differently. When the two reactants are used in a molecular ratio of 1:1, **3** forms exclusively with no obvious side reactions based on TLC and NMR analysis after the completion of the reaction.

To further understand the selectivity, the reaction process of **1** and **2b** was followed by proton NMR. As shown in Fig. 1, the formyl protons of **1** resonate as a singlet at $\delta$ 10.22 and the signal decreases readily as the reaction proceeds forward. Meanwhile, two singlets appear and increase at $\delta$ 8.97 and 10.42 which correspond to the methine proton of the Schiff's base intermediate and the proton of its remaining formyl group, respectively. After *ca.* 2 h, the resonance at $\delta$ 10.22 disappears, and there are no other notable resonances between the region of $\delta$ 8–11 apart from the two singlets at $\delta$ 8.97 and 10.42 and the three weak resonances around $\delta$ 10, suggesting that the formation of Schiff's base intermediate is highly selective.

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§ **3a**: FAB-MS, *m/z* 1207 (M + 1); $^{13}C$ NMR (75 MHz, [$^2H_6$]$Me_2SO$), 19.8 (methyl carbon), 45.8 (C-6′), 57.3, 59.0, 59.4, 59.5 and 60.0 (C-6), 67.7, 71.4, 71.6, 71.9, 72.0, 72.3, 72.5, 73.0, 73.2, 73.3, 73.5 and 73.6 (C-2, C-3 and C-5), 80.4, 81.1, 81.4, 81.6, 82.0 and 84.5 (C-4), 100.8, 101.5, 101.9 and 102.1 (C-1), 110.0, 118.4, 118.8, 121.4, 121.9, 122.0, 128.2, 132.4, 133.8, 139.3, 142.2, 150.7 and 156.9 (aromatic carbons), 193.6 (formyl carbon). **3b**: FAB-MS, *m/z* 1369 (M + 1); $^{13}C$ NMR (75 MHz, [$^2H_6$]$Me_2SO$), 20.5 (methyl carbon), 46.3 (C-6′), 58.2, 60.2, 60.4, 60.5 and 60.6 (C-6), 68.8, 72.2, 72.3, 72.4, 72.5, 72.7, 72.8, 73.1, 73.5 and 73.7 (C-2, C-3 and C-5), 80.6, 81.5, 82.0, 82.1, 82.2 and 84.5 (C-4), 101.4, 102.2 and 102.5 (C-1), 111.3, 118.6, 119.0, 119.3, 122.7, 123.4, 128.8, 132.7, 135.0, 139.6, 142.4, 151.2 and 157.2 (aromatic carbons), 193.9 (formyl carbon).

¶ **4a**: FAB-MS, *m/z* 2250 (M); $^{13}C$ NMR (75 MHz, [$^2H_6$]$Me_2SO$), 20.2 (methyl carbon), 46.0 (C-6′), 57.4, 59.1, 59.5 and 60.1 (C-6), 67.7 (C-5′), 71.5, 71.7, 71.9, 72.0, 72.1, 72.2, 72.3, 72.4, 72.7, 72.8, 73.1, 73.3, 73.4 and 73.7 (C-2, C-3 and C-5), 80.5, 81.2, 81.3, 81.7 and 82.1 (C-4), 84.1 (C-4′), 100.9, 101.5, 101.8, 102.0 and 102.2 (C-1), 110.0, 116.9, 118.7, 121.2, 121.9, 127.4, 133.7, 133.9, 142.2, 151.9 and 152.0 (aromatic carbons). **4b**: FAB-MS, *m/z* 2575 (M + 1); $^{13}C$ NMR (125 MHz, [$^2H_6$]$Me_2SO$), 20.2 (methyl carbon), 45.9 (C-6′), 57.6, 59.5, 59.7 and 60.0 (C-6), 67.9, 71.5, 71.9, 72.0, 72.1, 72.2, 72.4, 72.9 and 73.0 (C-2, C-3 and C-5), 80.1, 81.0, 81.3, 81.4 and 81.5 (C-4), 84.0 (C-4′), 101.0, 101.7, 101.9 and 102.0 (C-1), 110.4, 116.7, 118.5, 121.8, 122.4, 127.1, 133.5, 134.1, 141.8, 151.8 and 152.5 (aromatic carbons). **4c**: FAB-MS, *m/z* 2412 (M); $^{13}C$ NMR (75 MHz, [$^2H_6$]$Me_2SO$), 20.3 (methyl carbon), 45.8 and 45.9 (C-6′), 57.5, 57.7, 59.4, 59.5, 59.8, 60.0 and 60.1 (C-6), 67.6 and 67.8 (C-5′), 71.4, 71.6, 71.9, 72.0, 72.1, 72.2, 72.3, 72.5, 72.8, 72.9, 73.1, 73.2 and 73.3 (C-2, C-3 and C-5), 80.2, 80.4, 81.0, 81.2, 81.3, 81.6, 81.8 and 82.0 (C-4), 84.0 and 84.2 (C-4′), 101.0, 101.2, 101.8, 101.9, 102.0 and 102.1 (C-1), 109.9, 110.4, 116.7, 117.6, 118.4, 118.6, 121.3, 121.7, 121.9, 122.5, 127.2, 133.3, 133.9, 134.2, 134.3, 141.4, 142.6, 151.8, 152.0 and 152.7 (aromatic carbons).

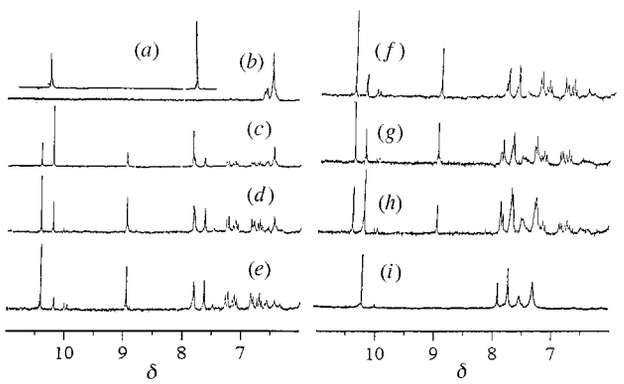
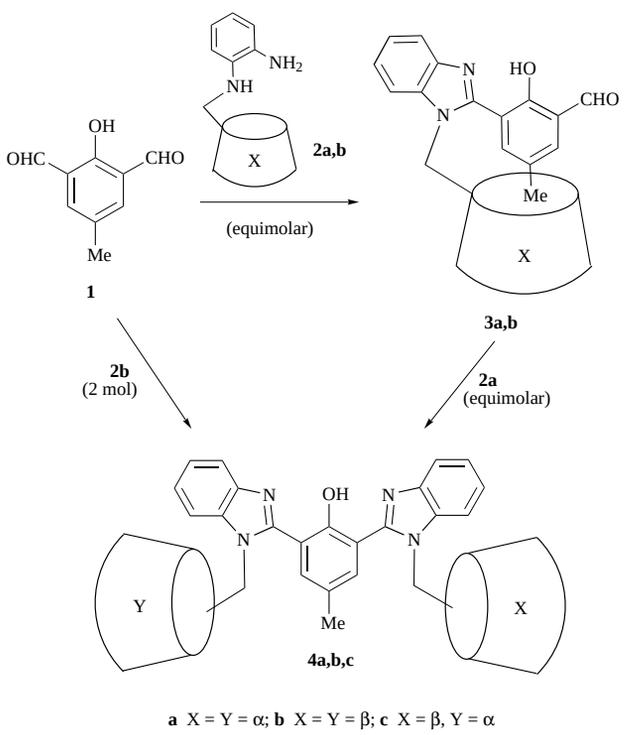



**Fig. 1** $^1$H NMR (200 MHz) signals of **1** in $CDCl_3$ (*a*) **2b**, (*b*) and mixture of **1** and **2** (1 : 1) in [$^2H_6$]$Me_2SO$ at (*c*) 20 min, (*d*) 1 h, (*e*) 2 h, (*f*) 3.5 h (air introduced), (*g*) 6.5 h, (*h*) 8.5 h and (*i*) 24 h (300 MHz). Cyclodextrin signals are not shown.




**a** X = Y = α; **b** X = Y = β; **c** X = β, Y = α

Thereafter, no obvious changes take place in the oxygen-free condition. Introduction of air into the sample tube results in a gradual decrease of the two singlets at $\delta$ 8.97 and 10.42 and the increase of the resonance at $\delta$ 10.2 which relates to the formyl proton of the final product **3b**. Finally, the Schiff's base disappears and the spectrum of the reaction mixture is almost the same as that of the isolated pure product **3b**. This observation reveals that the possible benzimidazole intermediate exists only in a very small concentration and the whole reaction is extremely clear.

The typical binding or catalytic properties of cyclodextrin dimers[6] and the difficulty in the synthesis of hetero-dimers of cyclodextrins[3,7] prompt us to examine further the reaction of **3** with **2**. The result shows that on being treated with another equivalent of an (*o*-aminoanilino)cyclodextrin, the aldehydes **3** can be completely converted to the Schiff's base intermediates in a couple of hours, but the next steps take a very long time to complete. The corresponding homo- or hetero-dimers of cyclodextrins can easily be obtained in moderate yields, which opens a new way to the hetero-dimers of cyclodextrins. Since no attempt was made to optimize the reaction yields, the actual yields are likely to be better than the observed ones.

The reaction phenomena[8] can be understood based on the possible intramolecular host–guest interaction. The inclusion of the methylphenyl moiety into the cyclodextrin cavity provides a decrease in enthalpy for the formation of the first imine bond and also provides the correct geometry for its subsequent cyclization and oxidation, but it does not exercise these favourable effects on the second condensation. As the result, the mono-Schiff's base can form exclusively and the construction of the first benzimidazolyl ring is facilitated while that of the second one is not.

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