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Synthetic methodology for cyclodextrin–dipyrromethane conjugates

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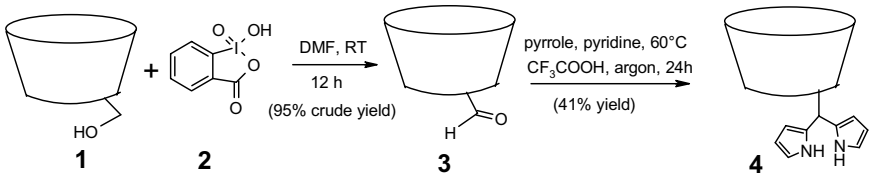
Abstract—A new method for synthesis for cyclodextrin–dipyrromethane conjugates consisting of a reaction between cyclodextrin monoaldehyde and pyrrole is presented here. Resulting dipyrromethane is characterized by spectroscopic and computational methods.

Cyclodextrins, the cyclic oligosaccharides[1] that have been at the forefront of supramolecular chemistry have been extensively modified[2] in an effort to enhance their utility.[3] Dipyrromethanes have played a prominent role as fluorescent tags (BODIPY)[4] and as precursors for important molecules such as porphyrins[5] and expanded porphyrin systems.[6] It is conceivable that merger of these two prominent systems by synthesis of cyclodextrin–dipyrromethane conjugates could produce molecules that provide molecular recognition in concert with fluorescence properties and possibly open the doors to new frontiers.

The strategy for synthesis of cyclodextrin–dipyrromethane **4** is shown in Scheme 1 and involves condensation of known β-cyclodextrin monoaldehyde **3** with pyrrole, in the presence of an acid catalyst as shown in Scheme 1.

The published procedure for synthesis of cyclodextrin monoaldehyde[7] was modified for convenience without sacrificing the yield. A mixture of *o*-iodoxybenzoic acid (IBX) **2** (5.0 g, 17.86 mmol) and β-cyclodextrin hydrate **1** (13.5 g, 11.89 mmol) in 100 mL DMF was stirred at room temperature for 24 h. The reaction mixture was filtered and the filtrate was diluted with 500 mL of acetone stirred overnight. This slurry was filtered and the residue was washed with acetone to obtain 12.80 g (95% crude yield) of the aldehyde **3**. A mixture of crude β-cyclodextrin monoaldehyde **3** (6.9 g, 6.09 mmol, contains a small amount of unreacted cyclodextrin) in a minimum amount of pyridine (~10 mL) and excess pyrrole (30 mL, 254 mmol) was stirred under argon for 2 h at 70 °C. TFA (300 μL, 3.89 mmol) was then syringed into the reaction mixture and stirred under argon for an additional 24 h at 70 °C. NaOH (3.6 mL of 0.1 N, to neutralize TFA) followed by a large excess of acetone (400 mL) were added to the reaction mixture and stirred for several hours. The mixture was filtered and the residue was washed with acetone and further stirred in methylene chloride to yield 6.26 g (82% crude yield) of the product assigned as **4**. TLC on silica gel using *n*-butanol, ethanol, water (5:4:3 by volume) showed one spot at $R_f = 0.35$ for β-cyclodextrin and another at $R_f = 0.70$ for compound **4**. A 100 mg of the crude product was



Scheme 1.

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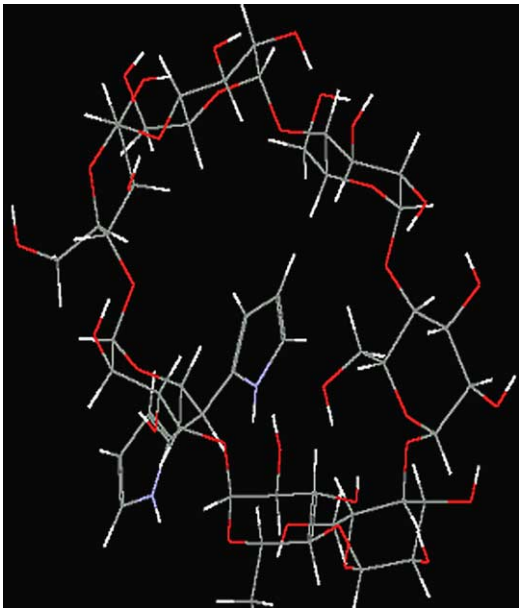

Figure 1. Molecular model of **4**.

further purified by a reverse phase HPLC[8] to yield 50 mg of the pure compound (41% from the starting material). Compound **4** was structurally characterized by NMR and mass spectral analysis.

The HSQC and ^{1}H NMR spectra in DMSO-d_6 shows peaks between 6.6 and 5.6 for the pyrrole rings, between 4.9 and 3.3 for the cyclodextrin unit and at 10.2 and 10.0 ppm for N–H protons. The ^{13}C NMR and DEPT NMR spectra in DMSO-d_6 shows the *meso*-carbon at 37.1 ppm (–CH), peaks for cyclodextrin between 58 and 102 ppm and a number of ^{13}C signals with chemical shifts characteristic of pyrroles between 106 and 132 ppm suggesting an unsymmetrical dipyrrole product. Although NMR for phenyldipyrromethane[9] indicates a symmetrical molecule, pyrrole moieties in compound **4** are diastereotopic and their NMR spectral signals are not identical. The lack of sharpness of signals in NMR spectra of **4** in the pyrrole region may also suggest that one of the pyrrole rings is oriented to the hydrophobic cavity of β-cyclodextrin. The computational calculations indicate that one of the pyrrole rings can reside inside the cavity (Fig. 1). Further support for

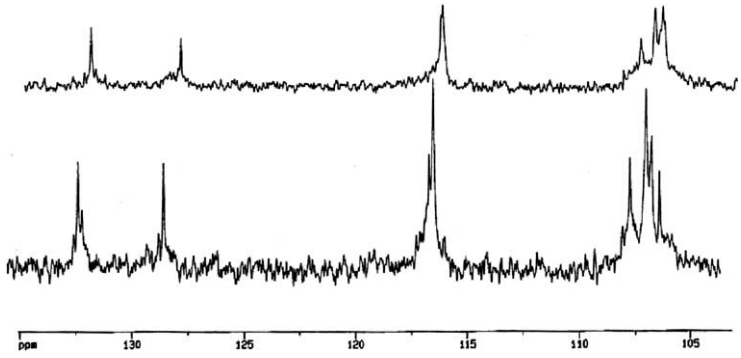

Figure 2. Variable temperature ^{13}C NMR of **4** in the pyrrole region. Upper spectrum is at 300 K and the lower one is at 343 K.

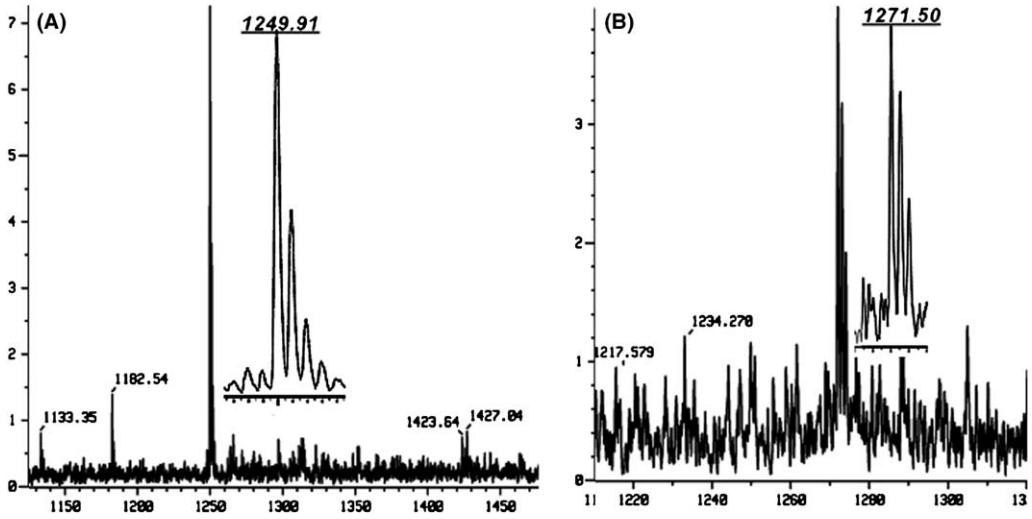

Figure 3. (A) Positive ESI-MS of **4** with TFA. The inset shows the expanded region around 1250 *m*/*z*. (B) Positive ESI-MS of **4** with NaOH. The inset shows the expanded region around 1270 *m*/*z*.

this suggestion comes from variable temperature ^{13}C NMR experiments at 343 and 300 K (Fig. 2), which display a sharper spectrum at 343 K than at 300 K suggesting a slightly restricted rotation about the cyclodextrin-*meso*-carbon due to steric hindrance. It is possible that due to the steric hindrance caused by cyclodextrin, the formation of higher oligomers of pyrrole containing cyclodextrin are minimized.

Additional supporting evidence for the structure of compound **4** was obtained from mass spectral analysis. The positive ESI-MS of CD–dipyrromethane **4** in water/TFA (Fig. 3A) showed a peak at 1249.9 *m*/*z*, which was ascribed as the protonated CD–dipyrromethane ($C_{50}H_{77}O_{34}N_2^+$, expected mass 1249.4 *m*/*z*). The simulated isotopic distribution is also in good agreement with the experimental results. In the absence of TFA (Fig. 3B), the peak at 1271.5 *m*/*z* is attributed to the sodiated CD–dipyrromethane ($C_{50}H_{76}O_{34}N_2Na^+$, expected mass 1271.4).

Synthetic methodology for cyclodextrin–dipyrromethane conjugates is thus completed and it is hoped that this will pave the way to synthesis of more interesting molecules consisting of a molecular recognition site and a multi-pyrrole (such as BODIPY, porphyrin) flourophores.

Acknowledgements

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References and notes

1. Bender, M. L.; Komiyama, M. *Cyclodextrin Chemistry*; Springer: Berlin, 1978.
2. Hedges, A. R.; Shieh, W. J. In *New Trends in Cyclodextrins and Derivatives*; Duche'ne, D., Ed.; Editions de Sante: Paris, France, 1991; Chapter 8; Khan, A.; Forgo, P.; Stine, K. J.; D'Souza, V. T. **1998**, *98*, pp 1977–1996.
3. Murakami, Y.; Kijuchi, J.; Hisaeda, Y.; Hayashida, O. *Chem. Rev.* **1996**, *96*, 721; Breslow, R. *Acc. Chem. Res.* **1995**, *28*, 146.
4. (a) Mikhalyov, I.; Gretskaya, N.; Bergstrom, F.; Johansson, L. B.-A. *Phys. Chem. Chem. Phys.* **2002**, *4*, 5663–5670; (b) Bergstrom, F.; Mikhalyov, I.; Hagglof, P.; Wortmann, R.; Ny, T.; Johansson, L. B.-A. *J. Am. Chem. Soc.* **2002**, *124*(2), 196–204.
5. Nishino, N.; Wagner, R. W.; Lindsey, J. S. *J. Org. Chem.* **1996**, *61*, 7534; Rao, P. D.; Dhanalekshmi, S.; Littler, B. J.; Lindsey, J. S. *J. Org. Chem.* **2000**, *65*, 7323–7344; Tamaru, S.-I.; Yu, L.; Youngblood, W. J.; Muthukumaran, K.; Taniguchi, M.; Lindsey, J. S. *J. Org. Chem.* **2004**, *69*, 765–777.
6. Bauer, V. J.; Clive, D. L. J.; Dolphin, D.; Paine, J. B., III; Harris, F. L.; King, M. M.; Loder, J.; Wang, S. W. C.; Woodward, R. B. *J. Am. Chem. Soc.* **1983**, *105*(21), 6429–6436; Sessler, J. L.; Seidel, D. *Angew. Chem., Int. Ed.* **2003**, *42*, 5134; Sessler, J. L.; Katayev, E.; Pantos, G. D.; Ustynyuk, Y. A. *Chem. Commun.* **2004**, 1276.
7. Cornwell, M.; Huff, J.; Bieniarz, C. *Tetrahedron Lett.* **1995**, *36*, 8371–8374.
8. HPLC conditions: Dynamax C18 column, 60 Å, ID 22 mm, and length 250 mm; mobile phase: a gradient of 95/5 water/acetonitrile (v/v) and 100% acetonitrile with a flow rate of 5 mL/min; detection wavelength: 286 nm.
9. Lee, C.; Lindsey, J. S. *Tetrahedron* **1994**, *50*, 11427.