

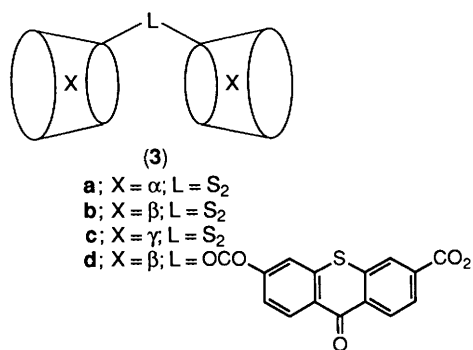
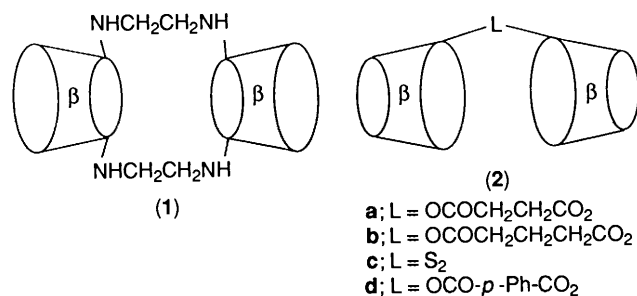
A New Synthesis of Cyclodextrin Dimers

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The synthesis and characterization of the linked cyclodextrins (**6a–c**) is reported.

A number of cyclodextrin dimers have been synthesized in order to investigate the co-operative binding properties of covalently linked cyclodextrins.^{1–7,†} In 1979, Tabushi *et al.*¹ reported the synthesis of the tetramine (**1**). Subsequently, Harada and co-workers² described the formation of the diesters (**2a**) and (**2b**), and Fujita and co-workers reported the preparation of the disulphides (**3a**) and (**3b**),³ and (**3c**).⁴ During the course of the

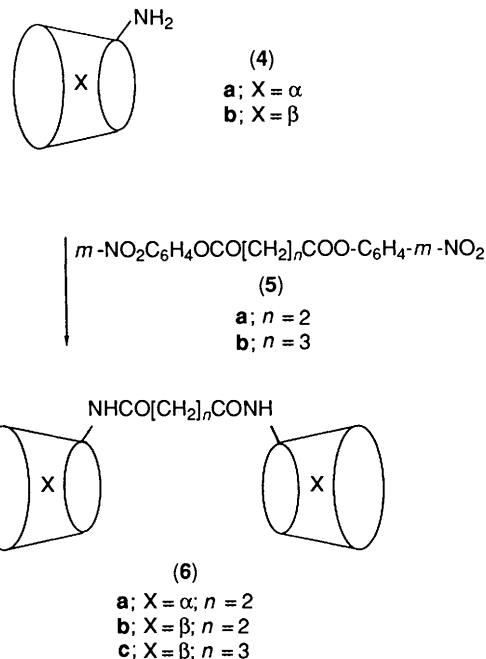


work described in this paper,⁵ Breslow *et al.*⁶ reported the synthesis of the disulphide (**2c**) and the diester (**3d**), and referred to an earlier synthesis in their laboratories of (**2d**).⁷

There are a number of limitations, however, associated with the synthesis, purification, and storage of the dimers (**1**)–(**3**), and their use to form inclusion complexes. For example, the yields reported for the preparation of (**1**), (**2a**), and (**2b**) were only 2.6, 0.5, and 0.5%, respectively, based on β -cyclodextrin, and no yields were reported for the synthesis of (**2c**) or (**3a–d**). Only (**2d**) was obtained in a yield of 10%, based on α -cyclodextrin. In this report we describe the synthesis and characterization of a new class of cyclodextrin dimers. We have prepared the diamides (**6a–c**) in yields of 19, 14, and 13%, respectively, based on the corresponding unmodified cyclodextrins.

Experimental

¹³C NMR spectra were recorded in D₂O, using dioxane (δ 67.8) as the internal reference. ¹H NMR were recorded in [²H]₆-



DMSO, using tetramethylsilane as the internal reference. HPLC was carried out on a Waters Carbohydrate Analysis Column (3.9 mm \times 30 cm), using water–acetonitrile (1:2 v/v) as eluant and a flow rate of 1.5 ml min⁻¹. Under these conditions α - and β -cyclodextrin each had R_T 6.0 min. Each of the diamides (**6a–c**) gave satisfactory microanalytical data and was fully characterized.

The succinate and glutamate diesters (**5a**) and (**5b**) were prepared by treatment of the corresponding diacids with *m*-nitrophenol and *N,N'*-dicyclohexylcarbodi-imide in ethyl acetate.^{2,8} The amines (**4a**) [δ_C 42.8 (t, C-6^A)] and (**4b**) [δ_C 41.3 (t, C-6^A)] were prepared from α - and β -cyclodextrin, in respective yields of 20 and 21%, through modification of the procedure of Melton and Slessor for the preparation of (**4a**).⁹ A mixture of the amine (**4a**) and the succinate diester (**5a**) (0.5 equiv.) in pyridine was set aside at room temperature for 5 d, and then it was concentrated under reduced pressure. Residual pyridine was removed from the crude product mixture by co-distillation with water *in vacuo*, after which precipitation from water–acetone (1:8 v/v) gave a 94% yield of the cyclodextrin

† A truncated cone is commonly used^{1–7} to represent the torus of a cyclic D-glucose polymer containing either six (α -cyclodextrin), seven (β -cyclodextrin) or eight (γ -cyclodextrin) anhydroglucose units joined by α -1,4-glucosidic linkages. A substituent drawn at the narrow end of the cone indicates that it replaces one of the C-6 hydroxy groups in the cyclodextrin, while a substituent drawn at the wide end of the cone indicates that it replaces either a C-2 or C-3 hydroxy group.

dimer (**6a**), as a white powder [HPLC, R_T 19.0 min; δ_H 2.29 (4 H, s, CH_2CO), and 7.8 (2 H, br s, NH); δ_C 32.2 (t, CH_2CO), 41.4 (t, C-6^A), 61.3 (t), 61.6 (t), 71.5 (d), 72.9 (d), 73.2 (d), 74.3 (d), 74.5 (d), 82.4 (d), 84.3 (d), 102.6 (d), and 175.9 (s, CO)]. Similar treatment of the amine (**4b**) with (**5a**) and (**5b**) gave (**6b**) [68% yield; HPLC, R_T 33.5 min; δ_H 2.07 (4 H, s, CH_2CO) and 7.6 (2 H, br s, NH); δ_C 31.9 (t, CH_2CO), 41.0 (t, C-6^A), 61.2 (t), 71.2 (d), 72.8 (d), 73.0 (d), 74.0 (d), 82.0 (d), 84.0 (d), 102.8 (d), and 175.5 (s, CO)] and (**6c**) [60% yield; HPLC, R_T 20.5 min; δ_H 1.75 (2 H, m, $\text{CH}_2\text{CH}_2\text{CH}_2$), 2.15 (4 H, m, CH_2CO), and 7.65 (2 H, br s, NH); δ_C 22.7 (t, $\text{CH}_2\text{CH}_2\text{CH}_2$), 35.9 (t, CH_2CO), 41.0 (t, C-6^A), 61.0 (t), 61.3 (t), 71.1 (d), 72.6 (d), 73.0 (d), 74.0 (d), 82.0 (d), 84.1 (d), 102.8 (d), and 176.7 (s, CO)], respectively. This approach is suitable for the preparation of substantial quantities of (**6a-c**) and has been used to prepare over 50 g of (**6b**).

Conclusions

The reactions to give dimers (**6a-c**) demonstrate the greater nucleophilicity of the primary amino substituents compared to the primary and secondary hydroxy groups in compounds (**4a**) and (**4b**). The diamides (**6a-c**) are more resistant to hydrolysis than esters such as (**2a**), (**2b**), (**2d**), and (**3d**), therefore they are easier to purify and more stable on storage. We expect that the methodology described above for the preparation of (**6a-c**) can be used to produce diamides that are tailored to form high-stability inclusion complexes with specific substrates. These studies are continuing in our laboratories.

Acknowledgements

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References

- 1 I. Tabushi, Y. Kuroda, and K. Shimokawa, *J. Am. Chem. Soc.*, 1979, **101**, 1614.
- 2 A. Harada, M. Furue, and S.-I. Nozakura, *Polymer J.*, 1980, **12**, 29.
- 3 K. Fujita, S. Ejima, and T. Imoto, *J. Chem. Soc., Chem. Commun.*, 1984, 1277.
- 4 K. Fujita, S. Ejima, and T. Imoto, *Chem. Lett.*, 1985, 11.
- 5 S. F. Lincoln, J. H. Coates, C. J. Easton, S. J. van Eyk, B. M. May, P. Singh, M. A. Stile, and M. L. Williams, *Internat. Pat. Appl. PCT/AU 89/00359*; Australian Provisional Pat. Appl. PJ 0165.
- 6 R. Breslow, N. Greenspoon, T. Guo, and R. Zarzycki, *J. Am. Chem. Soc.*, 1989, **111**, 8296.
- 7 Y. Chao, Ph.D. Dissertation, Columbia University, New York, 1972.
- 8 A. Harada, M. Furue, and S. Nozakura, *Macromolecules*, 1976, **9**, 705.
- 9 L. D. Melton and K. N. Slessor, *Carbohydrate Res.*, 1971, **18**, 29.

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