

SYNTHESIS OF NUCLEIC ACID BASE FUNCTIONALIZED β -CYCLODEXTRINS:
THE NUCLEOSIDE ANALOGUE

Katsuyuki Nagai, Hirosato Kondo, Nobutomo Tsuruzoe, Kenji Hayakawa,
and Ken Kanematsu*

Institute of Synthetic Organic Chemistry, Faculty of Pharmaceutical
Sciences, Kyushu University, Maidashi, Higashi-ku, Fukuoka 812, Japan

Abstract - The β -cyclodextrins functionalized with the nitrogen-bases
of nucleic acid such as thymine, uracil, cytosine, and adenine by a
flexible polymethylene bridge have been synthesized and their structures
were determined on the basis of the spectroscopic data.

Cyclodextrins (CDs) are known to show in many reactions the enzyme-like activities
such as the reaction rate enhancement, stereoselection, regioselection, and enantio-
selection.¹ These are due to their characteristic ability of formation of
inclusion complexes with various compounds. However, it is still needed to
synthesize the more effective enzyme models by chemical modifications of the CDs.
Their catalytic activities are sometimes remarkably improved by modifying the
hydroxyl groups of CDs with the suitable functional groups.^{2,3} Since the method
of a selective tosylation of the different hydroxyl groups of CDs had been de-
veloped,⁴⁻⁷ a variety of enzyme models have been synthesized from the appropriate
CD-tosylates.

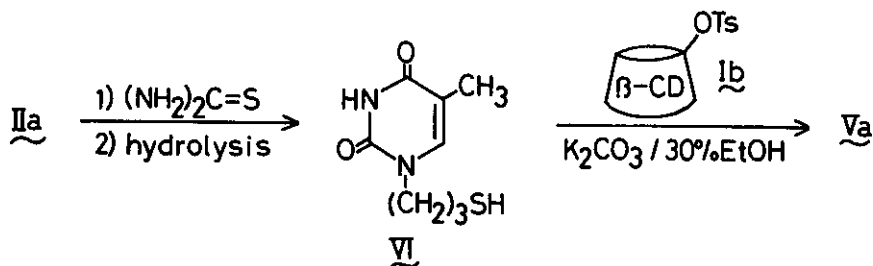
Considering the enormous biological importance of nucleosides, it seems to be inter-
esting to prepare and investigate the properties of the CDs which are functionalized
with the nitrogen-bases of nucleic acid, a good model of nucleoside. To the best
of our knowledge, however, there have been no reports on the chemical modifications
of CDs with such nitrogen-bases. We now report the preparation of the β -CD
derivatives attached to the nitrogen-bases by a flexible polymethylene bridge.
The synthesis is based on the nucleophilic substitution reaction of the halogeno-
alkylated nitrogen-bases and β -CD monothiol as shown in Scheme I. The 1-bromo-
propyl-2-pyrimidinones, IIa,b and III, were prepared from the corresponding pyrimi-
dine bases (thymine, uracil, and cytosine) in 20-60% yields via silylation with

Table 1

Compound	m.p.	IR(cm ⁻¹)	¹ H-NMR(ppm ^a), D ₂ O	UVλ _{max} ^{H₂O} nm (ε)
<u>Va</u>	282-288°C (decomp.)	3400 1690 (C=O) 1670 (C=O) 1640 1160	1.83(5H, Thy-CH ₃ , -CH ₂ -), 2.52(2H, -SCH ₂ -), 2.90(2H, CD-CH ₂ S-), 3.20- 4.10(42H, CD C ₂ -C ₆ H, -NCH ₂ -), 4.96(7H, CD C ₁ H), 7.27(1H, Thy-C ₆ H)	273(2.4×10 ³)
<u>Vb</u> ^c	240-249°C (decomp.)	3400 1690 (C=O) 1675 (C=O) 1640 1160	1.84(2H, -CH ₂ -), 2.49(2H, -SCH ₂ -), 2.91(2H, CD-CH ₂ S-), 3.20-4.00(42H, CD C ₂ -C ₆ H, -NCH ₂ -), 4.93(7H, CD C ₁ H), 5.71(d, 1H, Ur-C ₅ H, J=7.7 Hz), 7.45(d, 1H, Ur-C ₆ H, J=7.7 Hz)	266(2.18×10 ³)
<u>Vc</u> ^d	231-239°C (decomp.)	3400 1665 (C=O) 1640 1160	b) 2.08(2H, -CH ₂ -), 2.60(2H, -SCH ₂ -), 2.96(2H, CD-CH ₂ S-), 3.10-4.05(42H, CD C ₂ -C ₆ H, -NCH ₂ -), 4.80(7H, CD C ₁ H), 5.50(d, 1H, Cyt-C ₅ H, J=7.5 Hz), 7.40(d, 1H, Cyt-C ₆ H, J=7.5 Hz)	276(2.53×10 ³)
<u>Vd</u> ^e	270-278°C (decomp.)	3400 1640 1160	2.22(4H, -CH ₂ -, -SCH ₂ -), 2.85(2H, CD-CH ₂ S-), 3.05-4.02(42H, CD C ₂ -C ₆ H, -NCH ₂ -), 4.90(7H, CD C ₁ H), 7.96, 8.15 (2s, 2H, Ade-C ₂ H, C ₈ H)	263(4.47×10 ³)

a) The center of the broad absorption. b) in DMSO-d₆+D₂O c) Anal. Calcd for C₄₉H₇₈N₂O₃S·10H₂O, C, 39.68; H, 6.68; N, 1.89. Found: C, 39.66; H, 6.68; N, 1.69. d) Anal. Calcd for C₄₉H₇₉N₂O₃S·4H₂O, C, 42.80; H, 6.45; N, 3.06. Found: C, 42.61; H, 6.58; N, 3.41. e) Anal. Calcd for C₅₀H₇₉N₅O₃S·8H₂O, C, 41.10; H, 6.43; N, 4.71. Found: C, 41.04; H, 6.37; N, 4.75.

Scheme II



with thiourea to give the corresponding thiol VI in 77% yield, which was easily purified by a silica gel chromatography (Scheme II). This thiol was allowed to react with 6-O-tosyl-β-CD (Ib)⁶ in aqueous 30% EtOH in the presence of K₂CO₃ at room temperature. The similar work-up afforded the practically pure product without recrystallization, which was identical with the above-mentioned Va in all aspects. This route turned out to be much advantageous over the former one due to the high yield of product, easy purification, and the potential applicability to the multi-functionalization of CDs.

Further studies on the chemical reactivity of these water-soluble products as well as the double-functionalization of CDs using the ion-pairing of the nitrogen-bases are currently under way.

Acknowledgements: We are grateful to Dr. Kahee Fujita (Kyushu University) for the valuable suggestions.

REFERENCES

1. M. L. Bender, M. Komiyama, "Cyclodextrin Chemistry", Springer-Verlag, Berlin, 1978.
2. Y. Iwakura, Y. Uno, F. Toda, S. Onozuka, K. Hattori, and M. L. Bender, J. Am. Chem. Soc., 1975, 97, 4432.
3. R. Breslow and M. Hammond, J. Am. Chem. Soc., 1980, 102, 421.
4. F. Cramer and G. Mackesen, Chem. Ber., 1970, 103, 2138.
5. S. Umezawa and K. Tatsuta, Bull. Chem. Soc. Japan, 1968, 41, 464.
6. L. D. Melton and K. N. Slesson, Carbohydr. Res., 1971, 18, 29.
7. I. Tabushi, N. Shimizu, T. Sugimoto, M. Shiozuka, and K. Yamamura, J. Am. Chem. Soc., 1977, 99, 7100.
8. D. T. Browne, J. Eisinger, and N. J. Leonard, J. Am. Chem. Soc., 1968, 90, 7302.
9. N. J. Leonard, T. G. Scott, and P. C. Huang, J. Am. Chem. Soc., 1967, 89, 7137.
10. A. Shinoda, Master's Thesis, Kyushu University, 1980.

Received, 29th September, 1981