Supramolecular Chemistry
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713649759

Synthesis and properties of cyclo-α-1,4-manno-2,3-epoxides

Anthony W. Coleman[ab]; Ping Zhang[b]; Chang-Chun Ling[a]; Jacqueline Mahuteau[b]; Hélène Parrot-Lopez[c]; Marcel Miocque[b]
[a] CNRS UPR 180, Laboratoire de Physique, Centre Pharmaceutique, Université de Paris-Sud, Chatenay-Malabry, France [b] CNRS SDI 6233, Laboratoire de Chimie Organique, Centre Pharmaceutique, Université de Paris-Sud, Chatenay-Malabry, France [c] Laboratoire de Chimie Organique 2, Faculté de Pharmacie, Université de Paris V.,

To cite this Article Coleman, Anthony W. , Zhang, Ping , Ling, Chang-Chun , Mahuteau, Jacqueline , Parrot-Lopez, Hélène and Miocque, Marcel(1992) 'Synthesis and properties of cyclo-α-1,4-manno-2,3-epoxides', Supramolecular Chemistry, 1: 1, 11 — 14

To link to this Article: DOI: 10.1080/10610279208027435

URL: http://dx.doi.org/10.1080/10610279208027435

SUPRAMOLECULAR CHEMISTRY, Vol. 1, pp. 11–14
Reprints available directly from the publisher
Photocopying permitted by license only

COMMUNICATION

Synthesis and properties of cyclo-α-1,4-manno-2,3-epoxides

ANTHONY W. COLEMAN[1,2*], PING ZHANG[2], CHANG-CHUN LING[1], JACQUELINE MAHUTEAU[2], HÉLÈNE PARROT-LOPEZ[3] and MARCEL MIOCQUE[2]

[1] *CNRS UPR 180, Laboratoire de Physique, Centre Pharmaceutique, Université de Paris-Sud,* [2] *CNRS SDI 6233, Laboratoire de Chimie Organique, Centre Pharmaceutique, Université de Paris-Sud, Chatenay-Malabry, F92290, France and* [3] *Laboratoire de Chimie Organique 2, Faculté de Pharmacie, Université de Paris V.*

Treatment of per-2-*O*-tosyl-cyclodextrins with K_2CO_3 allows the synthesis of cyclomannoepoxides 2a, 2b, 2c in high yields (>90%). The glucopyranose structure of 2a, 2b, 2c, is assigned from the ^1H coupling pattern ($J_{1,2} = 0$ Hz, $J_{2,3} = 3.5$ Hz, $J_{3,4} = 0$ Hz), as a half chair conformation. 2b shows surfactant properties in water. Full analysis of the NMR spectra of 2a, 2b, 2c has been carried out. The inclusion and hydrolytic properties of 2 differ from those of the parent cyclodextrins as a result of a lack of secondary hydroxyl groups capable of forming hydrogen-bonded dimers.

The cyclodextrins, products of the enzymatic degradation of starch by the CGTase enzyme,[1] are composed of 6, 7 or 8 (α, β or γ) α-1,4-glucopyranose units. Their structure, a truncated cone with two hydrophilic faces surrounding a less-polar cavity, leads to a capacity to include a wide variety of guest molecules.[2] They have been widely employed in chiral separations, via classical crystallization methods,[3] GPC,[4] and HPLC.[5] Routes to cyclodextrins involving different conformations of the saccharide residue have involved, either total synthesis[6] or the formation of 3,6-anhydro derivatives.[7–8] Several authors have reported the synthesis of β-CD derivatives in which one glucopyranose is converted to a 2,3-mannoepoxide.[9–11] We wish to report the synthesis and properties of the cyclomanno-2,3-epoxides, derived from α-, β- and γ-CDs, involving clean total derivatisation at the secondary hydroxyl face. In such novel host molecules both the chirality and hydrophilic-hydrophobic balance are significantly modified. These molecules should be key intermediates in the modification of the pyranose geometry of the cyclodextrins.

Following the work of Defaye[8] (per-halogenation), and Fügedi[12] (per-silylation), we have recently reported the use of a protection-deprotection route[13] in the high yield synthesis of per-2-*O*-tosyl-β-cyclodextrin (**1b**). Extension of this route yields the corresponding α- and γ-CD compounds (**1a** and **1c**). Treatment of **1a**, **1b** or **1c** with K_2CO_3 in methanol at 40 °C for 6 hours give the title compounds (**2a**–**2c**) in >90% yield (Fig. 1).

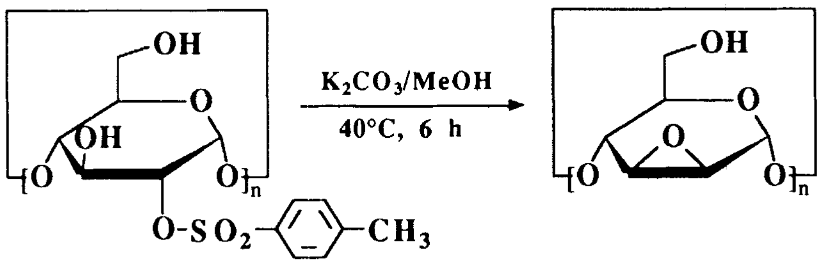
The physical properties of **2a**–**2c** are considerably modified with respect to the starting cyclodextrins,[14] with reduced aqueous solubility ($\sim 1\ g.l^{-1}$) and increased solubility in polar organic solvents, such as acetone and methanol. Removal of the cyclodextrin "head to head" pseudo-symmetry leads to an amphiphilic molecule possessing a hydrophilic primary hydroxyl face and a hydrophobic secondary ether face. Thus, it is not surprising that **2b** shows surfactant behaviour in water (Fig. 2) with a critical micellar concentration of 2×10^{-6} M.[15]

The 400 MHz ^1H nmr spectra of **2b** in pyridine-d_5, dmso-d_6 and acetone-d_6 are given in Fig. 3, and peak assignments and coupling constants are given in Table 1.

The H-2 and H-3 resonances for **2a**–**2c** are relatively solvent invariant AB patterns with $^3J_{1,2}$ and $^3J_{3,4}$ effectively zero, and $^3J_{2,3} = 3.5$ Hz, values typical for mannoepoxides.[16] Application of the Karplus equation to these coupling constants gives values for the H_1-H_2 and H_3-H_4 dihedral angles[17] consistent with the existence of **2a**–**2c** in essentially the half chair conformation, in which H-2 and H-3 are oriented towards the cavity interior. For all compounds, chemical shifts for the OH-6, H-5, H-6 and H-6′ protons are highly solvent dependent. In pyridine-d_5 the OH-6 resonance shows temperature dependence ($-2.59\ Hz \cdot {}^\circ C^{-1}$) typical of a proton accessible to the solvent. ^{13}C-^1H correlation spectroscopy for **2b** in pyridine-d_5 allows a full assignment of the ^{13}C NMR

---

* To whom correspondence should be addressed.



1a : n=6
1b : n=7
1c : n=8

2a : n=6
2b : n=7
2c : n=8

Figure 1

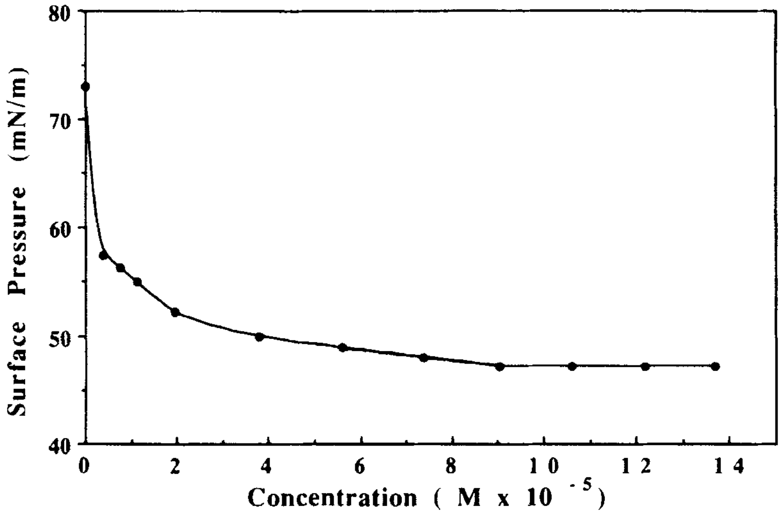


Figure 2 Concentration dependence of the surface tension of **2b** in water.

Table 1 Chemical shifts and coupling constants for protons H-1, H-2, H-3, H-4 and HO-6 in different solvents

	H-1	*H-2*	*H-3*	*H-4*	*HO-6*
2b	5.56	3.62	3.34	4.39	6.41
Pyridine-d_5	J_{12} = 0 Hz	J_{12} = 0 Hz	J_{23} = 3.5 Hz	J_{34} = 0 Hz	
		J_{23} = 3.5 Hz	J_{34} = 0 Hz	J_{45} = 9.0 Hz	(broad)
2b	5.42	3.57	3.34	4.03	4.71
Acetone-d_6	J_{12} = 0 Hz	J_{12} = 0 Hz	J_{23} = 3.5 Hz	J_{34} = 0 Hz	
		J_{23} = 3.5 Hz	J_{34} = 0 Hz	J_{45} = 9.2 Hz	$J_{6\text{-}OH}$ = 5.9 Hz
2b	5.23	3.21	3.44	3.90	4.65
DMSO-d_6	J_{12} = 0 Hz	J_{12} = 0 Hz	J_{23} = 3.5 Hz	J_{34} = 0 Hz	
		J_{23} = 3.6 Hz	J_{34} = 0 Hz	J_{45} = 9.2 Hz	(broad)
2b	5.92	4.17	3.99	4.60	
D_2O*	J_{12} = 0 Hz	J_{12} = 0 Hz	J_{23} = 3.5 Hz	J_{34} = 0 Hz	
		J_{23} = 3.6 Hz	J_{34} = 0 Hz	J_{45} = 8.2 Hz	
2b	5.34	3.53	3.31	4.03	
Methanol-d_4	J_{12} = 0 Hz	J_{12} = 0 Hz	J_{23} = 3.5 Hz	J_{34} = 0 Hz	
		J_{23} = 3.5 Hz	J_{34} = 0 Hz	J_{45} = 8.3 Hz	
2a	5.39	3.53	3.33	4.91	4.91
Acetone-d_6	J_{12} = 0 Hz	J_{12} = 0 Hz	J_{23} = 3.5 Hz	J_{34} = 0 Hz	
		J_{23} = 3.5 Hz	J_{34} = 0 Hz	J_{45} = 8.7 Hz	$J_{6\text{-}OH}$ = 5.9 Hz
2c	5.46	3.61	3.33	4.09	4.66
Acetone-d_6	J_{12} = 0 Hz	J_{12} = 0 Hz	J_{23} = 3.6 Hz	J_{34} = 0 Hz	
		J_{23} = 3.6 Hz	J_{34} = 0 Hz	J_{45} = 9.2 Hz	$J_{6\text{-}OH}$ = 5.9 Hz

* Spectra recorded at 80 °C with reference of HDO at 4.8 ppm.

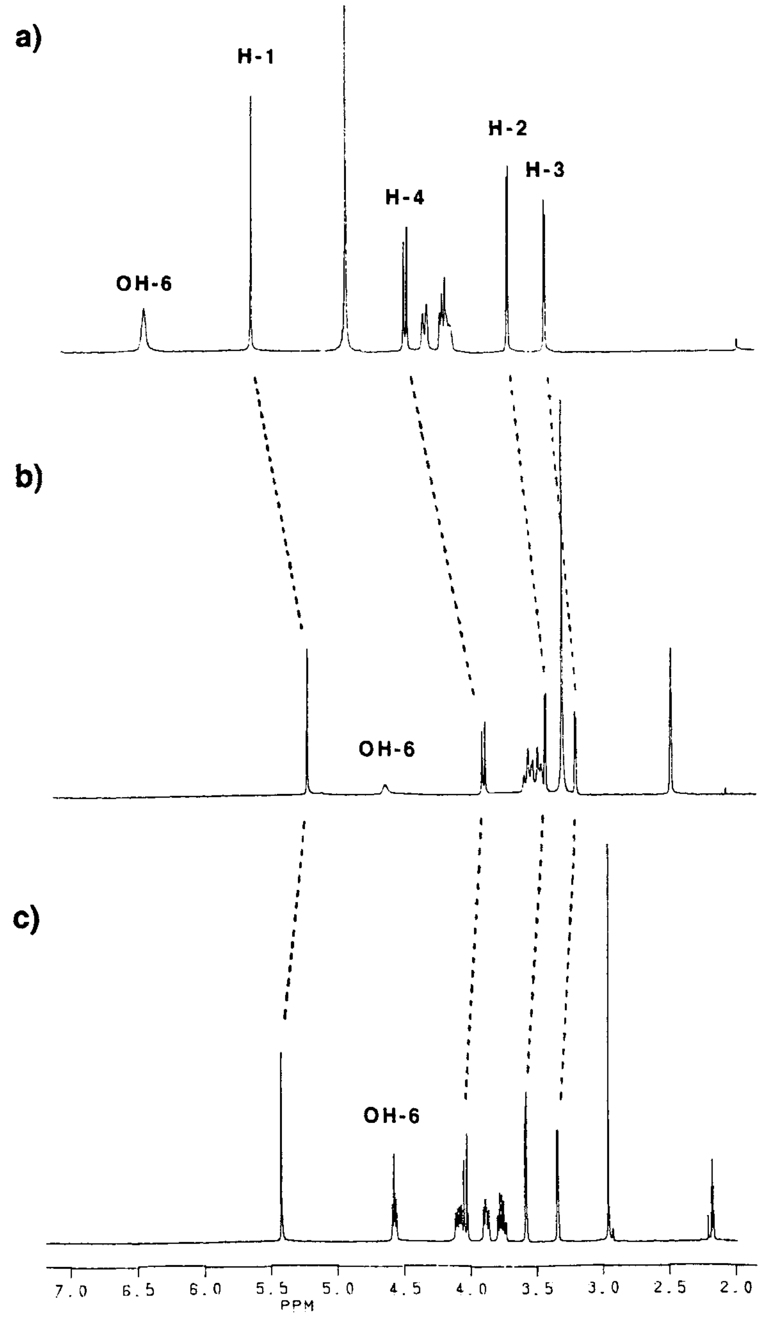


Figure 3 ^{1}H NMR Spectra (400 MHz) of **2** in: (a) pyridine-d_5, (b) dmso-d_6, and (c) acetone-d_6.

spectrum [95.9 (C-1); 70.5 (C-5); 61.1 (C-4); 61.9 (C-6); 54.2 (C-2); 49.6 (C-3), ppm].

The extremely low aqueous solubility limits investigation of the complexation properties of **2b** in solution. However, it is possible to isolate in the solid state 1:1 complexes of anethole, vanilin and *N*-acetylphenylalanine. For larger molecules such as bornyl acetate which form 2:1 complexes with β-CD, no complexation is observed with **2b**. This absence of complexation probably arises from a lack of the secondary hydroxyl groups needed for hydrogen-bonded dimer formation. ^{1}H nmr studies of **2a** with *p*-nitrophenol in D_2O show complexation-derived shifts of the aromatic protons of 0.4 ppm (meta) and 0.1 ppm (ortho), arising from a geometry in which the nitro group is oriented towards the primary hydroxyl face. The observed inclusion induced displacements are larger than those observed for α-CD and mono-6-glu-α-CD.[18]

The thioester hydrolysis of spiranolactone by β-cyclodextrin has been proposed to arise from a geometry in which the -S-CO-CH_3 group is in close proximity to the secondary hydroxyl groups of the two β-CD molecules forming the dimeric inclusion complex.[19] Interaction of **2b** with spiranolactone in methanol at 50 °C during 5 days lead to zero hydrolysis, this lack of catalytic activity arising from the absence of the necessary secondary hydroxyl groups in the cyclomannoepoxide.

(Received April 27, 1992)

REFERENCES

1. (a) Schardinger, F. (1904). *Wien. Klin. Wochenschr.* **17,** 207. (b) Schardinger, F. (1911). *Zentrabl. Bakteriol. Parasidenkd.* **29,** 188. (c) Saenger, W. (1980). *Angew. Chem. Int. Ed. Engl.* **19,** 344.
2. Szejtli, J. (1988). *Cyclodextrin Technology,* Kluwer: Dordrecht.
3. Warsch, Y. and Vögtle, F. (1987). *Top. Curr. Chem.* **140,** 21.
4. Schurig, V. and Nowotny, H.-P. (1990). *Angew. Chem. Int. Ed. Engl.* **29,** 939.
5. (a) Fujimura, K., Ueda, T. and Ando, T. (1983). *Anal. Chem.* **55,** 446. (b) Armstrong, D. W., Ward, T.J., Armstrong, R.D. and Beesley, T.E. (1986). *Science (Washington D.C.)* **232,** 1132.
6. Collins, P.M. and Ali, M.H. (1990). *Tetrahedron Lett.* **31,** 4517.
7. Ashton, P.R., Ellwood, P., Staton, I. and Stoddart, J.F. (1991). *Angew. Chem. Int. Ed. Engl.* **30,** 80.
8. Gadelle, A. and Defaye, J. (1991). *Angew. Chem. Int. Ed. Engl.* **30,** 78.
9. Pregel, M.J. and Buncel, E. (1991). *J. Can. Chem.* **69,** 130.
10. Breslow, R. and Czarnik, A.W. (1983). *J. Am. Chem. Soc.* **105,** 1390.
11. Murakami, T., Karata, K. and Morimoto, S. (1988). *Chem. Lett.* 553.
12. Fugedi, P. (1989). *Carbohydr. Res.* **192,** 366.
13. Coleman, A.W., Zhang, P., Parrot-Lopez, H., Ling, C.C., Miocque, M. and Mascrier, L. (1991). *Tetrahedron Lett.* **32,** 3997.
14. Physical data for **2a**: $[\alpha]_D^{20} = +128°$; $R_f = 0.52$ (2-Butanone/n-Butanol/H_2O, 9:1:1); mp. 268–269.5 °C. *Anal.* Calc: C, 50.00; H, 5.59. Found: C, 49.71; H, 5.69. **2b**: $[\alpha]_D^{20} = +147°$; $R_f = 0.51$ (2-Butanone/n-Butanol/H_2O, 9:1:1); mp. 270–282 °C. *Anal.* Calc: C, 50.00; H, 5.59. Found: C, 49.82; H, 5.55. **2c**: $[\alpha]_D^{20} = 169°$; $R_f = 0.53$ (2-Butanone/n-Butnaol/H_2O, 9:1:1); mp. 290–291 °C. *Anal.* Calc: C, 50.00; H, 5.59. Found: C, 49.65; H, 5.50.
15. Surface tension was measured on a Prolabo T. D. 2000 tensiometer using the stirrup technique.
16. Buchanan, J.G., Fletcher, R., Parry, K. and Thomas, W.A. (1969). *J. Chem. Soc. (B)* 377.
17. Karplus, M. (1963). *J. Am. Chem. Soc.* **85,** 2870.
18. Kanda, Y., Yamamoto, Y., Inoue, Y., Chûjô, R. and Kobayashi, S. (1989). *Bull. Chem. Soc. Jpn.* **62,** 2002.
19. Wouessidjewe, D., Crassoux, A., Duchêne, D., Coleman, A.W., Rysanek, N., Tsoucaris, G., Perly, B. and Djedaïni, F. (1989). *Carbohydr. Res.* **192,** 261.