A Permethylated Cyclic Fructo-oligosaccharide Host that can bind Cations in Solution

Yoshio Takai,[a] Yasuo Okumura,[a] Shigetoshi Takahashi,[a] Masami Sawada,*[a] Mishio Kawamura[b] and Takao Uchiyama*[b]

[a] *Material Analysis Center, the Institute of Scientific and Industrial Research, Osaka University, Mihogaoka, Ibaraki, Osaka 567, Japan*

[b] *Department of Biology, Osaka Kyoiku University, Tennoji-ku, Osaka 543, Japan*

Permethylated cycloinulohexose **1** acts, like an 18-crown-6 derivative with alkali and alkaline earth cations in organic solvents, where the cation is not bound by the central 18-crown-6 moiety, but by the upper OMe-3 groups of **1**.

Previously, we reported that cycloinulohexose ($C_{36}H_{60}O_{30}$) produced from inulin by cycloinulo-oligosaccharide fructanotransferase is a β-(2 → 1)-linked cyclohexose of D-fructofuranose, where an 18-crown-6 moiety is involved at the central skeleton (MS, NMR, X-ray crystallography).[1,2] Recently, we observed that the selectivity towards alkali and alkaline earth cations is similar to that of 18-crown-6 **2**, by means of thin-layer ligand-exchange chromatography (TLEC).[3] These findings are in remarkable contrast to α-cyclodextrin's properties. This is because α-cyclodextrin is a α-(1 → 4)-linked cyclohexose of D-glucopyranose and can bind neutral molecule(s) in its hydrophobic cone-shaped cavity.[4,5]

We selected the permethylated cycloinulohexose **1** (permethylated cyclofructan)[6–8] and evaluated the thermodynamic and kinetic character of the complexation between **1** and typical cations, and deduced the complex structure in solution.

Association constants (K_s) were determined in several solvents at 25 °C using ^{1}H NMR titration (non-linear least-squares method)[9,10] (Table 1). The K_s value of **1** (2.5×10^2 dm^3 mol^{-1} for K^+ in 70% MeOH) is about two orders of magnitude smaller than that of **2** (2.1×10^4 dm^3 mol^{-1} for K^+ in 70% MeOH).[11] However, the cation selectivity by K_s values is in the order $Na^+ < NH_4^+ < Cs^+ < K^+ < Ba^{2+}$, showing good agreement with that of **2** ($Li^+ < Na^+$, $NH_4^+ < K^+ < Ba^{2+}$ in MeOH)[12,13] and also for that of cycloinulohexose itself by TLEC ($Li^+ < Na^+ < Cs^+ < K^+$, $Rb^+ < Ba^{2+}$ in 50% MeOH).[3]

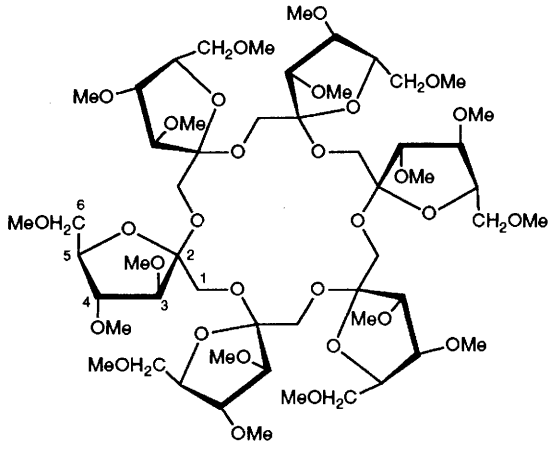
A rate constant was determined as a first-order approximation using the exchange method (line-shape fitting method).[14,15] A solution of **1** in acetonitrile shows three singlets for the OMe-3, OMe-4 and OMe-6 protons. When a 0.6 equiv. quantity of KSCN is added, these peaks broaden and shift downfield. When more KSCN (6 equiv.) is added, the peaks become sharp and shift to a much greater extent; this is due to formation of the complex. When the former solution is cooled to −40 °C, a significant spectral change is observed. Each methyl proton signal splits (*e.g.* 50 Hz for OMe-3; then $k_c < 50$ s^{-1})[16] into two singlets, which correspond to the free **1** and the potassium complex. A curve-fitting treatment for the broad line of OMe-3 proton signal at 25 °C gave the decomposition rate constant of the complex (k_{-1}) to be approximately 800 s^{-1}, and then k_1 is *ca.* 1×10^7 s^{-1} dm^3 mol^{-1}. These thermodynamic and kinetic properties suggest that **1** acts like an 18-crown-6 derivative.[12]

The complex ion structure was deduced by the method of induced-shift difference, which uses a pair of $K^+(SCN^-)$ and $Ba^{2+}(SCN^-_2)$ ions in acetone at 25 °C.[17] Both cations have almost the same size, but a different charge. Therefore, the difference in the induced shifts can cancel the contribution of the complicated conformational change effect on them and

Table 1 Association constants (K_s) of **1** with several cations at 25 °C by ^{1}H NMR titration

	K_s/dm^3 mol^{-1}			
Cation	70% MeOH[a]	MeOH[b]	MeCN	MeCOMe[d]
Na^+ (SCN^-)	0.6 ± 0.2	(2.6 ± 0.2) × 10		(1.5 ± 0.3) × 10^2
K^+ (SCN^-)	(2.47 ± 0.03) × 10^2		*ca.* 10^4	(6.1 ± 0.1) × 10^3
Cs^+ (SCN^-)		(3.6 ± 0.3) × 10^3)		(7.5 ± 0.4) × 10^2
NH_4^+ (SCN^-)	7.1 ± 0.3			
Ba^{2+} (SCN^-)				1.9 × 10^4[e]

[a] CD_3OD/D_2O (70/30). [b] CD_3OD (Aldrich, 99.8 atom% D). [c] CD_3CN (Aldrich, 99.5 atom% D). [d] CD_3COCD_3 (Wako, 99.9%). [e] Ref. 18.



1

evaluate only that of the net charge effect, and then the position of the cation can be reasonably deduced. The protons of OMe-3, H-3 and H-4 show larger values, and H-1, H-1′ relatively smaller ones [OMe-3 (induced-shift difference: 0.19 ppm), OMe-4 (0.06), OMe-6 (0.04), H-1, 1′ (0.14, 0.00), H-3 (0.16), H-4 (0.16), H-5 (*ca.* 0.1), H-6,6′ (*ca.* 0.1)]. These net electrostatic effects suggest that the cationic centre is close to the former protons but far from the latter ones. This means the cation is bound mainly by the oxygens of OMe-3 and not by those of the 18-crown-6 moiety. Judging from the crystal structure of cycloinulohexose[2] and low temperature ^{1}H NMR spectra of the potassium complex (OMe-3 peak splits into two peaks at −77 °C), the cation is estimated to be bound by the three alternate oxygens of OMe-3 (apparently by the six oxygens of OMe-3 at room temperature due to coalescence of the signals).

This new oligosaccharide **1** which can be derived from inulin serves as a relatively strong host for K^+ and Ba^{2+} cations. Since **1** has good solubility in organic solvents, the application to organic synthesis will be significant. We are further studying in detail these complexations of the functionalized saccharide.

We are grateful to Dr T. Imaki (Mitsubishi Kasei Co.) for the gift of **1**.

Received, 9th September 1992; Com. 2/04842F

References

1 M. Kawamura, T. Uchiyama, T. Kuramoto, Y. Tamura and K. Mizutani, *Carbohydr. Res.*, 1989, **192**, 83.
2 M. Sawada, T. Tanaka, Y. Takai, T. Hanafusa, T. Taniguchi, M. Kawamura and T. Uchiyama, *Carbohydr. Res.*, 1991, **217**, 7.
3 T. Uchiyama, M. Kawamura, T. Uragami and H. Okuno, *Carbohydr. Res.*, in the press.
4 R. J. Clarke, J. H. Coates and S. F. Lincoln, *Adv. Carbohydr. Chem. Biochem.*, 1988, **46**, 205.
5 W. Saenger, *Angew. Chem., Int. Ed. Engl.*, 1980, **19**, 344.
6 $C_{54}H_{96}O_{30}$ = 1225, m.p. 114–117 °C, $[\alpha]_D^{15}$ −103.3 (*c* 1.00, $CHCl_3$), ^{1}H NMR (360 MHz, CD_3CN), 3.88 (d, 1H, $^3J_{3,4}$ 6.5 Hz, H-3), 3.84 (m, 1H, H-5), 3.77 (d, 1H, $^2J_{11'}$ |9.9| Hz, H-1), 3.70 (t, 1H, H-4), 3.56 (d, 1 H, H-1′), 3.49 (m, 2H, H-6, H-6′), 3.45 (s, 3H, Me-3), 3.36 (s, 3H, Me-4), 3.34 (s, 3H, Me-6).
7 M. Sawada, M. Shizuma, Y. Takai, H. Yamada, T. Tanaka, Y. Okumura, Y. Hidaka, T. Hanafusa and S. Takahashi, *Bull. Chem. Soc. Jpn.*, 1992, **65**, 1275.
8 M. Sawada, L. Ouyang, Y. Takai, H. Yamada, M. Shizuma, T. Kinoshita, T. Mochizuki and T. Hanafusa, *Bull. Chem. Soc. Jpn.*, 1991, **64**, 1243.
9 K. Tone, BASIC, Baifukan, 1981, ch. 28. pp. 137–146.
10 H. Tsukube and H. Sohmiya, *J. Org. Chem.*, 1991, **56**, 875.
11 R. M. Izatt, R. E. Terry, D. P. Nelson, Y. Chan, D. J. Eatough, J. S. Bradshaw, L. D. Hansen and S. J. Christensen, *J. Am. Chem. Soc.*, 1976, **98**, 7626.
12 F. Vögtle and E. Weber, *The Chemistry of Ethers, Crown Ethers, Hydroxyl Groups and Their Sulfur Analogues*, ed. S. Patai, John Wiley, New York, Part 1, 1980, ch. 2, p. 68.
13 G. W. Gokel, D. W. Goli, C. Minganti and L. Echegoyen, *J. Am. Chem. Soc.*, 1983, **105**, 6786.
14 M. L. Martin, G. J. Martin and J.-J. Delpuech, *Practical NMR Spectroscopy*, Heyden, London, 1980, ch. 8.
15 M. Oki, *Applications of Dynamic NMR Spectroscopy to Organic Chemistry*, VCH, Florida, 1985, ch. 1.
16 D. A. Laidler and J. F. Stoddart, *J. Chem. Soc., Chem. Commun.*, 1976, 979.
17 D. Live and S. I. Chan, *J. Am. Chem. Soc.*, 1976, **98**, 3769.
18 Y. Kikuchi, Y. Kata, Y. Tanaka, H. Toi and Y. Aoyama, *J. Am. Chem. Soc.*, 1991, **113**, 1349.