Pergamon

Tetrahedron: *Asymmetry* 12 (2001) 2767–2774

TETRAHEDRON: *ASYMMETRY*

Hydroxymethyl-substituted crown acetals with 35-C-14 and 40-C-16 skeletal backbones: synthesis and molecular geometries†

Stefan Immel,* Frieder W. Lichtenthaler, Hans J. Lindner and Toshio Nakagawa

Institut für Organische Chemie, Technische Universität Darmstadt, D-64287 Darmstadt, Germany

Received 18 October 2001; accepted 19 October 2001

Abstract—An oxidation/reduction sequence readily converts β- and γ-cyclodextrin into hydroxymethyl-substituted crown acetals with 35-C-14 and 40-C-16 skeletal cores. X-Ray analysis of their well crystallizing peracetates reveals the 40-membered ring of the γ-CD derived octaacetal to mould into an undulated four-loop structure with alternating *gauche* and *anti*-conformations of the eight *meso*-butanetetrol units, the overall shape resembling a four-leaf clover. In the β-CD derived, 35-membered crown heptaacetal, six of the seven glycolaldehyde/butanetetrol segments are lined up in alternating *gauche*/*anti* arrangements with the seventh, uneven unit inserted in *gauche* orientation. In solution, however, the macrocycles are highly flexible as evidenced by their ^{1}H and ^{13}C NMR spectra, which at 300 K show only one set of signals for the respective -CHR-CHR-O-CHR-O- units (R = CH_2OH or CH_2OAc).

1. Introduction

Macrocycles exclusively containing acetal oxygens, and hence, deserving the designation *crown acetal*,[2] are rare, the presently known examples being limited to systems with one[3] or two[4] formaldehyde/alkanediol acetal units, i.e. containing only two or four oxygens in the ring.[5] Cycloacetals with a higher number of ring oxygen atoms, albeit never considered as such, happen to be the products generated by periodate oxidation of cyclic oligosaccharides. The polyaldehydes derived from α-, β-, and γ-cyclodextrin[6] de facto constitute macrocycles with 30-crown-12, 35-crown-14, and 40-crown-16 skeletal backbones, yet have eluded unequivocal structural characterization due to their manifold possibilities of elaborating cyclic acetals, hemiacetals and hemialdals. Of the products ensuing from borohydride reduction, the α- and β-cyclodextrin-derived polyhydroxymethyl-30-C-12 and 35-C-14 crown acetals **1** and **3** have been prepared,[7,8] yet only the 30-membered ring of the well-crystallizing peracetate of **1**, i.e. **2**, has yielded to an X-ray analysis, unveiling the macrocycle to be molded into an undulated three-loop core with a unique order of succession of the -CHR-CHR-O-CHR-O- units: alternating *gauche* and *anti*-conformations of the *meso*-butanetetrol portions and consecutive disposition of the glycolaldehyde–acetoxymethyl groups above and below the mean-plane of the backbone.[8] In solution, however, the macrocycle is highly flexible,[8] providing a suitable host for mimicking the induced-fit mode of molecular recognition[9]—rather than the rigid lock-and-key-type mechanism[10]—as the host can sterically adapt to a guest to be bound and incorporated. In continuation of our studies towards the generation of flexible hosts[11] to probe the induced-fit mode of guest inclusion, we here wish to report on the equally unique molecular geometries for the β- and γ-CD-derived crown acetals **4** and **6**.

2. Results and discussion

Periodate oxidation of β- and γ-CD was performed on a preparative scale (5–10 g) by keeping their aqueous solutions with a three molar excess of oxidant at 0–4°C for 5–7 days. The resulting CD–polyaldehydes obtained as chromatographically uniform powders, were subjected directly to reduction with $NaBH_4$ in methanol, yet the polyhydroxymethyl-substituted crown acetals **3** and **5** are preferably isolated the well-crystallizing peracetates **4** and **6**, respectively, obtainable with yields in the 80–90% range based on β- and γ-CD. Subsequent

* Corresponding author. Tel.: +49-6151-16 5277; fax: +49-6151-16 6674; e-mail: lemmi@sugar.oc.chemie.tu-darmstadt.de

† Part 29 of the series Molecular Modeling of Saccharides. For Part 28, see Ref. 1.

0957-4166/01/$ - see front matter
PII: S0957-4166(01)00469-4

Zemplén deacetylation (NaOMe/MeOH) then smoothly afforded the respective polyols, i.e. the heneicosa-(hydroxymethyl)-35-crown-14 heptaacetal **3**, and its homolog, the tetraicosa-(hydroxymethyl)-40-crown-16 octaacetal **5**, both in crystalline form. None of the crown acetals prepared showed any rotational value, which was to be expected, as the butanetetrol units generated from the CDs by the periodation–reduction sequence have *erythro* configuration and erythritol is a *meso* compound (Scheme 1).

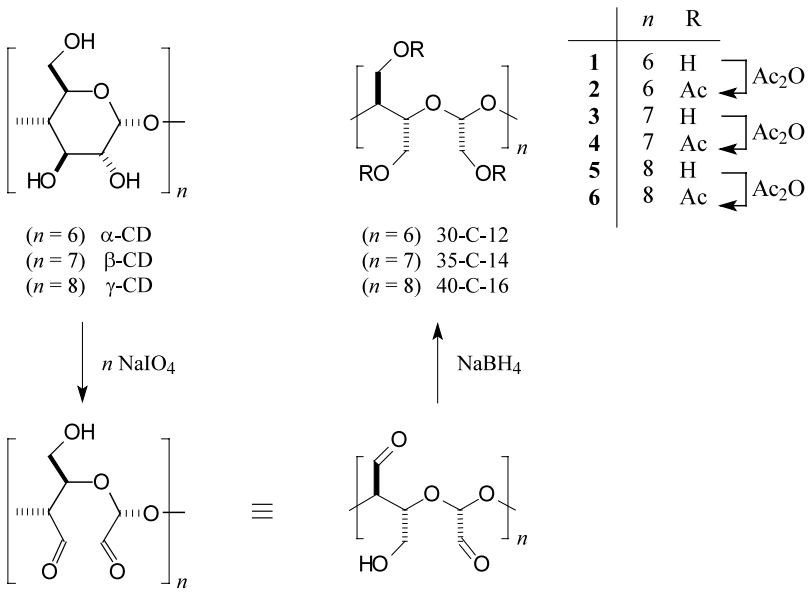
Unlike the hydroxymethyl-substituted crown acetals **3** and **5**, which as of now, only gave crystals unsuitable for X-ray analysis, their peracetates **4** and **6** did, straightforwardly unravelling their molecular geometries (cf. Fig. 1).

In the γ-CD-derived 40-C-16 octaacetal **6**, the 40-membered macrocycle is molded into four loops with the eight acetoxymethyl groups of the glycolaldehyde acetal units pointing alternatingly above and below the undulated mean-plane of the macrocyclic backbone. Similarly, the eight *meso*-butanetetrol units adopt alternating *gauche*- and *anti*-arrangements of their two acetoxymethyl groups (Fig. 1, top right). In this, the molecular arrangement is reminiscent of the folding of the α-CD-derived 30-C-12 analog **2**, in which the 30-membered ring is organized into three loops (Fig. 1, top left). Insertion of two further -CHR-CHR-O-CHR-O- groupings (with $R = CH_2OAc$) into the three looped 30-membered ring of **2** simply results in the elaboration of a fourth loop.

In the case of the β-CD-derived crown heptaacetal **4**, having seven, i.e. an uneven number of butanetetrol/glycolaldehyde segments, six of these units are lined up in alternating *gauche*/*anti* arrangements with the seventh residue being inserted into the macrocycle in *gauche* conformation (Fig. 1, top center); obviously incorporation of the 'uneven' butanetetrol unit in an *anti*-geometry would result in two successive *anti*-disposed glycol fragments inflicting considerable strain into the macrocycle.

The center row of Fig. 1 displays a single unit cell for the solid-state structures of **2**, **4**, and **6** with a colored representation of the Hirshfeld surfaces[12] of each molecule. These surfaces are roughly equivalent to the solvent accessible surfaces[13] for each molecule, yet for crystal lattices they are obtained as non-overlapping molecular surfaces arising from partitioning of the crystal space according to the volume occupied by each molecule. The front opened forms with ball-and-stick models inserted display the unit cell of **2** (Fig. 1, center left) to contain two molecules of the 30-C-12 hexaacetal, both molecules being symmetry-related with each other ($Z = 2$, space group P_n) through a sliding mirror plane. Obviously, the achiral compound **2** adopts two mirror image conformations with alternating (+)-*gauche*/*anti* (yellow Hirshfeld surface) and (−)-*gauche*/*anti* (orange) arrangements, respectively. Similar conditions are observed in the structures of **4** and **6** (space groups $\bar{P}$ and $C2/c$) in which four molecules per unit cell were established: in the case of **4**, two symmetry independent molecules are correlated with their mirror image conformers through symmetry operations (Fig. 1, center), whilst for **6** (Fig. 1, center right) all four molecules are symmetry related in the crystal lattice (pair wise mirror image conformers). In particular, the ribbon models of Fig. 1 (bottom row) display the mode of stacking of the individual macrorings in the solid-state structures.

Unlike the 30-C-12 crown acetal **2**, which crystallized from 95% ethanol as such, both the 35-C-14 and 40-C-16 homolog obtained in crystalline form from the same



Scheme 1. Synthetic access to large ring crown acetals with repetitive C-C-O-C-O- fragments in their skeletal backbones: α-, β-, and γ-cyclodextrin-derived hydroxymethyl substituted analogs composed of six, seven, and eight consecutive D-erythrose/glyoxal or—upon hydride reduction—*meso*-butanetetrol/glycolaldehyde segments.

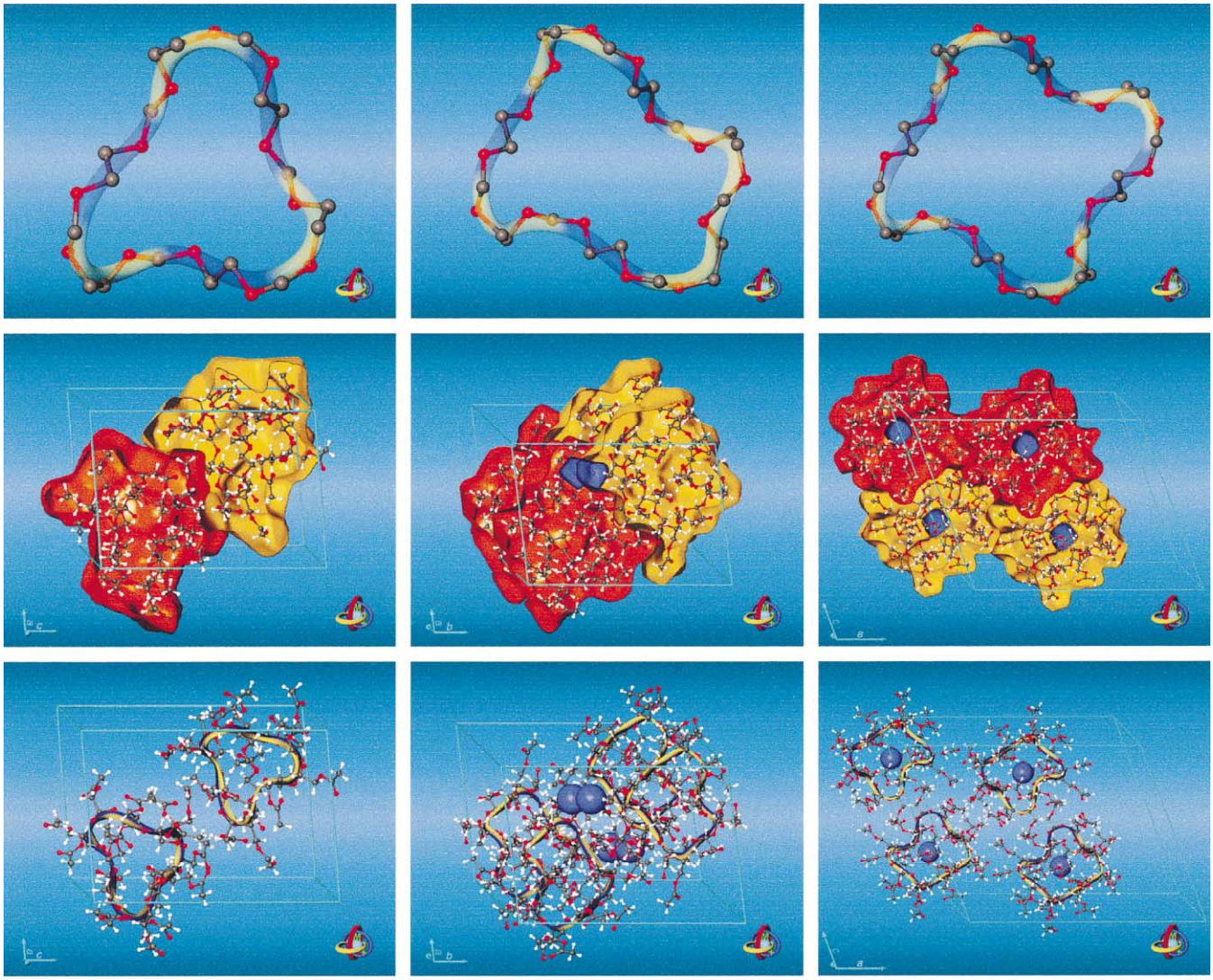


Figure 1. Solid-state structures of the 30-C-12 (**2**, left), 35-C-14 (**4**·H_2O, center), and 40-C-16 (**6**·H_2O, right) polyacetal peracetates. In the top row, all -CH_2OAc ring substituents and hydrogen atoms have been removed for visualization, the semi-transparent ribbon models are colored according to the alternating (+)-*gauche* (yellow) and *anti* (blue) conformations of the constituting *meso*-butanetetrol residues. The center entries display a single unit cell for each structure with the non-overlapping Hirshfeld surfaces indicating the crystal volumes occupied by each molecule. Symmetry related mirror image conformations of the achiral compounds with alternating (+)-*gauche*/*anti* and (−)-*gauche*/*anti* *meso*-butanetetrol units are labelled by yellow and red surface colors, respectively. The bottom row ribbon models show the mode with which water molecules (blue spheres) are incorporated into the crystal lattice of **4** and **6**: whilst in **4** the water occupies interstitial positions between the macrocycles (center row), in **6** each water molecule is fully included into a 40-C-16 octaacetal host (right row).

solvent, incorporated one water molecule per macrocycle (rather than ethanol) into the crystal lattice. Whilst in **4** the four water molecules per unit cell (blue surfaces and blue spheres in Fig. 1) occupy interstitial places between the macrocycles (in Fig. 1, center, only two of the four water molecules are visible, the others being covered by the surfaces of front crown-acetals), the water of crystallization is fully immersed into the macrocyclic hosts of **6**, occupying almost the center of geometry of the 40-C-16 octaacetals in an inclusion complex type fashion, de facto filling their entire inner space.

A detailed plot of the ring geometries of **4** and **6** is provided by Fig. 2, in which selected *meso*-butanetetrol residues have been labelled according to their conformation about the central C–C bond. Whilst the 'even' membered 40-C-16 octaacetal **6** allows for an fully alternating gauche/anti succession of the repeating unit within the ring, the 'uneven' 35-C-14 heptaacetal features two neighboring gauche residues in the macrocycle.

2.1. Solution geometries

The quite elaborate, well-organized structures found for the solid-state do not survive on dissolution in water in the case of the hydroxymethyl substituted crown acetals **3** and **5**, or in organic solvents such as chloroform for the peracetates **4** and **6**. As clearly evidenced by their ^1H

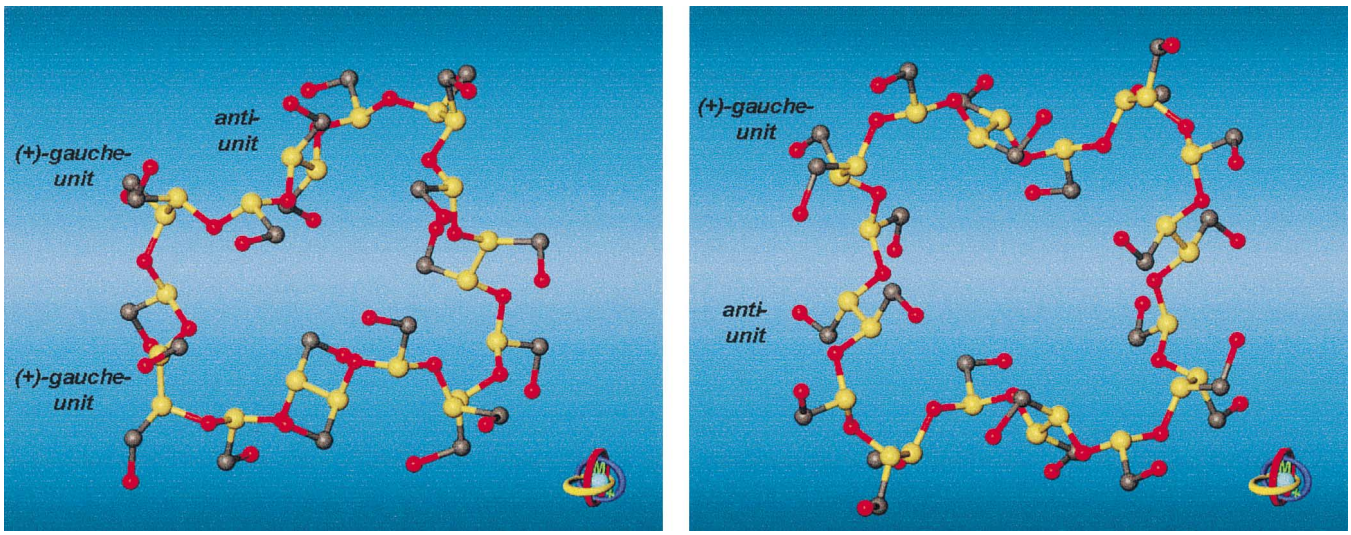


Figure 2. Comparison and ball-and-stick models of the solid-state ring conformations of the 35-C-14 heptaacetal and 40-C-16 octaacetal peracetates **4** and **6**. For visualization of the macrorings all ring carbon atoms are colored yellow, all hydrogen atoms and the acetyl groups of the substituents were left off for clarity. Representative *meso*-butanetetrol units are labeled according to their conformation (+)-*gauche* and *anti*; note the two consecutive (+)-*gauche*-oriented residues in the structure of the 'uneven' 35-membered ring of **2** on the left.

and ^{13}C NMR spectra, as of now measured only at 27°C (300 K), the macrocyclic crown acetals are highly flexible. Thus, for each, i.e. **3** and **5** in D_2O, **4** and **6** in $CDCl_3$), only one averaged set of signals is observed for the seven resp. eight -CHR-CHR-O-CHR-O- units: 5 Hz triplets for H-2 and doublets for the CH_2-protons of the glycolaldehyde acetal groups, 9–9.5 Hz triplets for H-4/H-5, and, invariably, the butanetetrol-4- and 5-CH_2OH protons as the AB part of an ABX system, with X being H-4 and H-5; the same holds for the ^{13}C NMR signals, showing three distinct resonances for the core carbons of the macrocycles, which could be unequivocally assigned on the basis of CH-decouplings. By consequence, in solution the 35-C-14 and 40-C-16 crown acetals are highly flexible macrocycles in which the seven resp. eight monomeric -CHR-CHR-O-CHR-O- units (with R = CH_2OAc), strung together to 35- and 40-membered cycles, are fully equilibrated and, hence, identical when observed in NMR time scale.

In turn, this high flexibility predisposes the crown acetals to adapt their conformation to guests for incorporation in a guest–host relationship and thus meet our aims for acquiring flexible hosts to study the induced-fit mode of molecular recognition. The peracetylated crown acetals **4** and **6**, as evidenced by Fig. 1 (mid-center and center right), display a distinct affinity to water, incorporating one molecule per macrocycle even when crystallized from 95% ethanol. The inclusion behavior of the crown acetals **3** and **5**, featuring 21 resp. 24 highly hydrophilic hydroxymethyl groups around the macrocycle, is different. The 35-C-14 heptaacetal **3** exhibits a distinct predilection for alcohols forming, on the basis of ^1H and ^{13}C NMR evidence, 1:1 complexes with ethanol or *n*-propanol when crystallized from these solvents. Fig. 3, depicting the surprisingly simple ^1H NMR spectrum of **3**·*n*-PrOH in D_2O gives ample proof of 1:1 complex. The type of binding though, i.e. whether the guest sits inside or outside the cavity—in D_2O it may be even in solution—must await X-ray analysis of the crystals, which as of now have not been obtained in a suitable form.

By contrast, the 40-crown-16 octaacetal **6** has no tendency at all to incorporate low molecular weight alcohols when crystallized therefrom, conceivably because its cavity can entertain only larger, possibly more hydrophobic guests. Investigations along this vein are presently being performed.

3. Experimental

3.1. General methods

Melting points were determined on a Bock Monoskop apparatus and are uncorrected. High-resolution mass spectra (ESI-MS) were recorded on Varian MAT 311 and MAT 212 spectrometers. ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance 500 instrument at 500 and 125 MHz at 300 K, respectively; ^{13}C NMR were proton decoupled. Chemical shifts are given in ppm relative to tetramethylsilane ($CDCl_3$) and sodium 2,2,3,3-tetradeutera-3-trimethylsilylpropionate (D_2O) as internal standards. Elemental analysis were determined on a Perkin–Elmer 240 elemental analyzer. Analytical thin-layer chromatography (TLC) was performed on precoated Merck plastic sheets (0.2 mm silica gel 60 F_{254}) with detection by UV (254 nm) and/or spraying with H_2SO_4 (50%) and heating.

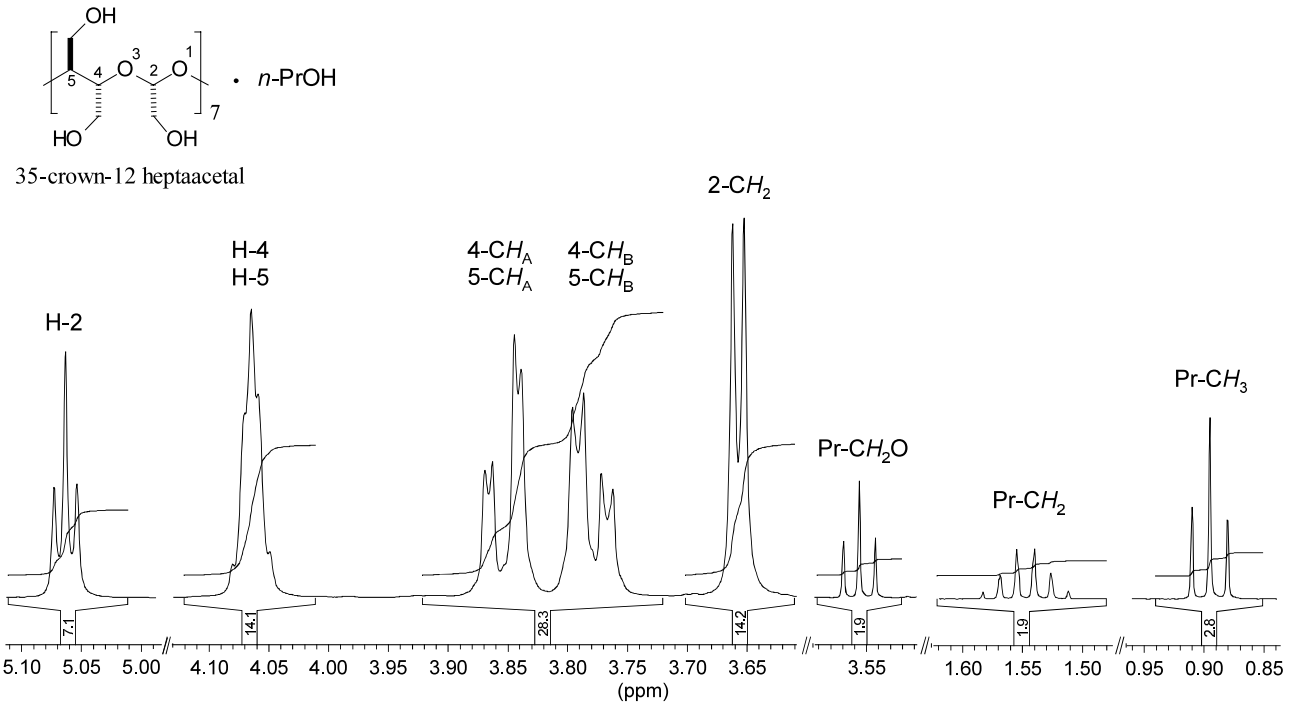


Figure 3. ^{1}H NMR spectrum (500 MHz in D_2O) of the 35-C-14 heptaacetal **3** obtained after dissolution of a sample of **3** previously crystallized from *n*-propanol. Besides a single time-averaged set of signals observed for the seven repeating units of **3**, the *n*-propanol resonances show the formation of a 1:1 inclusion complex.

3.1.1. X-Ray structures. Suitable crystals of cycloacetals **4** and **6** were analyzed on a Siemens CCD three-circle diffractometer with graphite-monochromated Mo Kα ($\lambda = 0.71073$ Å) radiation. The structures were solved by direct methods (SHELXL-97) and successive Fourier synthesis. Refinement (on F^2) was performed by the full-matrix least-squares method with SHELXL-97.[14] All non-hydrogen atoms were refined anisotropically; hydrogen atoms were considered in calculated positions with the 1.2 U_{eq} value of the corresponding bound atom. Experimental details of the structure determinations are summarized in Table 1.

Crystallographic data (excluding structure factors) for **4** and **6** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-143712 and CCDC-143713. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, fax: (+44) 1223 336-033, or e-mail: deposit@ccdc.cam.ac.uk.

3.1.2. Computational details. Calculation of the molecular Hirshfeld surfaces[12] and generation of molecular graphics was performed using the MolArch$^+$ program.[15]

3.2. Heneicosa-(acetoxymethyl)-35-crown-14 heptaacetal 4[16,17]

β-Cyclodextrin (7.39 g, 6.5 mmol) was added with stirring to a cooled (0–5°C), aqueous solution of $NaIO_4$ (13.9 g, 65 mmol, in 400 mL) and the clear solution was kept at 0°C in a dark ice-box for 7 days, whereafter TLC revealed a single spot ($R_f = 0.75$ in 2:2:1 *n*BuOH/MeOH/H_2O) of the respective tetradeca-aldehyde in one of the various hemiacetal and/or hemialdal hydrate forms possible. Then 1,2-ethanediol (1.09 mL, 19.5 mmol) was added with stirring to decompose excess $NaIO_4$ and the mixture was kept at 0°C overnight. An aqueous $BaCl_2$ solution (6.86 g, 32.9 mmol, in 30 mL) was then stirred into the mixture resulting in a precipitate, followed by evaporation of the filtrate to dryness in vacuo. The residue was suspended in dry MeOH (60 mL), kept in a refrigerator overnight, the solids were filtered off upon addition of charcoal, and the filtrate was evaporated to dryness in vacuo at ≈35°C. This procedure was repeated twice to give a white powder (8.4 g), which was dissolved in MeOH/water (100 mL, 3:1). Upon cooling (~0°C), $NaBH_4$ (2.0 g) was added with stirring and the mixture was kept at rt overnight. Addition of acetone (20 mL) to destroy the excess reagent, neutralization with cation exchange resin (IR-120, H^+ form), evaporation to dryness, and several co-evaporations of the residue with absolute MeOH left polyol **4** as a colorless solid which was dissolved in a mixture of pyridine (100 mL) and Ac_2O (50 mL), and kept overnight at rt. Subsequent evaporation to dryness in vacuo at 40°C, followed by co-evaporation with toluene (3×50 mL) afforded a syrup which was dissolved in hot EtOAc, treated with charcoal, filtered, and evaporated to dryness. The residue crystallized on dissolution in 95% EtOH and addition of small amounts of EtOAc to afford 11.62 g (88%) of **4** as colorless plates of mp 109–111°C; $[\alpha]_D^{22}$ 0.0 (*c* 2, $CHCl_3$); lit.:[7a] mp 106–107°C, 11% yield. ESI-MS: *m*/*z* 2053.2 ($M+Na^+$). ^{1}H NMR ($CDCl_3$): δ 5.14 (t, 7H, $J = 5.1$ Hz, 2-H), 4.47 (d, 14H, $J = 9.5$ Hz, 4-H, 5-H), 4.12 (broad 28H-m, AB part of an ABX system, 4-CH_2, 5-CH_2),

4.03 (d, 14H, $J=5.1$ Hz, 2-CH_2), 2.09 (s, 42H, 14AcCH_3), 2.05 (s, 21H, 7AcCH_3). ^{13}C NMR ($CDCl_3$): δ 169.5 (Ac*C*O), 99.5 (C-2), 74.7 (C-4, C-5), 63.5 (2-*C*H_2), 62.7 (4-*C*H_2, 5-*C*H_2), 19.6 and 19.7 (Ac*C*H_3). Anal. calcd for $C_{84}H_{126}O_{56}\cdot H_2O$[17] (2049.9): C, 49.22; H, 6.29. Found: C, 49.34; H, 6.21.

Crystals suitable for X-ray analysis were obtained by slow crystallization of **4** from 95% EtOH containing a small amount of EtOAc; crystal data are summarized in Table 1.

Table 1. Crystal data and structure refinement for the crown acetal per-*O*-acetates **4** and **6**

Compound	**4**·H_2O	**6**·H_2O
Empirical formula	$C_{84}H_{126}O_{56}\cdot H_2O$	$C_{96}H_{144}O_{64}\cdot H_2O$
Formula weight	2049.87	2340.13
Temperature (K)	173(2)	293(2)
Wavelength (Å)	0.71073	0.71073
Crystal system	Triclinic	Monoclinic
Space group	$\bar{P}$	$C2/c$
Unit cell dimensions		
a (Å)	17.140(2)	36.654(3)
b (Å)	23.284(3)	12.219(1)
c (Å)	26.374(3)	30.577(3)
α (°)	97.50(1)	90
β (°)	97.28(1)	116.41(2)
γ (°)	97.41(1)	90
Volume (Å^3)	10237(2)	12265.4(19)
Z	4	4
D_{calcd} (g cm^{-1})	1.330	1.267
Absorption coefficient (mm^{-1})	0.106	0.101
$F(000)$	4344	4959
Crystal size (mm)	$0.33\times0.22\times0.10$	$0.55\times0.40\times0.35$
Θ Range (°)	0.79–27.53	1.24–27.30
Limiting indices	$-21\le h\le21$; $-29\le k\le30$; $-33\le l\le32$	$-46\le h\le46$; $-15\le k\le15$; $-39\le l\le39$
Reflections collected	92760	77665
Independent reflections	39750 ($R_{int}=0.0942$)	12680 ($R_{int}=0.0493$)
Absorption correction	Empirical	Empirical
Max. and min. transmission	0.9927 and 0.9767	0.9761 and 0.9628
Refinement method	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2
Data/restraints/parameters	39750/66/2671	12680/14/756
Goodness-of-fit on F^2	1.071	1.384
Final R indices $[I>2\sigma(I)]$[a]	$R_1=0.1305$; $wR_2=0.2569$	$R_1=0.1463$; $wR_2=0.4019$
R indices (all data)	$R_1=0.2578$; $wR_2=0.3170$	$R_1=0.2436$; $wR_2=0.4648$
Largest difference peak and hole (e Å^{-3})	0.916 and −0.392	0.859 and −0.281

[a] For **4**: $w=1/[\sigma^2(F_o^2)+(0.1165P)^2+15.8740P$; for **6**: $w=1/[\sigma^2(F_o^2)+0.2000P)^2+0.0000P$, where $P=(F_o^2+2F_c^2)/3$.

3.3. Heneicosa-(hydroxymethyl)-35-crown-14 heptaacetal 3[16]

3.3.1. 1:1 Complex with 1-propanol (3·*n*-C_3H_7OH). To a solution of **4** (5.00 g, 2.46 mmol) in absolute MeOH (125 mL) were added a few drops of 2N methanolic NaOMe and the mixture was stirred at rt overnight. After neutralization with IR-120 (H^+ form) the solution was evaporated to dryness in vacuo, and the residue was crystallized from 1-PrOH: 2.54 g (86%) of colorless plates of mp 145–157°C. ESI-MS: m/z 1172.1 (M+Na^+). ^{1}H NMR (D_2O): δ 5.06 (t, 7H, $J=4.9$ Hz, 2-H), 4.06 (m. 14H, X-part of an ABX-system, 4-H, 5-H), 3.86 (dd, 14H, $J=3.0$ and 12.2 Hz, 4-CH_2^A, 5-CH_2^A), 3.78 (dd, 14H, $J=4.8$ and 12.2 Hz, 4-CH_2^B, 5-CH_2^B), 3.66 (d, 14H, $J=4.9$ Hz, 2-CH_2), 3.56 (t, 2H, $J=7.4$ Hz, EtCH_2O), 1.55 (sext., 2H, $J=7.4$ Hz, MeCH_2CH_2O), 0.89 (t, 3H, $J=7.4$ Hz, PrCH_3). ^{13}C NMR (D_2O): δ 101.6 (C-2), 77.4 (C-4, C-5), 62.7 (Et*C*H_2O), 62.2 (2-*C*H_2), 59.7 (4-*C*H_2, 5-*C*H_2), 23.7 (Me*C*H_2CH_2O), 8.7 (Pr*C*H_3). Anal. calcd for $C_{42}H_{84}O_{35}\cdot C_3H_7OH$ (1209.2): C, 44.70; H 7.67. Found: C, 44.65; H, 7.78.

3.3.2. 1:1 Complex with ethanol (3·EtOH). An aqueous solution of **3**·PrOH (0.85 g in 20 mL) was evaporated to dryness at 50°C in vacuo and the residue was subjected to another two evaporations from water. The resulting powder was crystallized from ethanol to yield 0.74 g (87%) of colorless plates exhibiting an unusually wide melting range of 125–157°C without decomposition, undoubtedly due to release of ethanol on melting; lit.[7b] mp 125–132°C for a sample believed to be **3**, but obtained by crystallization from ethanol. ^{1}H NMR (D_2O): δ 5.07 (t, 7H, $J=4.8$ Hz, 2-H), 4.6 (m, 14H, X-part of an ABX system, 4-H, 5-H), 3.86 and 3.77 (two dd for the AB part of an ABX system, 14H each, 4-CH_2 and 5-CH_2), 3.67 (d, 14H, 2-CH_2), 3.64 (q, 2H, EtCH_2), 1.19 (t, 3H, EtCH_3). ^{13}C NMR (D_2O): δ 105.4 (C-2), 80.8 (C-4, C-5), 65.9 (2-*C*H_2), 63.4 (4-*C*H_2, 5-*C*H_2). Anal. calcd for $C_{42}H_{84}O_{35}\cdot C_2H_5OH$ (1195.2): C, 44.22; H, 7.59. Found: C, 44.98; H, 7.50.

3.4. Tetraicosa-(acetoxymethyl)-40-crown-16 octaacetal 6[16]

To a stirred and cooled (0–5°C) aqueous solution of $NaIO_4$ (12.95 g, 60.5 mmol, in 400 mL) γ-cyclodextrin (7.14 g, 5.5 mmol) was added and the clear solution was kept at 0°C in a dark ice-box for 5 days whereafter TLC revealed a single spot ($R_f=0.75$ in 2:2:1 *n*BuOH/MeOH/H_2O). Then, 1,2-ethanediol (0.92 mL, 16.5 mmol) was added with stirring to decompose excess $NaIO_4$ and the reaction was worked up in a manner analogous to that described above for the periodation of β-CD. The respective polyaldehyde was obtained as white powder (8.32 g). Subsequent reduction with $NaBH_4$ (2.0 g) and acetylation with pyridine/Ac_2O (2:1, 150 mL) as described for the acquisition of **4** from β-CD gave a syrup that gradually crystallized on titration with EtOH/EtOAc and was isolated on standing overnight at ambient temperature: 10.6 g (82%) as colorless plates of mp 143.5–145°C; $[\alpha]_D^{22}$ 0.0 (*c* 2, $CHCl_3$). ESI-MS: m/z 2345.1 (M+Na^+). ^{1}H NMR ($CDCl_3$): δ 5.16 (t, 8H, $J=4.9$ Hz, 2-H), 4.49 (dd, 16H,

$J=9.4$ and 1.3 Hz, 4-H, 5-H, X-part), 4.13 and 4.09 (16H, dd and 16H-m, 4-CH_2 and 5-CH_2 as an ABX system), 4.00 (d, 16H, $J=5.0$, 2-CH_2), 2.08 (s, 48H, 4-AcCH_3, 5-AcCH_3), 2.05 (s, 24H, 2-AcCH_3). ^{13}C NMR ($CDCl_3$): δ 170.4 and 170.3 (Ac*C*O), 101.0 (C-2), 76.3 (C-4, C-5), 64.7 (2-*C*H_2), 63.9 (4-*C*H_2, 5-*C*H_2), 20.7 and 20.6 (Ac*C*H_3). Anal. calcd for $C_{96}H_{144}O_{64}\cdot H_2O$[17] (2340.1): C, 49.27; H, 6.29. Found: C, 49.29; H, 6.26.

Crystals for X-ray analysis were obtained by slow crystallization of **6** from 95% EtOH containing a small amount of EtOAc; crystal data are summarized in Table 1.

3.5. Tetraicosa-(hydroxymethyl)-40-crown-16 octaacetal 5[16]

Zemplén deacetylation of **6** (2.00 g, 0.85 mmol) was carried out in a similar manner described above for (**4**→**3**). Crystallization from 1-PrOH afforded colorless needles (1.00 g, 89%) of mp 163–165°C. ESI-MS: *m*/*z* 1335.3 (M+Na$^+$). ^{1}H NMR (D_2O): δ 5.07 (t, 8H, $J=4.5$ Hz, 2-H), 4.07 (broad m, 16H, X-part of an ABX-system, 4-H and 5-H), 3.83 and 3.78 (two dd of an AB system, 16H each, 4-CH_2 and 5-CH_2), 3.67 (d, 16H, 2-CH_2). ^{13}C NMR (D_2O): δ 105.7 (C-2), 81.1 (C-4, C-5), 65.7 (2-*C*H_2), 63.1 (4-*C*H_2, 5-*C*H_2). Anal. calcd for $C_{48}H_{96}O_{40}$ (1313.3): C, 43.90; H, 7.36. Found: C, 43.65; H, 7.44.

Acknowledgements

Appreciation is expressed to the Fonds der Chemischen Industrie, Frankfurt, and the Südzücker AG, Mannheim/Ochsenfurt, for financial support. Our thanks are also due to Wacker-Chemie, Burghausen, for a gift of β- and γ-cyclodextrin.

References

1. Immel, S.; Khanbabaee, L. *Tetrahedron: Asymmetry* **2000**, *11*, 2495–2507.
2. *Nomenclature*: Although polyacetals such as **1**–**6** are unlikely to adopt crown-like molecular geometries—the terminology for macrocyclic ethers was derived from their crown-like shape—it appears logical and practical as well to extend this generally accepted notational mode for crown ethers to their acetal analogs, resulting in the term *crown acetals* for macrocycles with acetal oxygens only. Likewise, it appears most appropriate to adopt the crown ether-type description for ring size and number of oxygens; accordingly, **1** is the octadeca-(hydroxymethyl)-derivative of a 30-crown-12 hexaacetal, whereas the respective β-CD and γ-CD-derived analogs **3** and **5** are cyclic hepta- and octaacetals with a 35-crown-14 and 40-crown-16 backbone, respectively.
3. (a) Pedersen, C. J. *J. Am. Chem. Soc.* **1970**, *92*, 391–394; (b) Kawakami, Y.; Suzuki, J.; Yamashita, Y. *Polym. J.* **1977**, *9*, 519–524; Kawakami, Y.; Sugiura, T.; Yamashita, Y. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 3053–3056; (c) Gold, V.; Sghibartz, C. M. *J. Chem. Soc., Perkin Trans. 1* **1983**, 453–457; (d) Oshima, T.; Nishioka, R.; Ueno, S.; Nagai, T. *J. Org. Chem.* **1982**, *47*, 2114–2117; Oshima, T.; Nagai, T. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 3979–3980; (e) Oshima, T.; Matsuda, F.; Fukushima, K.; Tamura, H.; Matsubayashi, G.; Arakawa, R. *J. Chem. Soc., Perkin Trans. 2* **1998**, 145–148; (f) Ouchi, M.; Inoue, Y.; Kanzaki, T.; Hakushi, K. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 887–888; Inoue, Y.; Ouchi, M.; Hakushi, K. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 525–530.
4. Known tetraoxacycloalkanes with two acetal units in their *n*-crown-4 skeletal backbone: (a) 10-C-4: Bassi, I. W.; Scordamaglia, T.; Fiori, L. *J. Chem. Soc., Perkin Trans. 2* **1975**, 1129–1132; (b) Substituted 10-C4-systems: Terzis, A.; Grindley, T. B. *Can. J. Chem.* **1979**, *57*, 2154–2158; Stoddart, J. F.; Szarek, W. A. *Can. J. Chem.* **1968**, *46*, 3061–3069; (c) 12-C-4; Borgen, G.; Dale, J. *J. Chem. Soc., Chem. Commun.* **1974**, 484–485; Dale, J. *Tetrahedron* **1974**, *30*, 1683–1694; (d) 14-C-4: Bassi, I. W.; Scordamaglia, R.; Fiori, L. *J. Chem. Soc. Perkin Trans. 2* **1972**, 1726–1729; (e) 16-C-4: Dale, J.; Ekeland, T. *Acta Chem. Scand., Ser. A* **1973**, *27*, 1519–1525; Groth, P. *Acta Chem. Scand., Ser. A* **1975**, *29*, 642–643; (f) 18-C-4, 24-C-4, 26-C-4, and 34-C-4: Hill, J. W.; Carothers, W. H. *J. Am. Chem. Soc.* **1935**, *57*, 925–928.
5. The *cyclo*-polyacetals generated by acid promoted oligomerization of 1,3-dioxolane are presumed to have 15-C-6, 20-C-8, and 25-C-10 structural backbones (Kawakami, Y.; Yamashita, Y. *Macromolecules* **1977**, *10*, 837–839), yet their ring size has not been established unambiguously.
6. (a) French, D.; McIntyre, R. J. *J. Am. Chem. Soc.* **1950**, *72*, 5148–5150; (b) Hisa-matsu, M.; Yamada, Y.; Nakashima, K.; Tobata, K. *Starch/Stärke* **1992**, *44*, 188–191.
7. (a) Stoddart, J. F.; Szarek, W. A.; Jones, J. K. N. *Can. J. Chem.* **1969**, *47*, 3213–3215; (b) Kandra, L.; Lipták, A.; Jodál, I.; Nánási, P.; Szejtli, J. *J. Inclusion Phenom.* **1984**, *2*, 869–875.
8. Immel, S.; Nakagawa, T.; Lindner, H.-J.; Lichtenthaler, F. W. *Chem. Eur. J.* **2000**, *6*, 3366–3371.
9. Koshland, D. E. *Angew. Chem.* **1994**, *106*, 2468–2472; *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2375–2378.
10. (a) Fischer, E. *Ber. Dtsch. Chem. Ges.* **1884**, *27*, 2985–2993; (b) Lichtenthaler, F. W. *Angew. Chem.* **1994**, *106*, 2456–2467; *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2364–2374.
11. (a) Nogami, A.; Nasu, K.; Koga, T.; Ohta, K.; Fujita, K.; Immel, S.; Lindner, H.-J.; Schmitt, G. E.; Lichtenthaler, F. W. *Angew. Chem.* **1997**, *109*, 1987–1991; *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1899–1902; (b) Fujita, K.; Chen, W.-H.; Yuan, D.-Y.; Nogami, Y.; Koga, T.; Fujioka, T.; Mihashi, K.; Immel, S.; Lichtenthaler, F. W. *Tetrahedron: Asymmetry* **1999**, *10*, 1689–1696; (c) Immel, S.; Fujita, K.; Lichtenthaler, F. W. *Chem. Eur. J.* **1999**, *5*, 3185–3192; (d) Gohlke, H.; Immel, S.; Lichtenthaler, F. W. *Carbohydr. Res.* **1999**, *321*, 96–104.
12. McKinnon, J. J.; Mitchell, A. S.; Spackman, M. A. *Chem. Eur. J.* **1998**, *4*, 2136–2141.
13. (a) Connolly, M. L. *J. Appl. Crystallogr.* **1983**, *16*, 548–558; (b) Connolly, M. L. *Science* **1983**, *221*, 709–713.

14. Sheldrick, G. M. *SHELXS-97 and SHELXL-97—Programs for Crystal Structure Solution and Refinement*; University of Göttingen: Germany, 1997.
15. Immel, S. *MolArch^{+}—MOLecular ARCHitecture Modeling Program*; Darmstadt University of Technology: Germany, 2001.
16. Systematic name for 35-crown-14 heptaacetal: 2,4,5,7,9,10,12,14,15,17,19,20,22,24,25,27,29,30,32,34,35-heneicosa-(hydroxymethyl)-1,3,6,8,11,13,16,18,21,23,26,28,31,33-tetradecaoxa-cyclopentatriacontane, **4** is the per-*O*-acetyl derivative thereof. Correspondingly, the 40-crown-16 octaacetals **5** and **6** are the tetracosa-hydroxymethyl and tetracosa-acetoxymethyl derivatives of a hexadecaoxa-cyclotetracontane.
17. That the crown acetal peracetates **4** and **6** crystallize with one molecule of water each—crystallization was effected from 95% EtOH/EtOAc—emerged from the X-ray data (cf. Fig. 1) and not from their microanalysis, as differentiation on that basis between anhydrous compound and monohydrate is not possible.