Studies on the Synthesis and Structure of New Urea-Linked Sugar Podando-Coronand Derivatives

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Dedicated to *Peter Köll* on the occasion of his 60th birthday

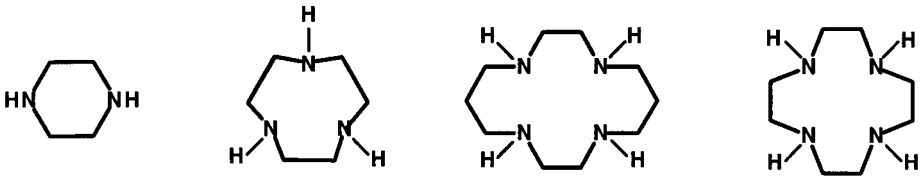
With the aim to develop direct, simple, and efficient coupling procedures involving saccharides and cyclodextrins (CDs), the modified *Staudinger* method, the phosphine imide method, was chosen as a promising versatile way to reach the goals. Thus, the new cyclam derivatives **6**–**9** were obtained in good yields (see *Scheme*). In the case of β-cyclodextrin, the method also allowed the synthesis of the icosa-*O*-acetyl-6^A-isocyanato-6^A-deoxy-β-CD sugar isocyanate **11** and of symmetrical or unsymmetrical carbohydrate carbodiimides **12** and **17** under smooth conditions and in a simple way. Structural, theoretical, and experimental investigations on several urea-like cyclams revealed the fundamental role played by permanent strong H-bonds between urea functions in the conformational equilibrium of the molecules.

Introduction. – Currently, a general and easy access to elaborated cyclodextrin (CD) hosts appears of primary importance in the development of new supramolecular devices. These products are interesting in the field of highly selective transition-metal and lanthanide complexation, eventually yielding supramolecules which may exhibit biomimetic esterase activity [1][2]. Moreover, elaborated CDs should be appropriate for the detection of transition-metal cations or of small organic compounds that can be hosted.

On screening the literature for direct, simple, and efficient coupling procedures involving saccharides and cyclodextrins, the modified *Staudinger* method, called phosphine imide method, appeared to be the method of choice for the synthesis of hosts having one or more internal cavities. This method has been applied by some of us to the synthesis of new glucopyranosyl cyclocarbamates [3], and the study of the mechanism [4] by semiempirical calculations predicted the *in situ* formation of an isocyanate intermediate. Shortly after this, experimental work allowed us to isolate for the first time a β-cyclodextrin isocyanate [5], thus confirming our previous theoretical conclusions. Recently, other authors applied the reaction successfully to the preparation of cyclodextrin-grafted chromatographic phases [6]. Continuing our scope and limitation studies, we were able to extend the reaction to thiourea-like β-CD dimers using CS_2 in place of CO_2 [7]. Thus, one could expect to be able to synthesize isothiocyanates of β-cyclodextrin in this way. However, corresponding experiments were unsuccessful [8].

We now discuss other aspects of the phosphine imide approach for the synthesis of cyclodextrin urea-like cyclams, symmetrical or unsymmetrical β-cyclodextrin-derived carbodiimides and ureas.

Results and Discussion. – *Syntheses.* For the coupling of cyclams **1**–**4** (piperazin is considered the simplest cyclam) with β-cyclodextrin (β-CD) units, an urea linkage including the N-atoms of the cyclam was used. This linkage was found advantageous in the case of cyclodextrin dimers [1] because it was easily formed, stable under various conditions, and amenable to H-bonds.



1 **2** **3** **4**

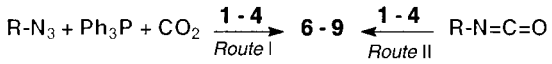
The synthesis of the new cyclam derivatives **6**–**9** was performed by applying the phosphine imide method (*Scheme*, *Route I*) [3]. Treatment of icosa-*O*-acetyl-6^A-azido-6^A-deoxy-β-CD (**5**) with triphenylphosphine and excess CO_2 in the presence of, *e.g.*, the secondary polyamine **1** under dry conditions in DMF afforded the corresponding urea **6a** in 56% yield. Under similar conditions, polyamines **2**–**4** gave ureas **7a**, **8a**, and **9a** in moderate (25–30%) yields after purification of crude products by column chromatography. The reactions were carried out at room temperature, either in DMF or in toluene which were both found to be good solvents, with a slight favor for the latter.

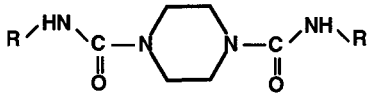
In spite of the simplicity of the one-pot procedure, the moderate yields of the ureas **6a**–**9a** suggested the use of the general way involving isocyanates for the synthesis of urea compounds (*Scheme*, *Route II*). As this approach had not been tried earlier in the case of the cyclams **1**–**4**, we started modeling the reaction with phenyl isocyanate (**10**), which gave the corresponding phenylureas **7f**–**9f** in very good yields. The easy formation of suitable monocrystals in the case of **7f** and **8f** allowed the study of their conformations by X-ray analysis and theoretical calculations (see below).

The synthesis of cyclodextrin-derived ureas by the method in *Route II* became possible since the required icosa-*O*-acetyl-6^A-isocyanato-6^A-deoxy-β-CD (**11**) was recently isolated as the first sugar isocyanate from the phosphine imide reaction [5]. Indeed, on attempts to synthesize bis(icosa-*O*-acetyl-6^A-deoxy-β-CD)carbodiimide (**12**) from azide **5** with triphenylphosphine and CO_2, isocyanate **11** and not the expected symmetrical carbodiimide **12** was formed. The structure of **11** was supported by its IR (2267 cm^{-1}) and ^{13}C-NMR data (–N=C=O at δ 125.03) [5], and by its reaction with morpholine or 1-methylpiperazine giving the corresponding urea derivatives **13** and **14**, respectively. Treatment of **14** with NH_4OH/MeOH at 60° gave a partially acetylated product (2.5–3 Ac in random distribution). Complete deacetylation was performed by NaOH/MeOH at 60° to give crystalline **15**.

Formation of **11** instead of **12** may be attributed to the decreased reactivity of both the isocyanate and the phosphine imide function linked to the bulky icosa-*O*-acetyl-β-cyclodextrin moiety. Consequently, the intermediate phosphine imine **16** formed from **5** with Ph_3P reacts much faster with the small CO_2 molecule to give isocyanate **11** than with the latter, which is present, moreover, in low concentration compared to CO_2. This assumption was corroborated by the one-pot reaction of **5** with Ph_3P in the presence of

Scheme





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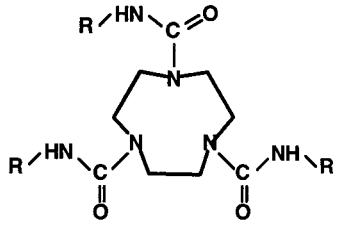

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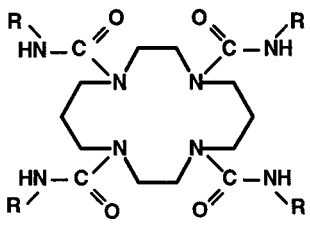

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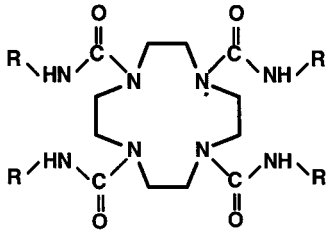

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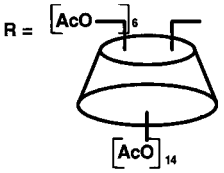
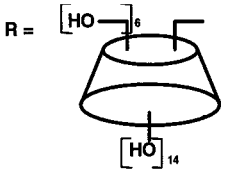
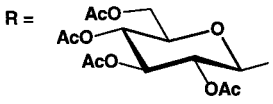


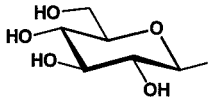
6a - 9a



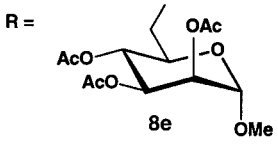
6b - 9b



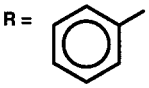
7c, 8c



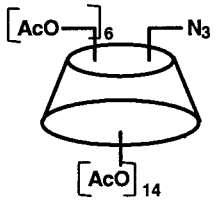
7d, 8d



8e



7f - 9f



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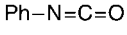

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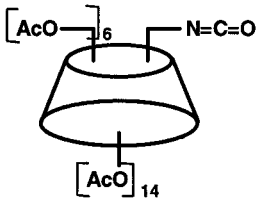
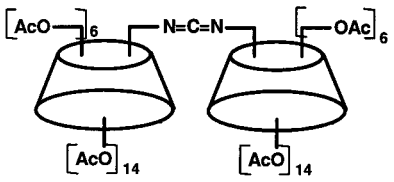


11

11, but without CO_2, which gave the new carbodiimide **12** as a white solid, as unambigously indicated by its IR (−N=C=N− at 2139 cm^{-1}, no −N=C=O at 2267 cm^{-1}) and ^{13}C-NMR data (−N=C=N− at δ 132.1).

Similarly to the synthesis of **12**, nonsymmetrical β-cyclodextrin-containing carbodiimides could be obtained. Thus, on treatment of 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl azide with Ph_3P in the presence of **11**, the mixed carbodiimide **17** was formed in 98% yield. The structure of the latter was established by the IR spectrum (2139 cm^{-1}) and the transformation to the nonsymmetrical urea **18** on treatment with AcOH in $CHCl_3$ solution.

Reaction of **11** with the cyclams **1**–**4** by *Route II* (see *Scheme*) afforded, as expected, the same ureas **6a**–**9a** as those obtained by the phosphine imide method (*Route I*). The isocyanate method, however, resulted in better yields and with easier purification of the products. The IR, NMR, and ES-MS data of the new products **6a**–**9a** (see *Exper. Part*) were in agreement with the proposed structures (IR: characteristic C=O and N−H frequencies of urea, besides ester bands). The highly complex ^{1}H-NMR spectra (strong splitting and overlapping of H−C(1) to (HO_2(6) of the glucosyl subunits and of the cyclam protons at δ 3.4–5.6), however, did not allow complete and unambiguous attribution.



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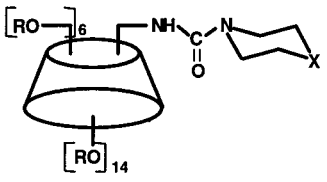
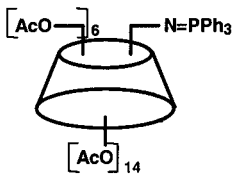


13 R = Ac, X = O
14 R = Ac, X = NMe
15 R = H, X = NMe



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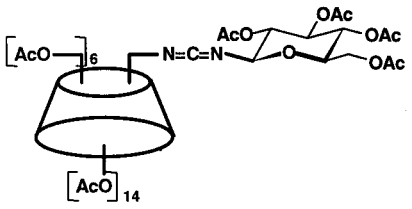

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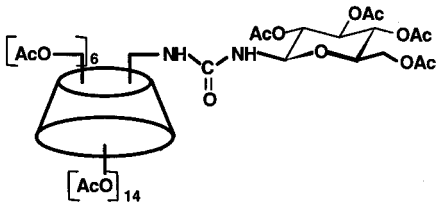

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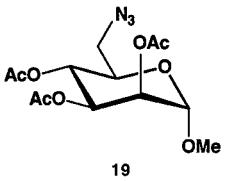

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To increase the solubility of the cyclodextrin derivatives in H_2O, the unprotected compounds **6b**–**9b** were prepared in excellent (*ca.* 90%) yields by *Zemplén* deacetylation of the icosa-*O*-acetyl derivatives **6a**–**9a**.

As we planned to study the role of sugar moieties in the complexation of cyclam derivatives, we synthesized ureas **6**–**8**, in which the β-CD moiety was replaced by a monosaccharide unit. Since the corresponding azidosugars are more easily avalaible than the isocyanates, we used the phosphine imide method (*Route I*). Thus, from 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl azide [9] and methyl 6-azido-6-deoxy-2,3,4-tri-*O*-acetyl-α-D-mannopyranoside (**19**), we obtained the new protected sugar urea cyclams **7c** and **8c** and **8e**, respectively. Conventional deblocking of the acetylated glucose derivatives **7c** and **8c** led to the non-protected **7d** and **8d**, respectively. The structures of all these derivatives were supported by their IR, ^{1}H- and ^{13}C-NMR, and ES-MS data (see *Exper. Part*).

Structure and Conformation of Urea-Like Cyclams. As mentioned above, the synthesized phenylurea model compounds **7f** and **8f** offered a good opportunity to gain deeper insight into the conformation of the urea-like cyclam family. The IR spectrum of the tris-phenylurea derivative **7f** in MeOH suggested strong intramolecular H-bonds between the carbonyl O-atom and the NH_2 protons (strong triplicate $\tilde{\nu}$ (C=O) at 1653 and 1623 cm^{-1}, *Fig. 1*). This was confirmed by the ^{1}H-NMR spectrum of **7f** recorded in $CHCl_3$ after addition of D_2O, which showed a very low exchange of the urea NHs, the signal intensities being unmodified after 5 h and decreased by only 30% after 10 h.

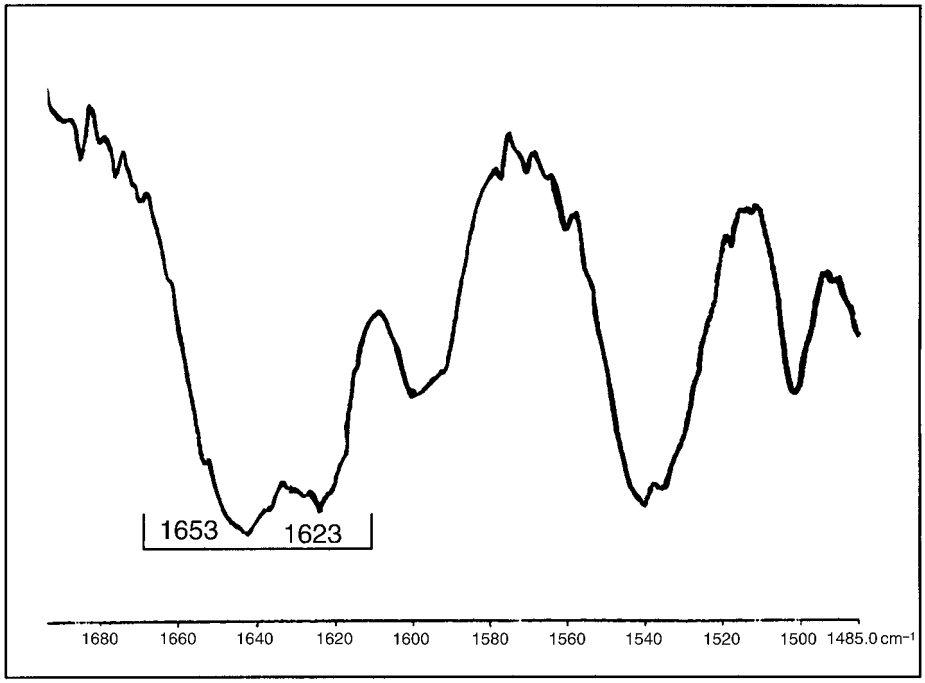

Fig. 1. *IR Spectrum of* **7f** *in MeOH: carbonyl region*

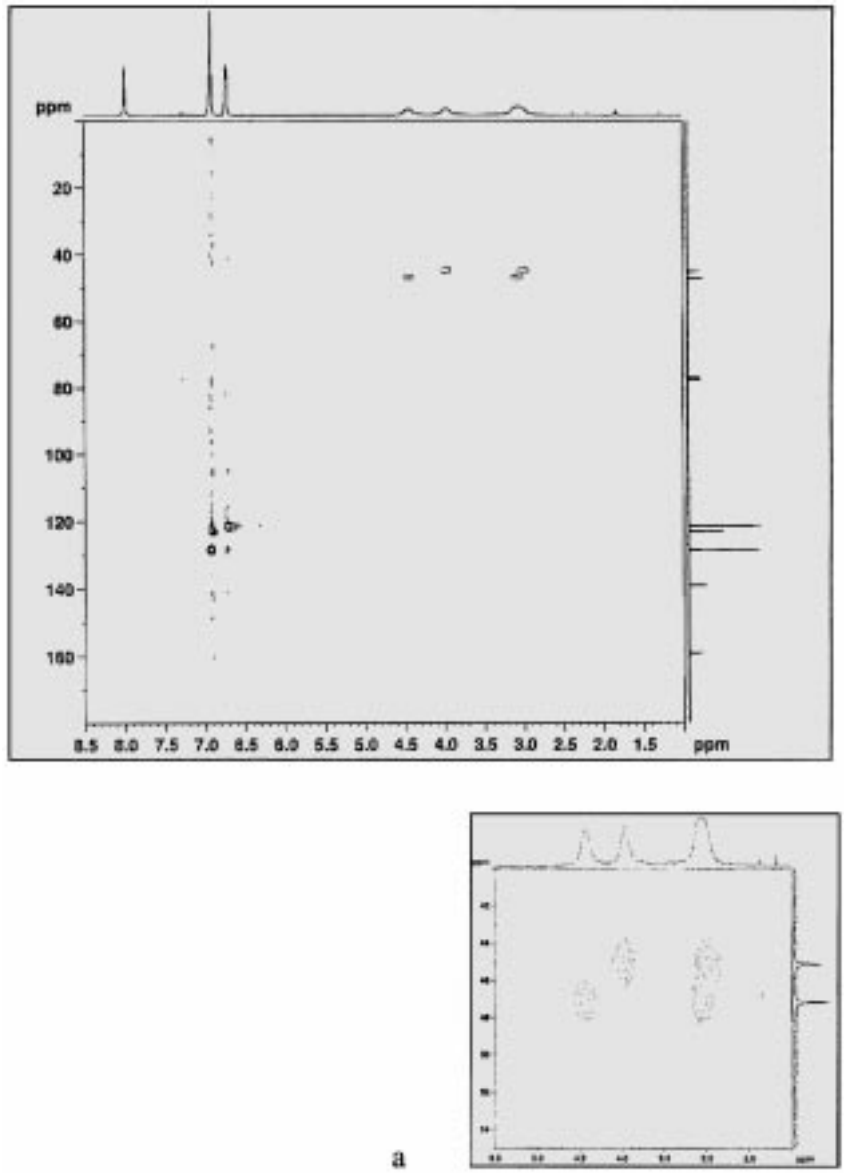

Fig. 2. *HSQC Plot of* **7f**. a) Protons of the cyclam moiety.

Furthermore, the HSQC plot of **7f** (*Fig. 2*) revealed nonequivalent CH_2 protons of the macrocycle (3 broad *m* at δ 3.09, 4.00, and 4.45), despite the C_{3v} symmetry of the molecule. This can be explained by a shielding effect on the CH_2 protons near one of the carbonyl groups and is very probably due to the different orientation 'in/out' of the carbonyl groups with respect to the macrocyclic azacrown. Such a situation determines a possible strong 'bifide' H-bond occurring between one CO 'in' and the two NHs of the

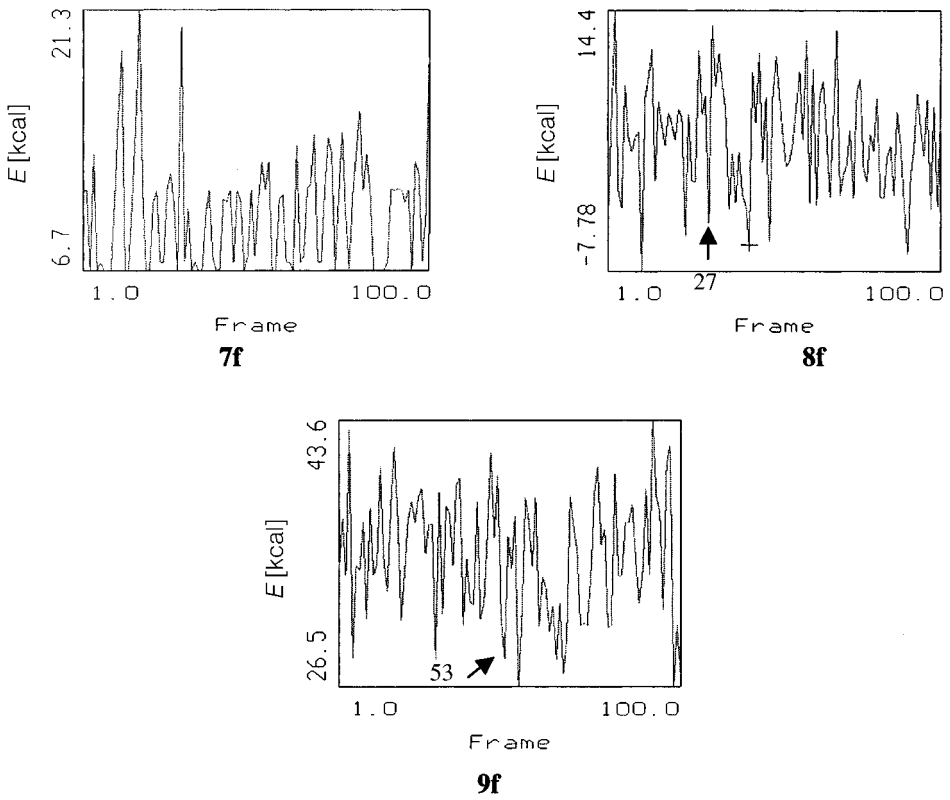

Fig. 3. *Samples of 100 conformations obtained by the simulated annealing experiment with DISCOVER® on* **7f**–**9f**

other two 'out' COs of the urea moieties. From a conformational point of view, the presence of such a H-bond should organize the molecule in a spatial 'basket' form. This feature was supported by molecular-dynamics computations conducted on **7f**–**9f** and on the β-CD derivative **7b** with software from *Biosym/MSI* of *San Diego Dynamics*. Calculations and minimizations were done with the DiscoverIII® program [10] and the AMBER [11] force field. In each case, a simulated high-temperature annealing experiment *in vacuo* (2000–300K) led to a representative sample of the 100 most stable conformations for **7f**–**9f** and **7b** (*Fig. 3*). Concerning **7f**, most of the conformers rapidly reached the same lowest energies (6.7 kcal mol^{-1}) the corresponding structures of which were printed out from the InsightII® molecular-modelling system. Looking at any of these lowest-energy conformers, one can see (*Fig. 4, a*) that the (phenylamino)carbonyl arms are lying on the same side of the azacrown mean plane. Moreover, in any of them, the predicted 'in' systematic orientation of one of the carbonyl groups with respect to the others is present, these others being 'out' oriented. As for **7f**, the calculations made on **8f** and **9f** gave two sets of representative samples from which the ten more stable conformations were retained. Among them, two structures with configurational singularities were selected, *i.e.* conformation *27* for **8f**

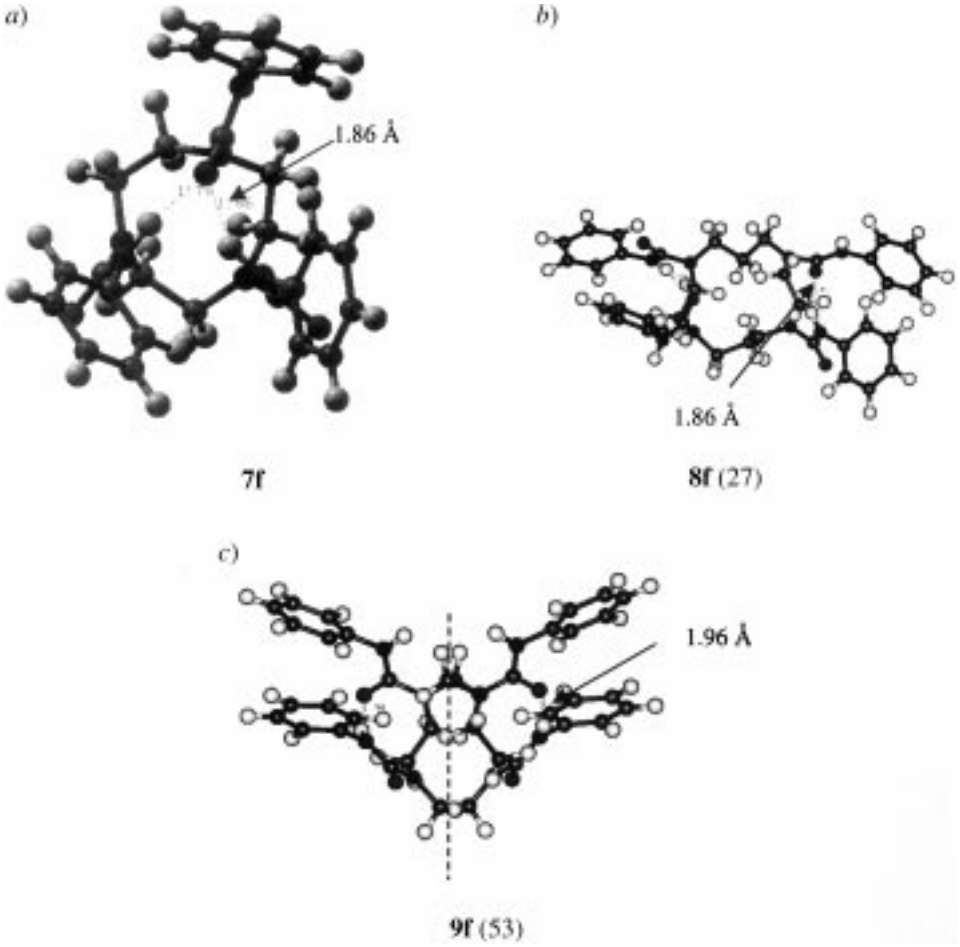

Fig. 4. *Ball-and-stick structures of* **7f–9f**: *three remarkable conformations obtained by the Insight II® molecular-modelling program*

and *53* for **9f** (*Fig. 4,b* and *c*). Conformation *27* of **8f** has a chair-like azamacrocycle with the Ph groups in alternating positions with respect to the mean plane of the macrocycle. One can notice the presence of two strong symmetrical H-bonds (1.86 and 1.85 Å) between two urea functions on each side of the macrocycle that stabilize this conformation. The latter corresponds to the crystal structure of **8f** (see below, *Fig. 5*). Similarly, in conformation *53* of **9f** (*Fig. 4,c*), two strong symmetrical H-bonds (1.96 Å) contribute to stabilize the particular geometry of a 'butterfly' arrangement with a cyclam macrocyclic twist, which determines a new plane of symmetry for the molecule.

Structural Results. Structural data are still limited to the crystal structure of **8f**, although the crystal structure of **7f** was also investigated. Unfortunately, in the latter case, the structure could not be resolved because of the too-high residual thermal agitation of the phenyl-ring atoms, which led to inaccurate refinements. The

experimental procedures for data collection, refinements, and crystal-structure data for **8f** are summarized in the *Table*. As seen in *Fig. 6*, the compound crystallizes with four solvent (DMSO) molecules in the unit cell. Some disorder exists in the crystal structure and was due to the important thermal agitation of the complexed DMSO molecules; it explains the uncertainty of their atom positions, as shown in the ORTEP representation (*Fig. 5*). The conformation in the crystal closely resembles conformation *27* found by the calculations on **8f** and confirms the effective presence of two strong symmetrical H-bonds O(1)–H–N(4) of 1.50 Å stabilizing the 'chair-like' conformation of the macrocycle and determining the spatial orientation of the carbonyl urea functions. Interestingly, alternating phenyl-ring positions similar to those found by the calculations are also observed in the crystal of **8f**.

Table. *Crystallographic Data for Compound* **8f**[a)]

	8f
Crystallized from	DMSO/MeOH
Empirical formula	$C_{42}H_{56}N_8O_6S_2$
	$C_{38}H_{44}N_8O_4 \cdot 2\,C_2H_6OS$
M_r	833.09
Crystal color	colorless
Crystal form	prisms
Crystal size [mm]	$0.20 \times 0.16 \times 0.14$
Temp. [K]	294
Crystal system	monoclinic
Space group	*P*2/*n*
Z	2
Volume [Å^3]	2216.6(7)
a [Å]	13.513(1)
b [Å]	8.527(1)
c [Å]	19.399(2)
α [°]	90.000
β [°]	97.365(6)
γ [°]	90.000
Density [g cm^{-3}]	1.25
F(000)	888
μ(MoK_α) [mm^{-1}]	0.174
θ_{max} [°]	30.48
Scan type	Φ scans
hkl limits	0.17; 0.12; −27; 27
Number of measured reflections	11502
Number of reflections used ($I > 3\sigma I$)	2066
Number of variables	259
R	0.109
wR	0.141
Goodness of fit	1.376
Last Δ_{max}/σ	0.0001
$\Delta\rho$ (max; min) [e Å^{-3}]	0.83; −0.21

[a)] The crystallographic data for **8f** have been deposited with the *Cambridge Crystallographic Data Centre* as deposition No. CCDC-125728. Copies of the data can be obtained, free of charge, on application to the CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: +44(1223)336033; e-mail: deposit@ccdc.cam.ac.uk).

[b)] Weighting scheme: $\Sigma w\ |F_0|-|F_c|^2$; $w = 4\ F_0^2/[\sigma^2(F_0)^2 + (0.0016\ F_0)^4] + 4.0$.

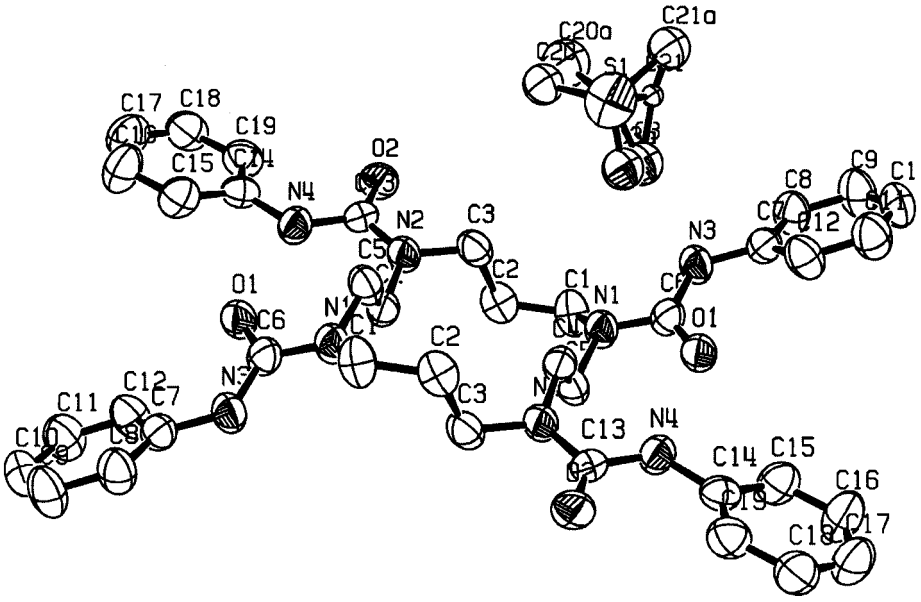

Fig. 5. *X-Ray crystal structure of* N,N′,N″,N‴*-tetraphenyl-1,4,8,11-tetraazacyclotetradecane-1,4,8,11-tetracarboxamide* (**8f**): *ORTEP representation* (ellipsoids with 50% probability)

Conclusion. – We synthesized for the first time a series of urea-like cyclams in a straightforward and safe manner and in moderate to good yields by means of the 'phosphine imide, one-pot' procedure, which avoids an isocyanate-preparation step. Nevertheless, the same reaction carried out under carefully controlled modified conditions, allowed the efficient preparation of symmetrical and/or unsymmetrical isocyanates and carbodiimides of sensitive sugar derivatives. The structure analyses of these compounds also revealed the fundamental role of intramolecular urea H-bonds played in the conformational equilibrium of urea-like cyclams. Very promising extensions of this reaction are currently under investigation with the aim to obtain an efficient functionalization of other sensitive natural products or, *e.g.*, to synthesize new supramolecular multi-cyclodextrin scaffolds. Considering the urea-like cyclam cyclodextrin derivatives, we have recently revealed their interesting complexation properties [12] with lanthanides. In our opinion, these latter studies deserve to be extended to different cations.

The *National Foundation for Scientific Research* (OTKA T14939 and T23371) and the *ARC Association* are acknowledged for financial support. We are endebted to Prof. *Jean Fischer* and Dr. *J. de Cian* for the X-ray measurements.

Experimental Part

General. TLC: silica gel *60* F_{254} (*E. Merck*) plates; detection by UV light and by charring with H_2SO_4. Column chromatography (CC): silica gel (*E. Merck*, 0.020–0.043 mesh). $[\alpha]_D$: *Zeiss Polamat-A* and *Perkin-Elmer 141* polarimeters. IR Spectra (KBr): *Nicolet 205* spectrometer. ^{1}H- and ^{13}C-NMR Spectra: *Varian VXR-400* or *-250* spectrometers; δ in ppm rel. to $SiMe_4$, some assignments by 2D-HETCOR experiments; locants 1^A, 2^A *etc.* refer to the linker-connected glucose unit of β-CD and locants 1^{B-G}, 2^{B-G} *etc.* to the remaining glucose units. MS: NBA = 3-nitrobenzyl alcohol.

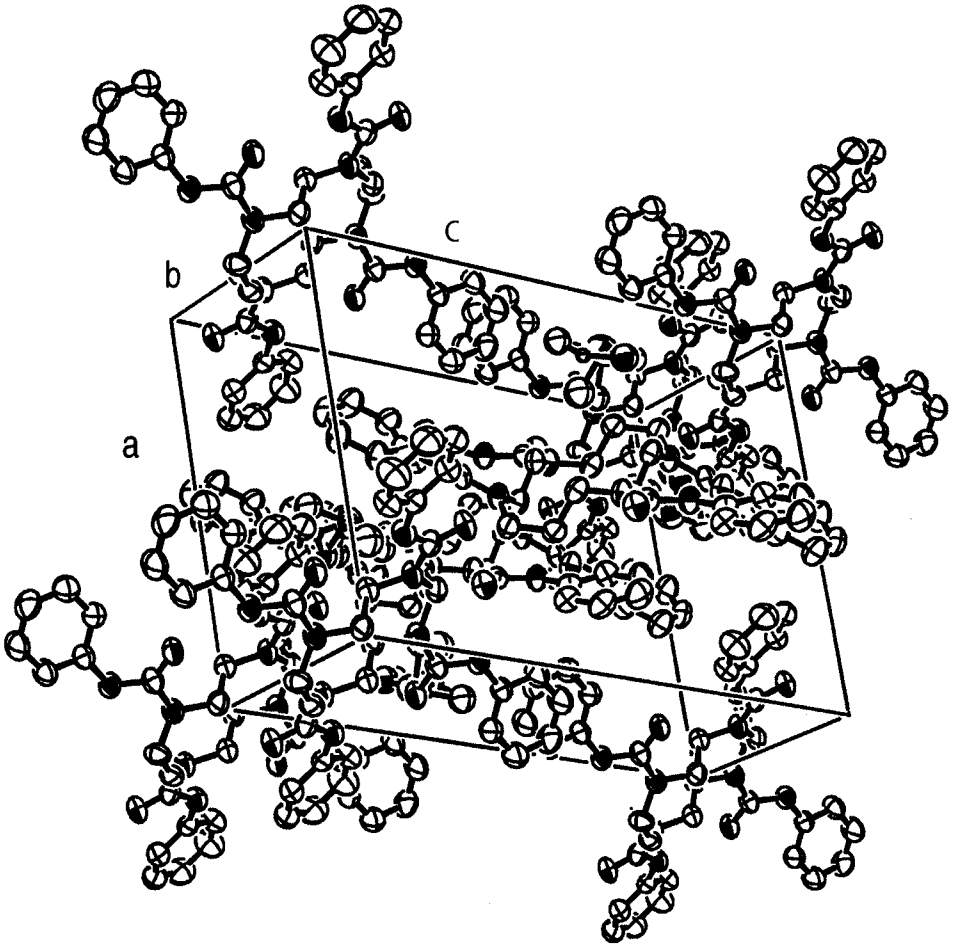

Fig. 6. *View of the unit cell of* N,N′,N″,N‴*-tetraphenyl-1,4,8,11-tetraazacyclotetradecane-1,4,8,11-tetracarboxamide* (**8f**)

6^A-C,*$6^{A'}$*-C-*[Piperazine-1,4-diylbis(carbonylamino)]bis[6^A-deoxy-β-cyclodextrin 2^A,2^B,2^C,2^D,2^E,2^F,2^G,3^A,3^B,3^C,3^D,3^E,3^F,3^G,6^B,6^C,6^D,6^E,6^F,6^G-Icosaacetate]* (**6a**). *Method a:* PPh_3 (0.66 g, 2.5 mmol, 30 equiv.) was added to a soln. of **5** (0.5 g, 0.25 mmol, 3 equiv.) in DMF (40 ml). Then piperazine (**1**; 0.0072 g, 0.083 mmol, 1 equiv.) in DMF (5 ml) was added, and CO_2 was bubbled gently through the mixture. The soln. was stirred for 24 h at r. t. After evaporation of the DMF, the residue was washed with H_2O (50 ml) and then extracted with CH_2Cl_2 (3 × 50 ml). The org. layer was dried ($MgSO_4$) and evaporated and the crude product purified by CC (CH_2Cl_2/MeOH 98:2): pure **6a** (0.19 g, 56%). White powder. R_f (CH_2Cl_2/MeOH 98:2) 0.26.

Method b: Piperazine (**1**; 0.0021 g, 0.025 mmol) in anh. toluene (12 ml) was added dropwise to isocyanate **11** (0.100 g, 0.05 mmol, 2 equiv.) in anh. toluene (6 ml). The mixture was stirred for 24 h at r.t. Then the product was precipitated by addition of cyclohexane and dried in a desiccator over P_2O_5: pure **6a** (0.10 g, 94%). White powder. R_f (AcOEt/acetone 70:30) 0.26, R_f (AcOEt/EtOH/H_2O 45:5:3) 0.4. IR (KBr): 3459 (NH), 1748 (C=O, Ac), 1654 (C=O, urea). ^{1}H-NMR ($CDCl_3$): 6.12 (*s*, 2 NH); 5.26–5.18 (*m*, 14 H, H–C(3^A), H–C($3^{B–G}$)); 5.13 (*s*, 1 H, H–C(1^A)); 5.01–4.98 (*m*, 12 H, H–C($1^{B–G}$)); 4.95 (*s*, 1 H, H–C($1'^A$)); 4.78–4.68 (*m*, 14 H, H–C(2^A), H–C($2^{B–G}$)); 4.54–4.44 (*m*, 24 H, H–C($6^{B–G}$)); 4.35–4.33 (*m*, 2 H, H–C(5^A)); 4.26–4.11 (*m*, 12 H,

H–C(5$^{B–G}$)); 3.71–3.58 (*m*, 14 H, H–C(4^{A}), H–C(4$^{B–G}$)); 3.58–3.55 (*m*, 4 H, H–C(6^{A})); 3.37 (*s*, 4 CH_2(pip)); 2.09–1.91 (*m*, 120 H, MeCO). ^{13}C-NMR ($CDCl_3$): 171–170 (Me*C*O); 158 (*C*ONH); 98–97 (C(1$^{A–G}$)); 78–77 (C(4^{A}), C(4$^{B–G}$)); 72–71–70 (C(2^{A}), C(3^{A}), C(5^{A}), C(2$^{B–G}$), C(3$^{B–G}$), C(5$^{B–G}$)); 63 (C(6$^{B–G}$)); 53 (C(6^{A})); 44 (CH_2(pip)); 21 (*Me*CO). ES-MS: 1043 ([*M* + Na − 2 H]$^{4+}$); 1384 ([*M* + Na]$^{3+}$); 2065 ([*M* + Na]$^{2+}$). Anal calc. for $C_{170}H_{228}N_4O_{110}$ (4085.24): C 49.95, H 5.62, N 1.37; found: C 49.03, H 5.71, N 1.41.

6^{A}-C,6$^{A'}$-C-[Piperazine-1,4-diylbis(carbonylamino)]bis[6^{A}-deoxy-β-cyclodextrin] (**6b**). To a soln. of **6a** (0.151 g, 0.037 mmol) in MeOH (5 ml), 1M NaOMe (1.48 ml, 40 equiv.) was added at 0° under Ar. The mixture was stirred for 1 h at 0° and 1 h at r.t. and then neutralized by addition to a batch of ion-exchange resin *Amberlyst IRN 77*. After filtration and evaporation, the residue was lyophilized: **6b** (0.07 g, 80%). White snow-like powder. R_f (dioxane 25% NH_3 soln. 10:7) 0.5. IR (KBr): 3600–3420 (NH, OH), 1651 (C=O, urea). ^{13}C-NMR (D_2O/CD_3OD): 158 (NCONH); 101 (C(1)); 82 (C(4)); 74–73 (C(2), C(3), C(5)); 60 (C(6^{B})); 42 (C(6^{A})); 40 (CH_2(piperazine)). ES-MS: 2406 ([*M* + H]$^{+}$), 1202 ([*M* + H]$^{2+}$). Anal. calc. for $C_{90}H_{148}N_4O_{70}$ (2404.5): C 44.93, H 6.20, N 2.33; found: C 44.00, H 6.06, N 2.00.

6^{A}-C,6′^{A}-C,6″^{A}-C-[(Octahydro-1H-1,4,7-triazonine-1,4,7-triyl)tris(carbonylamino)]tris[6^{A}-deoxy-β-cyclodextrin 2^{A},2^{B},2^{C},2^{D},2^{E},2^{F},2^{G},3^{A},3^{B},3^{C},3^{D},3^{E},3^{F},3^{G},6^{B},6^{C},6^{D},6^{E},6^{F},6^{G}-Icosaacetate] (**7a**). *Method a:* To PPh_3 (0.66 g, 2.5 mmol, 40 equiv.) and **5** (0.5 g, 0.25 mmol) in DMF (70 ml) under Ar, octahydro-1*H*-1,4,7-triazonine (**2**; (0.0044 g, 0.062 mmol) in DMF (5 ml) was added and dry CO_2 bubbled simultaneously through the soln. The mixture was stirred for 24 h at r.t. and then evaporated. H_2O (50 ml) was added to the residue and the mixture extracted with CH_2Cl_2 (3 × 50 ml). The org. layer was dried ($MgSO_4$) and evaporated and the crude product purified by CC (CH_2Cl_2/MeOH 98:2): pure **7a** (0.12 g, 30%). White powder. R_f (CH_2Cl_2/MeOH 98:2) 0.3.

Method b: A soln. of **2** (0.0012 g, 0.017 mmol) in toluene (12 ml) was added dropwise to **11** (0.10 g, 0.051 mmol, 3 equiv.) in DMF (6 ml). The mixture was stirred for 24 h at r.t. The soln. was concentrated to 1/3 of its initial volume and the product precipitated by addition of cyclohexane. After filtration and drying, the crude product was purified by CC (AcOEt/acetone 7:3): pure **7a** (0.051 g, 51%). White powder. R_f (AcOEt/acetone 7:3) 0.44. IR (KBr): 3459 (NH), 1748 (C=O, Ac), 1654 (C=O, urea). ^{1}H-NMR ($CDCl_3$): 5.22 (*m*, 21 H, H–C(3)); 5.10 (*d*, 2 H, H–C(1^{A})); 4.99 (*d*, 1 H, H–C(1′^{A})); 4.95 (*m*, 18 H, H–C(1$^{B–G}$)); 4.76–4.60 (complex *m*, 21 H, (H–C(2^{A}), H–C(2$^{B–G}$)); 4.22–4.12 (complex *m*, 3 H, H–C(5^{A})); 4.05 (*m*, 18 H, H–C(5^{B})); 3.70–3.55 (complex *m*, 21 H, H–C(6^{A})); 2.10–2.00 (several *s*, 180 H, 60 MeCO). ^{13}C-NMR ($CDCl_3$): 171–170 (Me*C*O); 158 (NCO–NH); 97–96 (C(1^{A})), C(1$^{B–G}$)); 77–76 (C(4^{A})), C(4$^{B–G}$)); 72–69 (C(2^{A}), C(3^{A}), C(5^{A}), C(2$^{B–G}$), C(3$^{B–G}$), C(5$^{B–G}$)); 63–62 (C(6$^{B–G}$), CH_2N (cyclam)); 42 (C(6^{A})); 21 (*Me*CO). ES-MS: 2067.7 ([*M* + 2 H^{+} + Na^{+}]$^{3+}$), 2045.6 ([*M* + 3 H^{+}]$^{3+}$). Anal. calc. for $C_{255}H_{342}N_6O_{165}$ (6127.0): C 49.95, H 5.62, N 1.37; found: C 48.95, H 5.68, N 1.15.

6^{A}-C,6′^{A}-C,6″^{A}-C-[(Octahydro-1H-1,4,7-triazonine-1,4,7-triyl)tris(carbonylamino)]tris[6^{A}-deoxy-β-cyclodextrin] (**7b**). As described for **6b**, with **7a** (0.10 g, 0.016 mmol), MeOH (5 ml), and 1M NaOH (979 µl, 60 equiv.): **7b** (0.047 g, 81%). White snow-like powder. R_f (dioxane/25% NH_3 soln. 10:7) 0.5. IR (KBr): 3708–3384 (NH, OH), 1651 (C=O, urea). ^{1}H-NMR ($CDCl_3$): 5.22 (*m*, 21 H, H–C(3)); 5.10 (*d*, 2 H, H–C(1^{A})); 4.99 (*d*, 1 H, H–C(1^{A}); 4.95 (*m*, 18 H, H–C(1$^{B–G}$)); 4.76–4.60 (complex *m*, 21 H, H–C(2^{A}), H–C(2$^{B–G}$)); 4.22–4.12 (complex *m*, 3 H, H–C(5^{A})); 4.05 (*m*, 18 H, H–C(5$^{B–G}$)); 3.70–3.55 (complex *m*, 21 H, H–C(6^{A})). ^{13}C-NMR (D_2O/CD_3OD): 158 (NCONH); 102 (C(1)); 82 (C(4)); 74–73 (C(2), C(3), C(5)); 61 (C(6$^{B–G}$)); 42 (C(6^{A})); 41 (CH_2 (cyclam)). ES-MS: 1206 ([*M* + 3 H]$^{3+}$), 1227 ([*M* + 2 H + Na]$^{3+}$). Anal. calc. for $C_{135}H_{222}N_6O_{105}$ (3607.2): C 44.93, H 6.20, N 2.33; found: C 44.00, H 6.00, N 2.00.

N,N′,N″-*[(Octahydro-1H-1,4,7-triazonine-1,4,7-triyl)tricarbonyl]tris[2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosylamine]* (**7c**). Through a soln. of **2** (0.029 g, 223 mmol) in anh. toluene (10 ml), anh. CO_2 was gently bubbled for 30 min. Then, 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl azide (0.250 g, 0.67 mmol, 3 equiv.) and PPh_3 (0.193 g, 0.73 mmol, 3.3 equiv.) were added to the mixture, and CO_2 bubbling was continued for 24 h. The soln. was concentrated to 1/2 the volume under vacuum, and cyclohexane was added to the residue. After filtration, the filtrate was evaporated and the residue purified by CC (AcOEt, then AcOEt/MeOH 3:1): pure **7c** (0.28 g, 24%). White powder. R_f (AcOEt) 0.2. IR (KBr): 3850–2945 (NH), 1731 (C=O, Ac), 1651 (C=O, urea). ^{1}H-NMR ($CDCl_3$): 5.78 (3 H, ^3J(1,2) = 8 H–C(1)); 5.34 (*t*, *J*(1,2), ^3J(5,4) = ^3J(5,6) = 8, 3 H, H–C(5)); 5.15 (*t*, ^3J(2,1) = ^3J(2,3) = 8, 3 H, H–C(2)); 5.05 (*t*, ^3J(4,3) = ^3J(4,5) = 8, 3 H, H–C(4)); 4.95 (*t*, ^3J(3,4) = ^3J(3,2) = 8, 3 H, H–C(3)); 4.38 (*dd*, ^3J(6,5) = 4, ^2J(6,6′) = 12, 3 H, H–C(6)); 4.29 (*dd*, ^3J(6,5) = 4, ^2J(6′,6) = 12, 3 H, H–C(6′)); 3.40 (*m*, 6 H, CH_2 (cyclam)); 2.12 (*m*, 18 H, MeCO, CH_2 (cyclam)). ^{13}C-NMR ($CDCl_3$): 171–170 (Me*C*O); 157 (CONH); 81 (C(1)); 77–76 (C(4)); 74, 73, 72, 71, 68, 67 (C(2), C(3), C(5)); 62–61 (C(6)); 49 (CH_2 (cyclam)); 21 (*Me*CO). ES-MS: 1250 (M^{+}). Anal. calc. for $C_{51}H_{72}N_6O_{30}$ (1248.4): C 49.04, H 5.81, N 6.73; found: C 49.00, H 5.60, N 6.60.

N,N′,N″-*[(Octahydro-1H-1,4,7-triazonine-1,4,7-triyl)tricarbonyl]tris[β-D-glucopyranosylamine]* (**7d**). As described for **6b** with **7c** (0.030 g, 0.024 mmol), in MeOH (5 ml), and 1M NaOMe (0.28 ml, 12 equiv.): **7d**

(0.012 g, 70%). White snow-like powder. R_f (dioxane/25% NH_3 soln. 10:7) 0.5. IR (KBr): 3708–3384 (NH, OH), 1651 (C=O, urea). ^{13}C-NMR (D_2O): 157 (CONH); 81 (C(1)); 78–77 (C(4)); 74, 73.5, 73, 72, 71, 68, 67 (C(2), C(3), C(5)); 62–61 (C(6)); 50 (CH_2N (cyclam)). ES-MS: 745 ($[M+H]^+$), 768 ($[M+Na]^+$); 783 ($[M+K]^+$).

Octahydro-N,N′,N′-*triphenyl-1*H-*1,4,7-triazonine-1,4,7-tricarboxamide* (**7f**). A soln. of **2** (0.036 g, 0.28 mmol, 1 equiv.) in toluene (7 ml) was added dropwise under Ar at r.t. to a soln. of phenyl isocyanate (**10**; 0.10 g, 0.839 mmol, 3 equiv.) in toluene (12 ml). After few minutes, a white precipitate appeared. The mixture was stirred for 24 h. Petroleum ether was then added to the soln. to complete precipitation of the product, which was filtered and dried overnight in a dessicator: pure **7f** (0.11 g, 78%). White powder. R_f (CH_2Cl_2/MeOH 95:5) 0.46. IR (KBr): 3280 (NH), 1644 (C=O). ^{1}H-NMR ($CDCl_3$): 7.99 (*s*, 1 H, NH)); 6.92 (*d*, $^3J=2$, 6 H, H_m); 6.91 (*d*, $^3J=2$, 3 H, H_p); 6.73–6.71 (*m*, $^3J=2$, 6 H, H_o); 4.45 (*m*, 3 H, H–C(3) (cyclam)); 4.00 (*m*, 3 H, H–C(3′ (cyclam)); 3.10 (*m*, 6 H, H–C(2), H–C(2′) (cyclam)). ^{13}C-NMR ($CDCl_3$): 159 (CONH); 139 (C(1)); 128 (C(3)); 123 (C(4)); 121 (C(2)); 47 (CH_2 (cyclam)); 45 (CH_2 (cyclam)). FAB-MS (NBA): 487.5 ($[M+H]^+$).

6^A-C,*6′^{A}*-C,*6″^{A}*-C,*6‴^{A}*-C-[*1,4,8,11-Tetraazacyclotetradecane-1,4,8,11-tetrayltetrakis(carbonylamino)]tetrakis-[6^A-deoxy-β-cyclodextrin [2^A,2^B,2^C,2^D,2^E,2^F,2^G,3^A,3^B,3^C,3^D,3^E,3^F,3^G,6^B,6^C,6^D,6^E,6^F,6^G-Icosaacetate]* (**8a**). *Method a:* To a soln. of **5** (2.0 g, 1 mmol, 5 equiv.) in DMF (100 ml) under Ar, PPh_3 (2.1 g, 8 mmol, 40 equiv.) and then 1, 4,8,11-tetraazacyclotetradecane (**3**; 0.040 g, 0.2 mmol) were added, while bubbling dry CO_2 through the soln. The mixture was stirred for 24 h under CO_2 bubbling, and then evaporated. The residue was treated with H_2O (50 ml) and extracted with CH_2Cl_2 (3 × 50 ml), the org. phase dried ($MgSO_4$) and evaporated, and the residue purified by CC (CH_2Cl_2/MeOH 98:2): pure **8a** (0.5 g, 30%). White powder. R_f 0.3 (CH_2Cl_2/MeOH 98:2).

Method b: A soln. of **3** (0.025 mmol, 0.0049 g, 1 equiv.) in toluene was added dropwise to a soln. of **11** (0.1 mmol, 0.2 g, 4 equiv.) in toluene (12 ml), and the mixture was heated at 75° for 48 h. After cooling, cyclohexane was added. The resulting precipitate was filtered, washed with cyclohexane, and dried under vacuum: **8a** (0.21 g, 48%). White powder. R_f (CH_2Cl_2/MeOH 95:5) 0.38. IR (KBr): 3459 (NH); 1748 (C=O, Ac); 1654 (C=O, urea). ^{1}H-NMR ($CDCl_3$): 5.32 (*m*, 28 H, H–C(3$^{A–G}$)); 5.22 (*d*, 2 H, H–C(1^A)); 5.08 (*m*, 24 H, H–C(1$^{B–G}$)); 5.00 (*d*, 2 H, H–C(1′^{A})); 4.92 (*t*, 2 H, CH_2 (cyclam)); 4.87 (*dd*, 2 H, H–C(2^A)); 4.80 (*m*, 24 H, H–C(2$^{B–G}$)); 4.71 (*dd*, 2 H, H–C(2^A)); 4.65–4.50 (complex *m*, 52 H, H–C(6$^{B–G}$)), CH_2 (cyclam)); 4.29–4.22 (*t*, 4 H, H–C(5^A)); 4.12 (*m*, 24 H, H–C(5$^{B–G}$)); 4.04 (*m*, 2 H, CH_2 (cyclam)); 3.80–3.65 (complex *m*, 28 H, H–C(4^A), H–C (4^D)); 3.58 (*m*, 8 H, H–C(6^A)); 2.10–2.00 (several *s*, 240 H, 80 MeCO)). ^{13}C-NMR ($CDCl_3$): 170–169 (Me*C*O); 158 (NCONH); 97–96 (C(1A), C(1$^{B–G}$)); 77–76 (C(4^A), C(4$^{B–G}$)); 71–69 (C(2^A), C(3^A), C(5^A), C(2$^{B–G}$), C(3$^{B–G}$), C(5$^{B–G}$)); 63–62 (C(6$^{B–G}$), CH_2N (cyclam)); 43 (C(6^A)); 21 (*Me*CO). ES-MS: 2074 ($[M+Na]^{4+}$), 2051 ($[M+2H]^{4+}$). Anal. calc. for $C_{342}H_{460}N_8O_{220}$ (8203.3): C 50.07, H 5.65, N 1.37; found: C 49.65, H 5.74, N 1.48.

6^A-C,*6′^{A}*-C,*6″^{A}*-C,*6‴^{A}*-C-*[1,4,8,11-Tetraazacyclotetradecane-1,4,8,11-tetrayltetrakis(carbonylamino)]tetrakis-[6^A-deoxy-β-cyclodextrin]* (**8b**). As described for **6b**, with **8a** (0.145 g, 0.017 mmol), MeOH (5 ml), and 1M NaOMe (1.41 ml, 80 equiv.): **8b** (0.08 g, 94%). White snow-like powder. R_f (dioxane/25% NH_3 soln. 10:7) 0.5. IR (KBr): 3708–3384 (NH, OH), 1651 (C=O, urea). ^{1}H-NMR (D_2O/CD_3OD): 5.32 (*m*, 28 H, H–C(3)); 5.22 (*d*, 2 H, H–C(1^A)); 5.08 (*m*, 24 H, H–C(1$^{B–G}$)); 5.00 (*d*, 2 H, H–C(1′^{A})); 4.92 (*t*, 2 H, CH_2 (cyclam)); 4.87 (*dd*, 2 H, H–C(2^A)); 4.80 (*m*, 24 H, H–C(2$^{B–G}$)); 4.71 (*dd*, 2 H, H–C(2^A)); 4.65–4.50 (complex *m*, 52 H, H–C(6$^{B–G}$), CH_2 (cyclam)); 4.29–4.22 (*t*, 4 H, H–C(5^A)); 4.12 (*m*, 24 H, H–C(5$^{B–G}$)); 4.04 (*m*, 2 H, CH_2 (cyclam)); 3.80–3.65 (complex *m*, 28 H, H–C(4$^{B–G}$)); H–C(4^A)); 3.58 (*m*, 8 H, H–C(6^A)). ^{13}C-NMR (D_2O/CD_3OD): 158 (NCONH); 100–99 (C(1)); 79 (C(4)); 71–69 (C(2), C(3), C(5)); 58 (C(6$^{B–G}$)); 58 (CH_2 (cyclam)); 47 (CH_2 (cyclam)); 40 (C(6^A)); 34 (CH_2 (cyclam)). ES-MS: 1205 (M^{4+}), 1227 ($[M+Na]^{4+}$).

N,N′,N″,N‴-*(1,4,8,11-Tetraazacyclotetradecane-1,4,8,11-tetrayltetracarbonyl)tetrakis[2,3,4,6-tetra*-O-*acetyl-β*-D-*glucopyranosylamine]* (**8c**). Through a soln. of **3** (0.027 g, 0.13 mmol) in toluene (10 ml), CO_2 was gently bubbled for 30 min. Then 2,3,4,6 tetra-*O*-acetyl-β-D-glucopyranosyl azide (0.25 g, 0.67 mmol, 5 equiv.) and PPh_3 (0.19 g, 0.73 mmol, 5.5 equiv.) in toluene (10 ml) were added, and CO_2 bubbling was continued for 24 h. The soln. was concentrated to H_2 volume and cyclohexane added. The precipitate formed was filtered and washed with cyclohexane. The filtrate was evaporated and the residue purified by FC (AcOEt, then AcOEt/MeOH 3:1): pure **8c** (0.20 g, 89%). White powder. R_f (AcOEt) 0.2. IR (KBr): 3850–3626 (NH), 1739 (C=O, Ac), 1654 (C=O, urea). ^{1}H-NMR (CD_3SOCD_3): 5.35–5.28 (H–C(1)); 4.92–4.87 (H–C(2), H–C(3)); 4.20–4.16 (H–C(5)); 4.06–3.96 (H–C(6)); 3.38–3.35 (H–C(3), H–C(4)); 3.34–2.89 (CH_2 (cyclam)); 4.80 (*d*, 4 H, H–C(1)); 3.80 (*s*, 4 H, H–C(6)); 3.65 (*s*, 4 H, H–C(6′)); 3.50 (*m*, CH_2 (cyclam)); 3.45 (*m*, CH_2 (cyclam)); 3.40–3.38 (*m*, 16 H, H–C(2), H–C(3), H–C(4), H–C(5)); 3.15–3.30 (*m*, CH_2 (cyclam)); 1.82–1.80 (*m*, CH_2 (cyclam)); 2.12 (*m*, 48 H, *Me*CO). ^{13}C-NMR (CD_3SOCD_3): 170–169 (Me*C*O); 156 (CONH); 80 (C(1)); 73–68 (C(2), C(3), C(4), C(5)); 62 (C(6)); 46 (CH_2 (cyclam)); 44 (CH_2 (cyclam)); 27 (CH_2 (cyclam)); 21 (*Me*CO).

ES-MS: 1694 ($[M+H]^+$), 1716 ($[M+H+Na]^+$). Anal. calc. for $C_{70}H_{100}N_8O_{40}$ (1692.6): C 49.64, H 5.95, N 6.62; found: C 49.50, H 5.11, N 6.52.

N,N′,N″,N‴-*(1,4,8,11-Tetraazacyclotetradecane-1,4,8,11-tetrayltetracarbonyl)tetrakis[β-*D*-glucopyranosylamine]* (**8d**). As described for **6b**, with **8c** (0.131 g, 0.077 mmol), MeOH (5 ml), and 1M NaOMe (17 equiv., 1.24 ml): **8d** (0.040 g, 51%). White snow-like powder. R_f (dioxane/25% NH_3 soln. 10:7) 0.45. IR (KBr): 3708–3384 (NH, OH); 1651 (C=O, urea). ^{1}H-NMR (D_2O): 5.35–5.28 (H–C(1)); 4.92–4.87 (H–C(2), H–C(3)); 4.20–4.16 (H–C(5)); 4.06–3.96 (H–C(6)); 3.38–3.35 (H–C(3), H–C(4)); 3.34–2.89 (CH_2 (cyclam)); 4.80 (*d*, 4 H, H–C(1)); 3.80 (*s*, 4 H, H–C(6)); 3.65 (*s*, 4 H, H–C(6′)); 3.50 (*m*, CH_2 (cyclam)); 3.45 (*m*, CH_2 (cyclam)); 3.40–3.38 (*m*, 16 H, H–C(2), H–C(3), H–C(4), H–C(5)); 3.15–3.30 (*m*, CH_2 (cyclam)); 1.82–1.80 (*m*, CH_2 (cyclam)). ^{13}C-NMR (D_2O): 156 (NCONH); 81(C(1)); 69–72–76 (C(2), C(3), C(4), C(5)); 62 (C(6), CH_2 (cyclam)); 46 (CH_2 (cyclam)); 27 (CH_2 (cyclam)). ES-MS: 1022 ($[M+H]^+$), 1043 ($[M+Na]^+$).

*6-*C,*6′-*C,*6″-*C,*6‴-*C-*[1,4,8,11-Tetraazacyclotetradecane-1,4,8,11-tetrayltetrakis(carbonylamino)]tetrakis-[methyl 2,3,4-*Tri-*O-acetyl-6-deoxy-*D*-mannopyranoside]* (**8e**). A mixture of **3** (0.028 g, 0.14 mmol, 1 equiv.) and a cat. amount of cesium carbonate in DMF (3 ml) was added to a mixture of **19** (0.250 g, 0.724 mmol, 5 equiv.) and PBu_3 (0.159 g, 0.79 mmol, 5.5 equiv.) in DMF (20 ml) under Ar. After the addition, Ar was replaced by a gentle bubbling of CO_2 which was continued for 24 h. The solvent was evaporated, H_2O (50 ml) added to the residue, the resulting soln. extracted with CH_2Cl_2 (3 × 50 ml), the org. layer dried ($MgSO_4$) and evaporated, and the crude product purified by CC (hexane, then hexane/AcOEt 1:1) pure **8e** (0.030 g, 14%). White powder. R_f (hexane/AcOEt 1:1) 0.25. IR (KBr): 3459 (NH); 1748 (C=O, Ac), 1654 (C=O, urea). ^{1}H-NMR ($CDCl_3$): 5.54 (*d*, $^3J(1,2)=8$, 4 H, H–C(1)); 5.25 (*t*, $^3J(2,3)=^3J(3,4)=8$, 4 H, H–C(3)); 4.98 (*t*, $^3J(2,1)=^3J(2,3)=8$, 4 H, H–C(2)); 4.78 (*t*, $^3J(5,6)=^3J(5,4)=8$, 4 H, H–C(5)); 4.65 (*t*, $^3J(4,5)=^3J(4,3)=8$, 4 H, H–C(4)); 4.21 (*dd*, $^3J(6,5)=4$, $^3J(6,6′)=12$, 4 H, H–C(6)); 4.19 (*dd*, $^3J(6′,5)=4$, $^3J(6′,6)=12$, 4 H, H–C(6′)); 3.24 (*s*, MeO, 12 H); 2.01 (*m*, 48 H, MeCO); 1.63 (*m*, 20 H, CH_2 (cyclam)). ^{13}C-NMR ($CDCl_3$): 171 (COMe); 158 (CONH); 99 (C(1)); 78 (C(4)); 70, 69, 67 (C(2), C(3), C(5)); 56 (C(6)); 48–46 (CH_2 (cyclam)); 42 (CH_2 (cyclam)); 28 (CH_2 (cyclam)); 25 (MeO); 21 (CO*Me*). ES-MS: 1603.5 ($[M+Na]^+$).

N,N′,N″,N‴-*Tetraphenyl-1,4,8,11-tetraazacyclotetradecane-1,4,8,11-tetracarboxamide* (**8f**). As described for **7f**, with **3** (0.042 g, 0.21 mmol, 1 equiv.), toluene (25 ml): **10** (0.10 g, 0.840 mmol, 4 equiv.), and toluene (12 ml) (8 days): pure **8f** (0.14 g, 98%). White powder. R_f (CH_2Cl_2/MeOH 95:5) 0.5. IR (KBr): 3313 (NH), 1651 (CO). ^{1}H-NMR ((D_6)DMSO): 8.30 (NH); 7.50 (*d*, $^3J(o,m)=7.6$, 8 H, H_o)); 7.18 (*dd*, $^3J(m,o)=7.6$, $^3J(m,p)=8.2$, 8 H, H_m); 6.93 (*t*, $^3J(p,m)=7.3$, 4 H, H_p)); 3.84 (*t*, 8 H, H–C(5) (cyclam)); 3.62 (*s*, 8 H, H–C(2) (cyclam)); 2.51 (*m*, 4 H, H–C(6) (cyclam)). ^{13}C-NMR ((D_6)DMSO): 156 (CONH); 140 (C_{ipso}); 129 (C_m); 123 (C_p); 121 (C_o); 48 (C(2) (cyclam)); 46 (C(5) (cyclam)); 29 (C(6) (cyclam)). FAB-MS (NBA): 677.2 ($[M+H]^+$).

*6^A-*C,*6′^{A}-*C,*6″^{A}-*C,*6‴^{A}-*C-*[1,4,7,10-Tetraazacyclododecane-1,4,7,10-tetrayltetrakis(carbonylamino)]tetrakis[6^A-deoxy-β-cyclodextrin [2^A,2^B,2^C,2^D,2^E,2^F,2^G,3^A,3^B,3^C,3^D,3^E,3^F,3^G,6^B,6^C,6^D,6^E,6^F,6^G-Icosaacetate]* (**9a**). To a soln. of **5** (2.0 g, 1.0 mmol, 5 equiv.) in DMF (100 ml) under Ar, PPh_3 (2.1 g, 8 mmol, 40 equiv.) and then 1,4,7,10-tetraazacyclododecane (**4**; 0.034 g, 0.2 mmol) were added, while bubbling CO_2 through the soln. The mixture was stirred 24 h under continuous CO_2 bubbling and then evaporated, the residue treated with H_2O (50 ml) and extracted with CH_2Cl_2 (3 × 50 ml), the org. layer dried ($MgSO_4$) and evaporated, and the residue purified by CC (CH_2Cl_2/MeOH 98:2): pure **9a** (0.49 g, 30%). White powder. R_f (CH_2Cl_2/MeOH 98:2) 0.3. IR (KBr): 3459 (NH), 1748 (C=O, Ac), 1654 (C=O, urea). ^{1}H-NMR ($CDCl_3$): 5.4–5.2, 4.9–4.7, 4.2–3.95 (3 m, 84 H, H–C(2^A), H–C(3^A), H–C(5^A), H–C(2^B), H–C(3^B), H–C(5^B)); 5.18–4.95 (*m*, 42 H, H–C(1^A), H–C(1^B), H–C(4^A), H–C(4^B)); 4.6–4.4, 4.4–4.2 (*m*, H–C(6^A), H–C(6^B)); 3.80–3.65 (*m*, 14 H, H–C(4^A), H–C(4$^{B–G}$)); 3.10 (CH_2 (cyclam)); 1.4 (CH_2 (cyclam)); 2.0–2.3 (*m*, 80 H, Me_3). ^{13}C-NMR ($CDCl_3$): 170 (*C*OMe); 158 (CONH); 99 (C(1)); 79 (C(4)); 70 (C(2), C(3), C(5)); 62 (C(6)); 37 (CH_2 (cyclam)); 31 (CH_2 (cyclam)); 20 (Me).

*6^A-*C,*6$^{A′}$-*C,*6$^{A″}$-*C,*6$^{A‴}$-*C-*[1,4,7,10-Tetraazacyclododecane-1,4,7,10-tetrayltetrakis(carbonylamino)]tetrakis[6^A-deoxy-β-cyclodextrin]* (**9b**). As described for **6b**, with **9a** (0.030 g, 0.0036 mmol), MeOH (5 ml), and 1M NaOMe (0.294 ml, 80 equiv.) **9b** (0.01 g, 79%). White snow-like powder. R_f (dioxane/25% NH_3 soln. 10:7) 0.5. IR (KBr): 3708–3384 (NH, OH), 1651 (C=O, urea). ^{1}H-NMR (D_2O): 5.40–5.20, 4.90–4.70, 4.20–3.95 (3 *m*, 84 H, H–C(2^A), H–C(3^A), H–C(5^A), H–C(2$^{B–G}$), H–C(3$^{B–G}$), H–C(5$^{B–G}$)); 5.18–4.95 (*m*, 42 H, H–C(1^A), H–C(1$^{B–G}$), H–C(4^A), H–C(4$^{B–G}$)); 4.60–4.40, 4.40–4.20 (2 *m*, H–C(6^A), H–C(6$^{B–G}$)); 3.80–3.65 (*m*, 14 H, H–C(4^A), H–C(4$^{B–G}$)); 3.10 (CH_2 (cyclam)); 1.40 (CH_2 (cyclam)). ^{13}C-NMR (D_2O): 102 (C(1)); 81 (C(4)); 73–72 (C(2), C(3), C(5)); 60 (C(6^A), C(6$^{B–G}$)); 37–36 (CH_2 (cyclam)); 32 (CH_2 (cyclam)). FAB-MS (glycerol): 3451 (M^+). Anal. calc. for $C_{180}H_{216}N_8O_{60}$ (4809.6): C 62.63, H 6.30, N 3.24; found: C 61.12, H 6.09, N 3.20.

N,N′,N″,N‴-*Tetraphenyl-1,4,7,10-tetraazacyclotetradecane-1,4,7,10-tetracarboxamide* (**9f**). As described for **7f**, with **4** (0.036 g, 0.21 mmol, 1 equiv.), toluene (25 ml), **10** (0.10 g, 0.840 mmol, 4 equiv.), and toluene (12 ml)

(2 days): pure **9f** (0.12 g, 89%). White powder. R_f (CH_2Cl_2/MeOH 95:5) 0.5. IR (KBr): 3313 (NH), 1651 (CO). ^{1}H-NMR ((D$_6$)DMSO): 8.30 (*s*, NH); 7.43 (*d*, 8 H, H$_o$); 7.23 (*t*, 8 H, H$_m$); 6.97 (*t*, 4 H, H$_p$); 3.68 (*s*, 16 H, CH_2 (cyclam)). ^{13}C-NMR ((D$_6$)DMSO): 158 (CONH); 131 (C$_m$); 125 (C$_p$); 122 (C$_o$); 51 (CH_2 (cyclam)). FAB-MS (NBA): 649.2 ([$M+H$]$^+$).

2^A,2^B,2^C,2^D,2^E,2^F,2^G,3^A,3^B,3^C,3^D,3^E,3^F,3^G,6^B,6^C,6^D,6^E,6^F,6^G-Icosa-O-*acetyl-6^A-deoxy-6^A-isocyanato-β-cyclodextrin* (**11**). Icosa-*O*-acetyl-6^A-azido-6^A-deoxy-β-cyclodextrin (**5**; 3.0 g, 1.5 mmol) was dissolved in anh. toluene (90 ml) and dried by azeotropic distillation at atmospheric pressure. After the removal of H_2O by distilling *ca.* 60 ml of toluene and cooling the soln. to r.t., the descending condenser was replaced by a reflux one ($CaCl_2$-filled tube). Dry CO_2 was bubbled through the soln. for 0.5 h. Then Ph_3P (0.564 g, 2.15 mmol) in anh. toluene (24 ml) was added dropwise within 1 h at r.t. under stirring and continuous bubbling of CO_2. The slow stream of CO_2 was maintained for an additional 20 h, then cyclohexane (90 ml) was added to precipitate a white solid. After stirring for 2 h, the product was filtered, washed with cyclohexane (3 × 8 ml), and dried in a vacuum desiccator over NaOH pellets: **11** (2.76 g, 92%). White powder. R_f (AcOEt/EtOH 95:5) 0.7; R_f (AcOEt) 0.35. M.p. 140–145°. $[\alpha]_D = +122$ ($c = 1$, $CHCl_3$). IR (KBr): 2267 (N=C=O), 1757 (AcO). ^{1}H-NMR ($CDCl_3$): 5.34–5.20 (*m*, 7 H, H–C(3$^{A–G}$)); 5.16–5.04 (*m*, 7 H, H–C(1$^{A–G}$)); 4.87–4.76 (*m*, 7 H, H–C(2$^{A–G}$)); 4.63–4.52 (*m*, 6 H, H$_a$–C(6$^{B–G}$)); 4.32–4.02 (*m*, 13 H, H–C(5$^{A–G}$), H$_b$–C(6$^{B–G}$)); 3.87–3.67 (*m*, 9 H, H–C(4$^{A–G}$), H$_{a,b}$–C(6^A)); 2.15–2.04 (several *s*, 60 H, MeCO). ^{13}C-NMR ($CDCl_3$): 170.71–169.32 (Me*C*O); 125.03 (N=C=O); 96.94–96.53 (C(1)); 77.36–76.43 (C(4)); 71.06–69.40 (C(2), C(3), C(5)); 62.68–62.33 (C(6$^{B–G}$)); 43.58 (C(6^A)); 20.82–20.71 (MeCO).

N,N′-*Bis(2^A,2^B,2^C,2^D,2^E,2^F,2^G,3^A,3^B,3^C,3^D,3^E,3^F,3^G,6^B,6^C,6^D,6^E,6^F,6^G-Icosa*-O-*acetyl-6^A-deoxy-β-cyclodextrin-6^A*-C-*yl)carbodiimide* (=*6^A*-C,*6′^{A}*-C-*(Methanetetrayldinitrilo)bis[2^A,2^B,2^C,2^D,2^E,2^F,2^G ,3^A,3^B,3^C,3^D,3^E,3^F,3^G,6^B,6^C,6^D,6^E,6^F,6^G-icosa*-O-*acetyl-6^A-deoxy-β-cyclodextrin];* **12**). A soln. of **5** (0.30 g, 0.15 mmol) in anh. toluene (20 ml) was dried by azeotropic distillation as described for **11** (*ca.* 10 ml). Then, **11** (0.30 g, 0.15 mmol) was added. The mixture was treated by dropwise addition of Ph_3P (0.05 g, 0.19 mmol) in anh. toluene (2 ml) within 0.3 h under stirring at r.t. After 3 days standing (TLC (AcOEt/acetone 2:1): no starting materials left), cyclohexane (22 ml) was added. The precipitate was filtered after stirring for 1 h and dried in a vacuum desiccator over NaOH pellets: **12** (0.56 g, 94%). White powder. R_f (AcOEt/acetone 4:1) 0.5. M.p. 92–98°. $[\alpha]_D = +100$ ($c = 3.3$, $CHCl_3$). IR (KBr): 2139 (N=C=N), 1749 (AcO). ^{1}H-NMR ($CDCl_3$): 5.39–5.05 (*m*, 28 H, H–C(1$^{A–G}$), H–C(3$^{A–G}$)); 4.88–4.72 (*m*, 14 H, H–C(2$^{A–G}$)); 4.60–4.50 (*m*, 12 H, H$_a$–C(6$^{B–G}$)); 4.39–4.07 (*m*, 24 H, H–C(5$^{B–G}$), H$_b$–C(6$^{B–G}$)); 3.92–3.84 (*m*, 6 H, H–C(5^A), H$_{a,b}$–C(6^A)); 3.79–3.63 (*m*, 14 H, H–C(4$^{A–G}$)); 2.15–1.92 (several *s*, 120 H, MeCO). ^{13}C-NMR ($CDCl_3$): 170.9–169.3 (Me*C*O); 132.1 (N=C=N); 96.7 (C(1)); 77.7–76.4 (C(4)); 71.0–69.4 (C(2), C(3), C(5)); 62.4 (C(6$^{B–G}$)); 46.1 (C(6^A)); 20.7 (*Me*CO).

2^A,2^B,2^C,2^D,2^E,2^F,2^G,3^A,3^B,3^C,3^D,3^E,3^F,3^G,6^B,6^C,6^D,6^E,6^F,6^G-Icosa-O-*acetyl-6^A-deoxy-6^A-[(morpholin-4-ylcarbonyl)amino]-β-cyclodextrin* (**13**). To a soln. of **11** (0.4 g, 0.2 mmol) in anh. toluene (5 ml), morpholine (0.020 g, 0.23 mmol) was added, and the mixture was stored at r.t. for 18 h under protection from moisture (TLC (AcOEt/EtOH 95:5): new spot at R_f 0.55, no **11** left). The product was precipitated by addition of cyclohexane (15 ml), filtered, and washed twice with cyclohexane to give pure **13** (0.3 g, 72%). M.p. 165–167°. $[\alpha]_D = +125$ ($c = 1.4$, $CHCl_3$). IR (KBr): 1752 (AcO), 1650, 1522 (NHCON). ^{1}H-NMR ($CDCl_3$): 5.40–5.06 (*m*, 14 H, H–C(3$^{A–G}$), NH, H–C(1$^{B–G}$)); 4.98 (*d*, 1 H, H–C(1^A)); 4.88–4.71 (*m*, 7 H, H–C(2$^{A–G}$)); 4.69–4.46 (*m*, 6 H, H$_a$–C(6$^{B–G}$)); 4.41–4.02 (*m*, 13 H, H–C(5$^{A–G}$), H$_b$–C(6$^{B–G}$)); 3.82–3.51 (*m*, 13 H, H–C(4$^{A–G}$), H$_{a,b}$–C(6^A), CH_2O (morph)); 3.43, 3.34 (*m*, 4 H, CH_2N (morph)); 2.13–2.01 (several *s*, 60 H, *Me*CO). ^{13}C-NMR ($CDCl_3$): 170.99–169.31 (Me*C*O); 157.73 (NHCON); 97.32–96.37 (C(1)); 77.78–76.05 (C(4)); 71.23–69.25 (C(2), C(3), C(5)); 66.56 (CH_2O (morph)); 63.01–62.38 (C(6$^{B–G}$)); 44.13 (CH_2N (morph)); 41.63 (C(6^A)); 20.90–20.72 (*Me*CO).

2^A,2^B,2^C,2^D,2^E,2^F,2^G,3^A,3^B,3^C,3^D,3^E,3^F,3^G,6^B,6^C,6^D,6^E,6^F,6^G-Icosa-O-*acetyl-6^A-deoxy-6^A-[(4-methylpiperazin-1-ylcarbonyl)amino]-β-cyclodextrin* (**14**). As described for **13**, with **11** (0.8 g, 0.4 mmol), toluene (10 ml), and 1-methylpiperazine (0.071 g, 0.71 mmol) (3 days; TLC (AcOEt/EtOH 9:1): R_f 0.15). Workup with cyclohexane (30 ml): pure **14** (0.74 g, 88%). White powder. M.p. 163–165°. $[\alpha]_D = +125$ ($c = 1.5$, $CHCl_3$). IR (KBr): 1750 (AcO), 1655, 1520 (NHCON). ^{1}H-NMR ($CDCl_3$): 5.38–5.24 (*m*, 7 H, H–C(3$^{A–G}$)); 5.21 (*dd*, H–C(3^A)); 5.12–5.08 (*m*, 7 H, H–C(1$^{A–G}$)); 5.05 (br. *dd*, NH); 5.01 (*d*, 1 H, H–C(1^A)); 4.88–4.76 (*m*, 6 H, H–C(2$^{B–G}$)); 4.75 (*dd*, 1 H, H–C(2^A)); 4.66–4.50 (*m*, 5 H, H$_{a,b}$–C(6$^{B–G}$)); 4.49–4.10 (*m*, 13 H, H–C(5$^{B–G}$), H$_{a,b}$–C(6$^{B–G}$)); 4.04 (*ddd*, 1 H, H–C(5^A)); 3.80–3.66 (*m*, 7 H, H–C(4$^{B–G}$), H$_a$–C(6^A)); 3.61 (*dd*, 1 H, H–C(4^A)); 3.55 (*ddd*, 1 H, H$_b$–C(6^A)); 3.40 (*m*, 4 H, $CONCH_2$); 2.39 (*t*, 4 H, $MeNCH_2$); 2.29 (*s*, MeN); 2.13–2.02 (several *s*, 60 H, MeCO). ^{13}C-NMR ($CDCl_3$): 170.84–169.24 (Me*C*O); 157.51 (NHCON); 97.15 (C(1^A)); 97.04–96.40 (C(1$^{B–G}$)); 77.48–76.44 (C(4$^{B–G}$)); 76.86 (C(4^A)); 71.13 (C(5^A)); 70.98–70.17 (C(2$^{B–G}$), C(3$^{B–G}$)); 70.93 (C(3^A)); 70.33

(C(2^{A})); 69.57–69.31 (C(5$^{B–G}$)); 62.99–62.43 (C(6$^{B–G}$)); 54.72 (MeN*C*H$_2$); 46.11 (MeN); 43.84 (CON*C*H$_2$); 41.35 (C(6^{A})); 20.89–20.73 (*Me*CO).

6^{A}-Deoxy-6^{A}-[(4-methylpiperazin-1-yl-carbonyl)amino]-β-cyclodextrin (**15**). A soln. of **14** (0.486 g, 0.231 mmol) in MeOH (8 ml) was diluted with H_2O (7 ml), and after addition of 5% aq. NaOH soln. (4 ml, 5 mmol), the mixture was heated at 50–60° for 0.3 h (TLC (EtOH/25% aq. NH_3 soln. 3:2): new spot at R_f 0.2 and no **14**). The mixture was concentrated to *ca.* 3 ml *in vacuo*, when the product started to crystallize. After addition of MeOH (25 ml), the mixture was heated to 50°, then cooled to 10°. The crystals were filtered and washed with cold MeOH: pure **15** (232 mg, 80%). M.p. >330°. $[\alpha]_D = +157$ ($c = 1$, AcOH/H_2O 1:1), +133 ($c =$ 0.75, DMSO). IR (KBr): 1632, 1540 (NHCON). ^{1}H-NMR ((D$_6$)DMSO, 60°): 6.06 (br. *t*, NH); 5.63–5.45 (*m*, 14 H, OH–C(2$^{A–G}$), OH–C(3$^{A–G}$)); 4.89–4.80 (*m*, 7 H, H–C(1$^{A–G}$)); 4.31–4.21 (*m*, 6 H, OH–C(6$^{B–G}$)); 3.79 (*ddd*, 1 H, H$_a$–C(6^{A})); 3.76–3.51 (*m*, 26 H, H–C(3$^{A–G}$), H–C(5$^{A–G}$), H–C(6$^{B–G}$)); 3.46–3.10 (*m*, 14 H, H–C(2$^{A–G}$), H–C(4$^{A–G}$)); 3.25 (*m*, 4 H, CONCH$_2$); 2.97 (*ddd*, H$_b$–C(6^{A})); 2.23 (*t*, 4 H, MeNCH$_2$); 2.17 (*s*, MeN). ^{13}C-NMR ((D$_6$)(DMSO): 157.50 (NHCON); 102.35–101.45 (C(1)); 84.55–80.84 (C(4)); 73.50–70.58 (C(2), C(3), C(5)); 60.25–59.77 (C(6$^{B–G}$)); 54.63 (MeN*C*H$_2$); 45.98 (M); 43.30 (CON*C*H$_2$); 41.76 (C(6^{A})).

N-(*2^{A},2^{B},2^{C},2^{D},2^{E},2^{F},2^{G},3^{A},3^{B},3^{C},3^{D},3^{E},3^{F},3^{G},6^{B},6^{C},6^{D},6^{E},6^{F},6^{G}-Icosa*-O-*acetyl-6^{A}-deoxy-β-cyclodextrin-6^{A}-C-yl)-*N′-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)carbodiimide* (=*2^{A},2^{B},2^{C},2^{D},2^{E},2^{F},2^{G},3^{A},3^{B},3^{C},3^{D},3^{E},3^{F},3^{G},6^{B},6^{C},6^{D},6^{E},6^{F},6^{G}-Icosa-O-acetyl-6^{A}-deoxy-6^{A}-{[[(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)imino]methylene]amino}-β-cyclodextrin;* **17**). To a solution of 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl azide (0.20 g, 0.54 mmol) and **11** (1.00 g, 0.50 mmol) in anh. toluene (20 ml), Ph_3P (0.15 g, 0.57 mmol) in anh. toluol (10 ml) was added dropwise within 0.3 h under stirring and protection from moisture at r.t. After standing overnight (TLC (AcOEt): no **11** left), addition of cyclohexane (60 ml) precipitated a white solid, which was filtered and dried in a vacuum desiccator over NaOH pellets: **17** (1.06 g, 91%). White powder. R_f (AcOEt/acetone 4:1) 0.65. M.p. 145–150°. $[\alpha]_D = +37.8$ ($c = 1$, $CHCl_3$). IR (KBr): 2151 (N=C=N), 1747 (AcO). ^{1}H-NMR ($CDCl_3$): 5.38–5.04 (*m*, 16 H, H–C(1$^{A–G}$), H–C(3$^{A–G}$), H–C(3′), H–C(4′)); 4.95 (*dd*, 1 H, H–C(2′)); 4.84–4.73 (*m*, 8 H, H–C(2$^{A–G}$), H–C(1′)); 4.58–4.49 (*m*, 6 H, H$_a$–C(6$^{B–G}$)); 4.34–4.06 (*m*, 14 H, H–C(5$^{B–G}$), H$_b$–C(6$^{B–G}$), H$_{a,b}$–C(6′)); 4.00–3.68 (*m*, 11 H, H–C(4$^{A–G}$), H–C(5′), H–C(5^{A}), H$_{a,b}$–C(6^{A})); 2.03–1.94 (several *s*, 72 H, MeCO). ^{13}C-NMR ($CDCl_3$): 170.7–169.3 (MeCO); 132.1 (N=C=N); 97.0–96.7 (C(1)); 84.5 (C(1′)); 77.7–76.4 (C(4)); 73.7–72.6 (C(2′), C(3′), C(5′)); 71.4–69.4 (C(2), C(3), C(5)); 68.1 (C(4′)); 62.4 (C(6$^{B–G}$)); 61.8 C(6′)); 45.9 (C(6^{A})); 20.7–20.5 (*Me*CO).

N-(*2^{A},2^{B},2^{C},2^{D},2^{E},2^{F},2^{G},3^{A},3^{B},3^{C},3^{D},3^{E},3^{F},3^{G},6^{B},6^{C},6^{D},6^{E},6^{F},6^{G}-Icosa*-O-*acetyl-6^{A}-deoxy-β-cyclodextrin-6^{A}-C-yl)-*N′-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)urea* (=*2^{A},2^{B},2^{C},2^{D},2^{E},2^{F},2^{G},3^{A},3^{B},3^{C},3^{D},3^{E},3^{F},3^{G},6^{B},6^{C},6^{D},6^{E},6^{F},6^{G}-Icosa-O-acetyl-6^{A}-deoxy-6^{A}-{[[(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)amino]carbonyl}amino}-β-acyclodextrin;* **18**). To a soln. of **17** (0.10 g, 0.05 mmol) in $CHCl_3$ (2 ml), AcOH (0.5 ml) was added at r.t., and the mixture was allowed to stand overnight (TLC (AcOEt): no **17** left). After evaporation, the residue was triturated with ^{i}PrOH (2 ml) and the solid filtered and dried: **18** (74 mg, 73%). White powder. R_f (AcOEt) 0.15. M.p. 166–170°. $[\alpha]_D = +24.8$ ($c = 1$, $CHCl_3$). IR (KBr): 1747 (AcO), 1556 (NHCO).

X-Ray Crystal-Structure Determination of **8f** (see *Table* and *Figs. 5* and *6*). All diffraction data were recorded on a *Nonius Kappa-CCD* diffractometer with MoK_α radiation (graphite monochromator, λ 0.71073 Å). Cell parameters were refined with the scalepack part of DENZO [13]. Reflection intensities were corrected for *Lorentz* and polarization factors but not absorptions. The structure was solved by direct methods with the SIR. program [14], and refined by full matrix least squares on *F* with the OpenMoleN package [15]. All non-H-atoms were given anisotropic displacement parameters. H-Atoms were introduced in structure-factor calculations as fixed contributors located at their theoretical positions, $d(C–H) = 0.95$ Å, $B(H) =$ 1.3 Beqv (attached C). Figures were produced with the ORTEP-III program [16].

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