4,5-Dihydroxyimidazolidin-2-ones in α-ureidoalkylation of *N*-carboxy-, *N*-hydroxy-, and *N*-aminoalkylureas

2.* α-Ureidoalkylation of *N*-(hydroxyalkyl)ureas**

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The α-ureidoalkylation of *N*-(hydroxyalkyl)ureas (ureido alcohols) with 1,3-H_2- and 1,3-Me_2-4,5-dihydroxyimidazolidin-2-ones was systematically studied. The yields of glycolurils decrease both in going from 1,3-H_2- to 1,3-Me_2-4,5-dihydroxyimidazolidin-2-one and with increasing length (or with branching) of the hydroxyalkyl chain in ureido alcohols. The optimal reaction time for ureido alcohols is 1 h. The X-ray diffraction study showed that 2-(2-hydroxy-1,1-dimethylethyl)glycoluril crystallizes as a conglomerate. The enantiomeric analysis of 2-(2-hydroxyethyl)glycoluril was carried out by chiral-phase HPLC.

Key words: *N*-(hydroxyalkyl)glycolurils, 4,5-dihydroxyimidazolidin-2-ones, *N*-(hydroxyalkyl)ureas (ureido alcohols), racemates, enantiomers, conglomerate, X-ray diffraction and enantiomeric analysis.

Since glycolurils (2,4,6,8-tetraazabicyclo[3.3.0]octane-3,7-diones) belong to a new class of psychotropic compounds,[2—4] the development of procedures for the enantiomeric resolution of glycolurils is necessary for the design of optically pure drugs. The formation of conglomerates (mixtures of enantiomerically pure crystals) is the simplest way of preparing enantiomerically pure compounds. As has been demonstrated in our previous study,[1] one of approaches to the synthesis of glycolurils capable of crystallizing as conglomerates could be based on the functionalization of the substituents at the nitrogen atoms by introducing such groups that can be involved in hydrogen bonding (for example, carboxy, hydroxy, or amino groups). We have thoroughly developed this approach based on the synthesis of *N*-(carboxyalkyl)glycolurils, among which we have found two conglomerates.[1,5] To search for new conglomerates among glycolurils, it is of interest to introduce hydroxyalkyl groups at the nitrogen atoms of glycolurils. Previously, we have synthesized several representatives of this type of compounds by the α-ureidoalkylation of *N*-(hydroxyalkyl)ureas (hereinafter, ureido alcohols) with 4,5-dihydroxyimidazolidin-2-ones (DHI).[6,7]

With the aim of extending the range of conglomerate-forming glycolurils, in the present study we investigated in detail the α-ureidoalkylation of ureido alcohols using various DHI as ureidoalkylating agents and developed an optimal procedure for the preparation of *N*-(hydroxyalkyl)glycolurils.

Some *N*-(carboxylalkyl)glycolurils are known to exist as conglomerates. The latter were prepared with the use of 1,3-H_2- and 1,3-Me_2-DHI. Hence, *N*-(hydroxyalkyl)-glycolurils **1a—l** were synthesized by the α-ureidoalkylation of ureido alcohols **2a—g** with DHI **3a,b** at 85 °C in an aqueous medium at pH 1—2 (Scheme 1).

The results of research on the dependence of the yields of compounds **1a—l** on the reaction time and the character of substitution at the nitrogen atoms of 4,5-dihydroxyimidazolidin-2-ones **3a,b** and in ureido alcohols **2a—g**, as well as on the lengths and branching of the alkyl chain in ureido alcohols, are presented in the diagram (Fig. 1). The dependence of the yield of *N*-(hydroxyalkyl)glycolurils **1** on the reaction time was investigated with the use of the most readily accessible ureido alcohol **2a** and 4,5-dihydroxyimidazolidin-2-one **3a**. The investigation showed that the yield of **1a** is 55% (1 h), 56% (2 h), and

* For Part 1, see Ref. 1.

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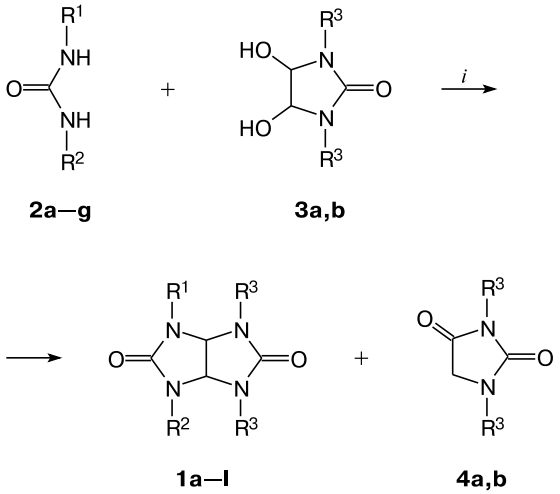
Scheme 1



i. pH 1—2, 1 h, 85 °C

Compound	R^1	R^2	R^3
1a	H	$(CH_2)_2OH$	H
1b	H	$(CH_2)_3OH$	H
1c	H	CMe_2CH_2OH	H
1d	H	$CHEtCH_2OH$	H
1e	H	$(CH_2)_2C_6H_4OH$-*p*	H
1f	H	$(CH_2)_2OH$	Me
1g	H	CMe_2CH_2OH	Me
1h	H	$(CH_2)_2C_6H_4OH$-*p*	Me
1i	Me	$(CH_2)_2OH$	H
1j	Me	CMe_2CH_2OH	H
1k	Me	$(CH_2)_2OH$	Me
1l	Me	CMe_2CH_2OH	Me
2a	H	$(CH_2)_2OH$	—
2b	H	$(CH_2)_3OH$	—
2c	H	CMe_2CH_2OH	—
2d	H	$CHEtCH_2OH$	—
2e	H	$(CH_2)_2C_6H_4OH$-*p*	—
2f	Me	$(CH_2)_2OH$	—
2g	Me	CMe_2CH_2OH	—
3a	—	—	H
3b	—	—	Me
4a	—	—	H
4b	—	—	Me

58% (3 h), *i.e.*, the yield increases only slightly with time. Hence, all subsequent studies were carried out by storing the reaction mixtures for 1 h. The reactions of ureido alcohols **2a** and **2b** containing the hydroxyethyl and hydroxypropyl substituent, respectively, with 4,5-dihydroxyimidazolidin-2-one **3a** afford glycolurils in 55% (**1a**) and 40% (**1b**) yields, respectively, which indicates that the yields of *N*-(hydroxyalkyl)glycolurils substantially decrease with increasing length of the hydroxyalkyl substituent in ureido alcohols. A comparison of the yield of glycoluril **1a** (55%) with the yields of **1c** (46%) or **1d** (43%) shows that the use of ureido alcohols **2c** or **2d** containing branched hydroxyalkyl substituents in these reactions leads to a decrease in the yield of glycolurils. A comparison of the yields of glycolurils **1f** (34%) and **1g** (31%), of **1i** (45%)

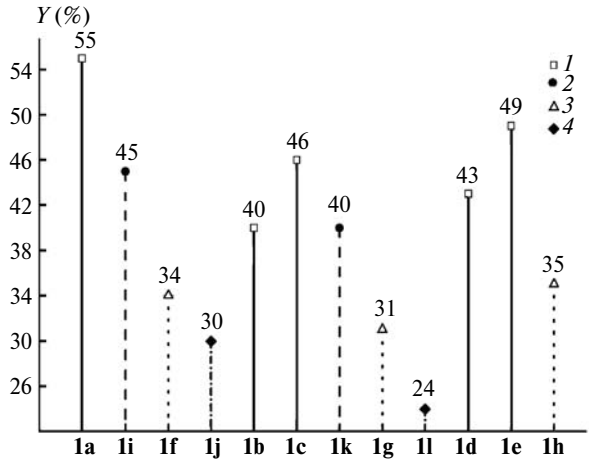


Fig. 1. Diagram of the yields (*Y*) of *N*-(hydroxyalkyl)glycolurils **1a—l** (average values) *versus* the character of substitution at the nitrogen atoms of 4,5-dihydroxyimidazolidin-2-ones **3a,b** and the length and branching of the alkyl chain in ureido alcohols **2a—g**: *1*, **3a** + ureido alcohol, *2*, **3a** + *N*-methylureido alcohol, *3*, **3b** + ureido alcohol, *4*, **3b** + *N*-methylureido alcohol.

and **1k** (40%), and of **1j** (30%) and **1l** (24%) confirms that the branching of the alkyl substituents in ureido alcohols **2** results in a decrease in the yields of glycolurils **1**. The replacement of the hydroxyalkyl substituent in ureido alcohols by the *p*-hydroxyphenylethyl substituent (**2e**) leads to a slight decrease (**1a** (55%) and **1e** (49%)) or to no decrease (**1f** (34%) and **1h** (35%)) in the yields of the corresponding glycolurils **1e**,**h**. All the processes under consideration were accompanied by the formation of the well known hydantoins **4a**,**b** as by-products that were formed through the pinacol rearrangement of DHI **3a,b**.[4] We did not isolate compounds **4a,b**, but they were detected by ^{1}H NMR spectroscopy of the oily residues obtained after the removal of the solvent from the mother liquors.

Hence, the yield of glycolurils **1** in the α-ureidoalkylation of ureido alcohols **2** decreases with increasing length and branching of the alkyl chain in the hydroxyalkyl substituents of these ureido alcohols, as well as in the presence of an alkyl substituent at the second nitrogen atom of the starting ureido alcohol and the methyl groups in DHI.

To examine the ability of glycolurils **1** to crystallize as conglomerates, we studied the crystallization of these compounds from 50% aqueous methanol, anhydrous methanol, chloroform, and ethyl acetate and investigated the complexation of some glycolurils **1** with transition metal salts. The crystallization of glycolurils **1** did not give crystals suitable for X-ray diffraction; in all cases we obtained powders. In attempting to prepare the coordination compound of glycoluril **1c** with $CdCl_2$, we carried out the reaction under the conditions analogous to those used in the synthesis of the complexes (80 °C, 1.5 h, H_2O instead of EtOH as the solvent)[8] during 2 days and iso-

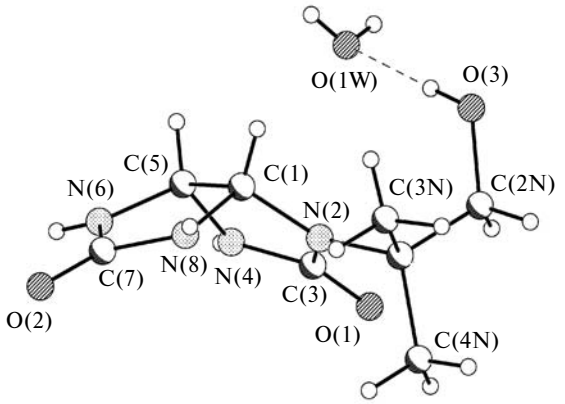


Fig. 2. Molecular structure of hydrate **1c**.

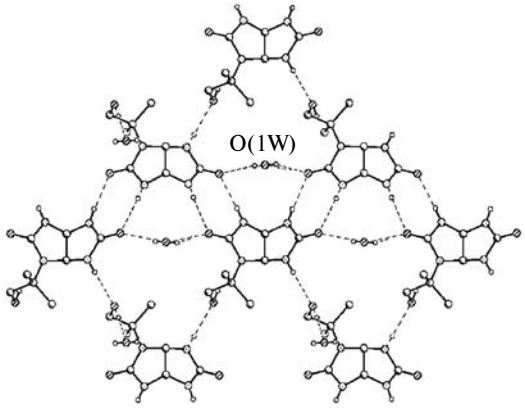


Fig. 3. Fragment of the hydrogen-bonded homochiral layer in the crystal structure of **1c**.

lated transparent crystals from the mother liquor. The melting point of these crystals differs by 80 °C from that of the starting racemic compound **1c**. Nevertheless, the IR spectroscopic data did not provide evidence for the formation of the complex. The single-crystal X-ray diffraction study showed that the compound thus obtained is the starting glycoluril **1c** crystallized as a solvate in the chiral space group $P2_12_12_1$ ($Z = 4$, $Z' = 1$) (Fig. 2, Table 1). The principal geometric parameters of **1c** are similar to the expected values.[1,5,9,10] The five-membered rings C(1)N(2)C(3)N(4)C(5) and C(1)C(5)N(6)C(7)N(8) adopt an envelope conformation with the N(4) and C(1) atoms, respectively, deviating from the mean planes by 0.10 and 0.12 Å, respectively.

In the crystal, the molecules are linked by N—H...O hydrogen bonds (N...O, 2.724(2)—2.931(2)A) to form homochiral layers having pores of a size of 6.49S9.28 Å. The pores are occupied by water molecules hydrogen-bonded to the C=O groups of **1c** and to the hydroxy groups of the molecules from the adjacent layers, resulting in the formation of a three-dimensional framework (Fig. 3).

Table 1. Selected bond lengths (d) and bond angles (ω) in the structure of **1c**

Bond	d/Å	Bond angle	ω/deg
O(1)—C(3)	1.235(2)	N(8)—C(1)—N(2)	114.56(17)
C(1)—N(8)	1.452(3)	N(8)—C(1)—C(5)	102.99(16)
C(1)—N(2)	1.456(3)	N(2)—C(1)—C(5)	103.25(16)
C(1)—C(5)	1.568(3)	C(3)—N(2)—C(1)	111.28(16)
C(1N)—N(2)	1.486(3)	O(1)—C(3)—N(4)	123.94(19)
N(2)—C(3)	1.365(3)	O(1)—C(3)—N(2)	126.46(19)
O(2)—C(7)	1.239(2)	N(4)—C(3)—N(2)	109.58(17)
C(3)—N(4)	1.359(3)	C(3)—N(4)—C(5)	112.28(17)
N(4)—C(5)	1.440(3)	C(7)—N(6)—C(5)	113.35(18)
C(5)—N(6)	1.448(3)	C(7)—N(8)—C(1)	112.10(18)
N(6)—C(7)	1.348(3)		
C(7)—N(8)	1.363(3)		

In this case, the unexpected formation of the conglomerate can be attributed to the influence of $CdCl_2$ on the kinetics of the growth of homo- and heterochiral crystals of **1c**. Thus, $CdCl_2$ can inhibit the growth of racemic crystals due to the coordination to the molecules on its surface. Similar effects were considered in detail for the crystal growth of amino acids.[11] The role of the reversible complexation with $CdCl_2$, which can preorganize the molecules through the formation of supramolecular associates favorable for the growth of homochiral crystals, cannot be ruled out as well. Since the solution of this problem requires information on the structural features (including the morphology, the energy of the faces, *etc.*) of both homochiral and heterochiral crystals, it is nowadays impossible to reveal with certainty the role of $CdCl_2$. We plan to consider this problem in the future.

Racemic *N*-(hydroxyalkyl)glycolurils, which do not form conglomerates, were resolved by chiral-phase HPLC. We have used this method for the first time for the enantiomeric analysis of functionalized glycolurils in the case of *N*-(carboxyalkyl)glycolurils. In spite of considerable technical difficulties, which have been discussed in detail in the study,[1] we examined the possibility of the use of chiral-phase HPLC for *N*-(hydroxyalkyl)glycolurils.

Electrostatic interactions between the acidic group and the tertiary nitrogen atom of the quinuclidine residue of the quinine alkaloid, which is used as a chiral selector for the HPLC phase ProntoSIL Chiral AX QN-1 (Bischoff, Germany), proved to be useful in the case of *N*-(carboxyl)-containing compounds. The ion-exchange mode of chromatography is provided by the presence of competing ions of acetic acid and ammonium acetate in the methanol eluent. Hydroxyl-containing glycoluril **1a** incapable of electrostatic binding is not retained on the phase ProntoSIL Chiral AX QN-1 and is not resolved even in pure MeOH. In 50% aqueous MeOH, racemate **1a** was unexpectedly easily resolved on a Chirobiotic TAG column (250×4 mm; Advanced Separation Technologies Inc.,

Table 2. Yields, melting points, ^{1}H NMR spectroscopic data (DMSO-d_6), and elemental analysis data for *N*-(hydroxyalkyl)glycolurils

Compound	M.p. /°C	Found / Calculated (%)			Molecular formula	δ (*J*/Hz)
		C	H	N		
1a*	172—173[7]					
1b	139—141	42.02 42.00	6.01 6.04	28.02 27.99	$C_7H_{12}N_4O_3$	1.57 (m, 2 H, CH_2); 2.98 (m, 1 H, CH_2); 3.16 (m, 1 H, CH_2); 3.36 (m, 2 H, CH_2); 4.42 (m, 1 H, OH); 5.17, 5.24 (both d, 2 H, 2 CH, *J* = 7.9); 7.25 (br.s, 2 H, 2 NH); 7.40 (br.s, 1 H, NH)
1c*	227—229[7]					
1d	338—340	44.88 44.85	6.60 6.59	26.12 26.15	$C_8H_{14}N_4O_3$	0.80 (m, 3 H, C—CH_3); 1.38, 1.47 (both m, 1 H each, C—CH_2); 3.19, 3.53 (both, 1 H each, CH_2—OH); 4.42 (m, 1 H, OH); 5.18, 5.32 (both d, 1 H each, 2 CH, *J* = 7.9); 7.17 (br.s, 3 H, 3 NH)
1e	302—305	54.99 54.96	5.41 5.38	21.35 21.36	$C_{12}H_{14}N_4O_3$	2.58, 2.78 (both m, 1 H each, CH_2); 3.18, 3.51 (both m, 1 H each, CH_2); 4.45 (br.s, 1 H, OH); 5.07, 5.12 (both d, 1 H each, 2 CH, *J* = 8.3); 6.71, 6.97 (both d, 2 H each, 4 CH, *J* = 8.7); 7.42 (br.s, 2 H, 2 NH); 7.62 (br.s, 1 H, NH)
1f	160—162	44.84 44.85	6.57 6.59	26.13 26.15	$C_8H_{14}N_4O_3$	2.70 (s, 2 H, CH_3); 2.83 (s, 6 H), 2.60 (s, 3 H, CH_3); 2.68 (s, 3 H, CH_3); 3.02 (m, 2 H, CH_2); 3.53 (m, 2 H, CH_2); 4.07 (br.m, 1 H, OH); 5.07, 5.59 (both d, 1 H each, 2 CH, *J* = 6.6); 6.60 (br.s, 1 H, NH)
1g	198—200	49.59 49.57	7.51 7.49	23.11 23.13	$C_{10}H_{18}N_4O_3$	1.20 (s, 3 H, CH_3); 1.21 (s, 3 H, CH_3); 2.71 (s, 3 H, CH_3); 2.84 (s, 3 H, CH_3); 3.40, 3.62 (both m, 1 H each, CH_2); 4.85 (m, 1 H, OH); 5.11, 5.44 (both d, 1 H each, 2 CH, *J* = 8.0); 7.25 (br.s, 1 H, NH)
1h	289—291	57.91 57.92	6.27 6.25	19.32 19.30	$C_{14}H_{18}N_4O_3$	2.60, 2.77 (both m, 1 H each, CH_2); 2.62 (s, 3 H, CH_3); 2.79 (s, 3 H, CH_3); 3.17, 3.48 (both m, 1 H each, CH_2), 4.43 (br.s, 1 H, OH); 5.03, 5.11 (both d, 1 H each, 2 CH, *J* = 8.5); 6.67, 7.00 (both d, 2 H each, 4 CH, *J* = 8.6); 7.62 (br.s, 1 H, NH)
1i**	142—144[6]	41.98 42.00	6.06 6.04	28.01 27.99	$C_7H_{12}N_4O_3$	
1j	211—212	47.37 47.36	7.10 7.07	24.52 24.55	$C_9H_{16}N_4O_3$	1.24, 1.26 (both s, 3 H each, 2 CH_3); 2.78 (s, 3 H, CH_3); 3.29, 3.65 (both m, 1 H each, CH_2); 4.82 (m, 1 H, OH); 5.10, 5.54 (both d, 1 H each, 2 CH, *J* = 8.0); 7.23 (br.s, 2 H, 2 NH)
1k	135—137	47.33 47.36	7.05 7.07	24.53 24.55	$C_9H_{16}N_4O_3$	2.70 (s, 3 H, CH_3); 2.83 (br.s, 6 H, 2 CH_3); 3.15 (m, 1 H, CH_2); 3.53 (m, 1 H, CH_2); 3.70 (m, 2 H, 2 CH_2); 4.91 (br.m, 1 H, OH); 5.09, 5.84 (both d, 1 H each, 2 CH, *J* = 7.2)
1l	184—186	51.53 51.55	7.88 7.87	21.85 21.86	$C_{11}H_{20}N_4O_3$	1.23 (s, 3 H, CH_3); 1.26 (s, 3 H, CH_3); 2.69 (s, 3 H, CH_3); 2.72 (s, 3 H, CH_3); 2.80 (s, 3 H, CH_3); 3.42, 3.61 (both m, 1 H each, CH_2); 4.91 (m, 1 H, OH); 5.02, 5.61 (both d, 1 H each, 2 CH, *J* = 8.1)

* The ^{1}H NMR spectrum and the elemental analysis data have been published earlier.[7]
** ^{1}H NMR spectrum was published in the study.[6]

USA), in which the macrocyclic antibiotic Teicoplanin Aglycone with eight chiral centers covalently bound to silica gel was used as the sorbent (UV detector, 206 nm) (Fig. 4). On the contrary, glycoluril **1a** was not retained and not resolved on the ligand-exchange sorbent with the copper complex of *N*-decylhydroxyproline in aqueous methanol. Evidently, the ability of **1a** to form the chelate complex with copper is very low.

To sum up, the systematic study of the α-ureidoalkylation of 4,5-dihydroxyimidazolidin-2-ones with ureido alcohols showed that the yields of *N*-(hydroxyalkyl)glycolurils depend on the reaction time and the character of substitution at the nitrogen atoms of 4,5-dihydroxyimidazolidin-2-ones, as well as on the length and branching of the alkyl chain in ureido alcohols. The general procedure was developed for the synthesis of the target

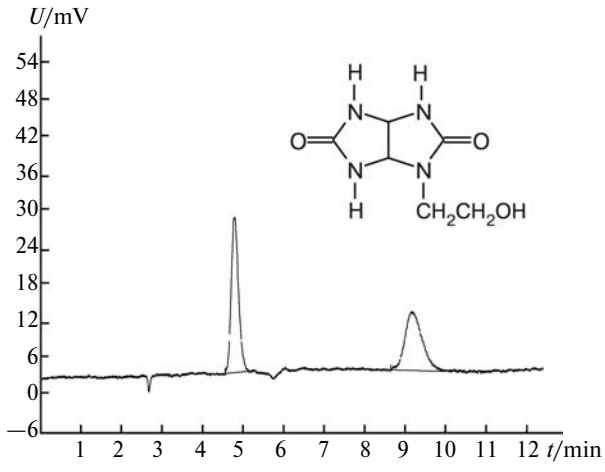


Fig. 4. Chromatogram of glycoluril **1a**.

glycolurils. The ability of glycolurils to form conglomerates was investigated. The X-ray diffraction study showed that 2-[2-hydroxy-1,1-(dimethyl)ethyl]glycoluril (**1c**) crystallizes as the conglomerate. The enantiomeric analysis of 2-(2-hydroxyethyl)glycoluril (**1a**) was carried out by chiral-phase HPLC.

Experimental

Amino alcohols, urea, dimethylurea, and 40% aqueous glyoxal were commercially available (Acros). Ureido alcohols **2a—e** were synthesized by the reaction of the corresponding amino alcohols with KOCN according to procedures described in the literature.[7] 1-Methylureido alcohols **2f,g** were synthesized by the reactions of the corresponding amino alcohols with MeCNO according to the procedure used for the synthesis of 1-alkyl-3-methylureas.[12] 4,5-Dihydroxyimidazolidin-2-ones **3a,b** were synthesized by the reactions of the corresponding ureas with glyoxal according to known procedures.[13,14]

The NMR spectra were recorded on Bruker AM-250 (^{1}H, 250 MHz) and Bruker AM-300 (^{13}C, 75.5 MHz) spectrometers; the chemical shifts are given on the δ scale with respect to Me_4Si as the internal standard. The melting points were determined on a GALLENKAMP instrument (Sanyo).

X-ray diffraction data. Crystals of **1c** ($C_8H_{16}N_4O_4$, M = 232.25) are rhombic, space group $P2_12_12_1$ at 120 K a = 9.1423(16) Å, b = 10.6687(18) Å, c = 10.9582(18) Å, V = 1068.8(3) Å^3, Z = 4 (Z' = 1), d_{calc} = 1.443 g cm^{-3}, μ(Mo-Kα) = 1.16 cm^{-1}, $F(000)$ = 496. The intensities of 14444 reflections were measured on a Bruker SMART 1000 CCD diffractometer (λ(Mo-Kα) = 0.71072 Å, ω-scanning technique, 2θ < 60°), and 1786 independent reflections (R_{int} = 0.0354) were used in the refinement. The structure was solved by direct methods and refined with anisotropic and isotropic displacement parameters by the full-matrix least-squares method based on F^2. The hydrogen atoms were located in difference Fourier maps and refined isotropically. The final R factors for **1c** were wR_2 = 0.1044 and GOOF = 1.110 for all independent reflections (R_1 = 0.0513 based on F for 1578 observed reflections with $I > 2\sigma(I)$). All calculations were carried out with the use of the SHELXTL PLUS 5.0 program package.[15]

The enantiomeric resolution of neutral compound 1a was performed on a Chirobiotic TAG column (250S4 mm; Advanced Separation Technologies Inc.), in which the macrocyclic antibiotic Teicoplanin Aglycone with eight chiral centers was covalently bound to silica gel. The chromatography was carried out in 50% aqueous MeOH with the UV detection at 210 nm.

Synthesis of target *N*-(hydroxyalkyl)glycolurils 1a—l (general procedure). Concentrated hydrochloric acid (0.2 mL) was added (in an aqueous medium to pH 1 of the reaction mixture) to a solution of the corresponding ureido alcohol **2a** (**2b—g**) (0.02 mol) and the corresponding 1,3-H_2- or 1,3-Me_2-4,5-dihydroxyimidazolidin-2-one (**3a,b**) (0.02 mol) in a minimum amount of H_2O or Pr^iOH (depending on the solubility of the starting compounds). The reaction mixture was kept at 85 °C for 1 h. Glycolurils **1e,h** were isolated as precipitates that formed upon the storage of the reaction mixture in a refrigerator for 10 h and then crystallized from H_2O. The reaction mixture containing **1a** (**1b—g**) was concentrated to one-half of the initial volume and then kept in a refrigerator for 12 h. The precipitate of **1a** (**1b—j**) that formed was filtered off and crystallized from water. The reaction mixture containing **1f** (**1g**) was concentrated to the oily state and triturated with MeOH. The precipitate of **1f** (**1g**) that formed was filtered off and crystallized from MeOH. Glycolurils **1k,l** were extracted with $CHCl_3$, and the extracts were concentrated to dryness. 2-(3-Hydroxyethyl)- (**1a**), 2-(3-hydroxypropyl)- (**1b**), 2-(2-hydroxy-1,1-dimethylethyl)- (**1c**), 2-(1-(hydroxymethyl)propyl)- (**1d**), 2-(2-(4-hydroxyphenyl)ethyl)- (**1e**), 6-(2-hydroxyethyl)-2,4-dimethyl- (**1f**), 6-(2-hydroxy-1,1-dimethylethyl)-2,4-dimethyl- (**1g**), 6-(2-(4-hydroxyphenyl)ethyl)-2,4-dimethyl- (**1h**), 2-(2-hydroxy-1,1-dimethylethyl)-4-methyl- (**1j**), 2-(2-hydroxyethyl)-4,6,8-trimethyl- (**1k**), and 2-(2-hydroxy-1,1-dimethylethyl)-4,6,8-trimethyl-2,4,6,8-tetraazabicyclo[3.3.0]octane-3,7-diones (**1l**) were synthesized.

The physicochemical characteristics and the elemental analysis data for compounds **1a—l** are given in Table 2.

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