Synthesis of new chiral mono-, di-, tri-, and tetraalkylglycolurils

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Two general procedures were developed for the synthesis of chiral *N*-mono-, *N*,*N*´-di-, *N*,*N*´*N*˝-tri-, and *N*,*N*´,*N*˝,*N*˝´-tetraalkylglycolurils based on the reactions of 4,5-dihydroxyimidazolidin-2-ones or glyoxal with one or two moles of alkylureas, respectively, by acid catalysis. The reactions of *N*-monoalkyl- and *N*,*N*´-dialkylureas with glyoxal proceed regioselectively. The mechanism of these reactions was suggested and partly confirmed by quantum-chemical calculations and experimental data. The enantiomeric separation of some chiral glycolurils by chiral-phase HPLC was carried out for the first time.

Key words: glycolurils, chirality, 4,5-dihydroxyimidazolidin-2-ones, mono- and dialkylureas, quantum-chemical calculations, enantiomeric analysis and separation, regioselectivity.

It is well known that *N*-alkyl-substituted 2,4,6,8-tetraazabicyclo[3.3.0]octane-3,7-diones (glycolurils) exhibit a wide spectrum of biological activities,[1—5] in particular, they possess psychotropic activity.[1—3] Some compounds of this class influence the cytochrome-P-450-dependent liver monooxygenase system: 2,6´-Bu_2-glycoluril exhibits activity suppressesing the liver monooxygenase system, whereas 2,6-Bz_2-glycoluril, on the contrary, stimulates the enzyme-inducing activity.[4] In addition, 2-Bu- and 2,6-Me_2-glycolurils are used as the starting compounds in the synthesis of glycidyl derivatives (for example, 4,8-di(1,2-epoxypropyl)-2,6-dimethylglycoluril) showing cytostatic effects.[5] The above-mentioned glycolurils, like most glycolurils, are chiral.[6] In biological assays, these compounds were used, apparently, as racemates, because the enantiomeric separation was not discussed. However, it is known that racemates and individual enantiomers involved in medicines can differ substantially in activity, toxicity, and side effects.[7]

The problem of preparation of pure *N*-alkylglycolurils has received attention only in the very recent past. Earlier, we have found two compounds, *viz.*, 2,6-dimethyl- and 2,6-diethylglycolurils, which can crystallize as conglomerates.[8,9] Data on the conglomerate-forming properties of other *N*-alkylglycolurils containing chiral atoms are lacking in the literature. This can be attributable to the fact that, in spite of numerous publications on the synthesis and biological properties of *N*-alkylglycolurils,[1—22] representatives of this type of compounds are scarce, most of them being covered by patents[5,13,14,18—20] or described in brief communications.[7,12,16,21] These compounds have not been characterized spectroscopically and procedures for their synthesis have not been optimized. The aim of the present study was to develop a general approach to the synthesis of mono-, di-, tri-, and tetraalkyl-substituted glycolurils and extend the range of compounds by introducing various alkyl substituents.

Known procedures for the synthesis of glycolurils are based on condensation of ureas with glyoxal[2,4,10—15,18,19] and 4,5-dihydroxyimidazolidin-2-ones.[2,10,13,18—21] To prepare new representatives of chiral 2-monoalkylglycolurils **1**, we decided to use a procedure based on cyclocondensation of 1-alkylureas **2a—f** with 4,5-dihydroxyimidazolidin-2-one (**3a**), which was prepared according to a known procedure (Scheme 1).[23] The reactions of the latter with compounds **2a,b** were carried out in water, whereas the reactions with compounds **2c—f** were performed in isopropanol at 80—90 °C for 1—1.5 h. In both cases, a catalytic amount of hydrochloric acid was added.

An analogous approach was used to synthesize 2,4-dialkylglycolurils **4**. In this case, the reactions of 4,5-dihydroxyimidazolidin-2-one **3a** were carried out with 1-alkyl-3-methylureas **5a—f**, the reactions with compounds **5a—c,f** being performed in water, whereas the reactions with compounds **5d,e** being carried out in isopropanol. These reactions, like the above-described reac-

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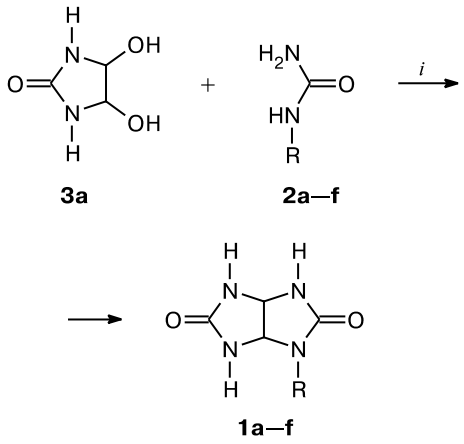
Scheme 1



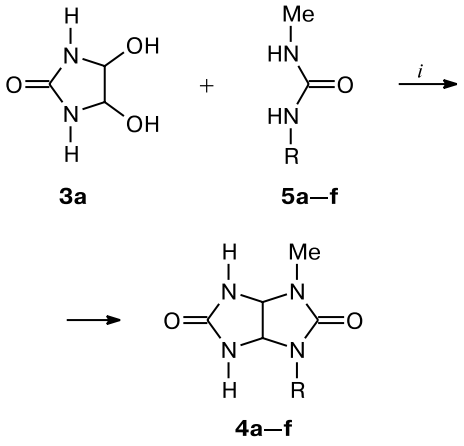
3a **2a—f** **1a—f**

i. HCl (cat.)

R = Et (**a**), Pr (**b**), Bu^s (**c**), Bu^t (**d**), *cyclo*-C_6H_{11} (**e**), $C_{12}H_{25}$ (**f**)

tions, were performed by acid catalysis at 80—90 °C (Scheme 2). In both cases, the target glycolurils **1** and **4** were prepared in 60—92% yields.

Scheme 2



3a **5a—f** **4a—f**

i. HCl (cat.)

R = Et (**a**), Pr (**b**), Bu^s (**c**), Bu^t (**d**), *cyclo*-C_6H_{11} (**e**), Bu (**f**)

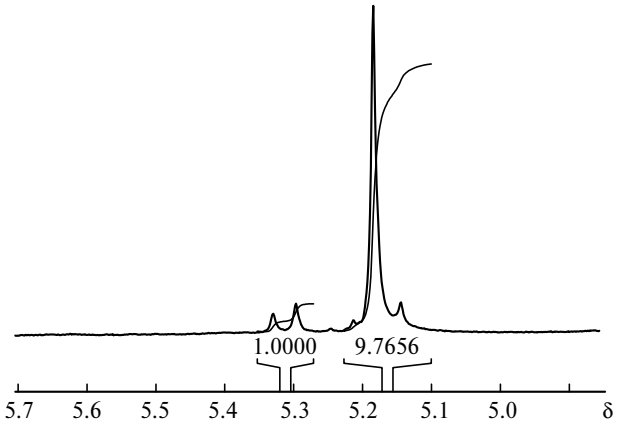


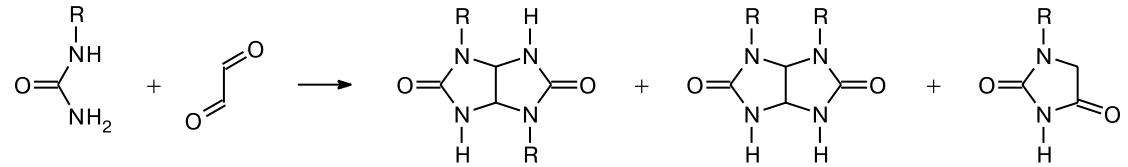
Fig. 1. Region of the signals for the protons of the CH—CH groups in a concentrated reaction mixture of compounds **6b** (δ 5.18, s) and **7b** (δ 5.17 and 5.32, both d).

The investigation of the reaction of 1-methylureas **2h** with glyoxal has demonstrated[11] that cyclocondensation afforded a mixture of 2,6- and 2,8-dimethylglycolurils **6h** (*trans* isomer) and **7h** (*cis* isomer) in a ratio of 7 : 4 with respect to the products isolated. Hence, to develop a general method for the synthesis of chiral 2,6-dialkylglycolurils **6**, it was necessary to study the regioselectivity of the reactions of glyoxal with 1-alkylureas containing various alkyl substituents **2a,b,d,e,g,h** (Scheme 3).

The reaction was carried out according to a conventional procedure by heating the reaction mixture in water or isopropanol at 80—90 °C in the presence of a catalytic amount of hydrochloric acid. The reaction products were analyzed by ^{1}H NMR spectroscopy of the reaction mixtures concentrated to dryness. The *trans* to *cis* isomer ratios (compounds **6** and **7**) were estimated from the ratios of the signals for the protons of the CH—CH groups at δ 4.8—5.5. The signals for these protons in the *trans* isomers appear as singlets, whereas the corresponding signals for the *cis* isomers appear as AMX systems (see Figs 1 and 2).

It was found that the reactions of glyoxal with monoalkylureas **2a,b,d,e,g** always occur regioselectively to give *trans* isomers **6** as the major products; the ratios were as follows: **6a** : **7a** = 3 : 1, **6b** : **7b** ≈ 9 : 2, **6d** : **7d** = 5 : 2,

Scheme 3



2a,b,d,e,g,h **6a,b,d,e,g,h** **7a,b,d,e,g,h** **8a,b,d,e,g,h**

R = Et (**a**), Pr (**b**), Bu^t (**d**), *cyclo*-C_6H_{11} (**e**), Bu (**g**), Me (**h**)

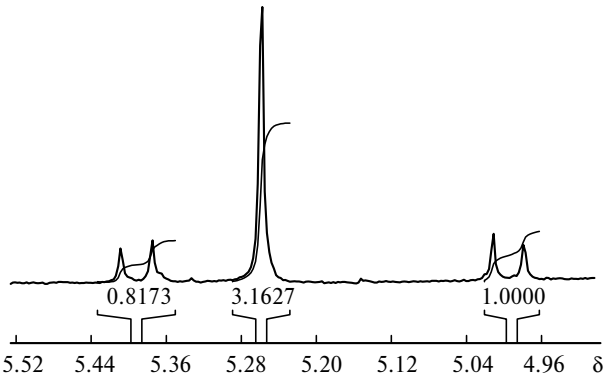


Fig. 2. Region of the signals for the protons of the CH—CH groups in a concentrated reaction mixture of compounds **6g** (δ 5.26, s) and **7g** (δ 4.99 and 5.39, both d).

6e : **7e** = 7 : 2, and **6g** : **7g** ≈ 2 : 1. The ratio of compounds **6** and **7** was determined from the integral intensity ratios of the signals for the protons of the CH—CH groups at δ 4.8—6.0. The isolation of 2,6- and 2,8-dimethylglycolurils **6** and **7** in pure form was carried out by fractional crystallization. The yields of *trans*- and *cis*-glycolurils were 40—63 and 12—20%, respectively. Hydantoins **8** were obtained as by-products.*

The mechanism of formation of the bicyclic systems of 2,6- and 2,8-dialkylglycolurils, as well as the mechanism of formation of glycolurils from glyoxal and ureas, is still debated.[10,12,16] Two main pathways of these reactions were suggested in the literature:[10,12,16] 1) through the intermediate formation of 1-alkyl-4,5-dihydroxyimidazolidin-2-one **3** from glyoxal and one 1-alkylurea molecule and 2) through the linear product **B** prepared by the reaction of glyoxal with two urea molecules. Ureidocarbinol **A** was assumed to be the precursor of both intermediates **3** and **B** (Scheme 4).

If the reaction follows the first pathway, intermediate **3** that formed in the second step of the reaction is protonated in the presence of an acid followed by elimination of the water molecule to generate the carbonium ion **C**. The latter reacts with the second urea molecule and gives the final glycoluril through the intermediate **D** and the second carbonium ion **E**. Two alternative reaction pathways through the intermediates **D**,**E** or **D″**,**E″** are possible depending on which urea fragment, NH_2 or NHR, is bound to the carbonium ion **C** to give *trans* isomer **6** or *cis* isomer **7**, respectively.

If the reaction follows the second pathway, glycolurils are, apparently, produced by two successive cyclizations of the linear intermediate **B**. The first cyclization affords the intermediate **D´**, which is transformed into the carbonium ion **E´**. The latter undergoes cyclization to the final glycoluril **6**. However, the reactions of glyoxal with monoalkylureas **2** always produced mixtures of *trans*- and *cis*-glycolurils **6** and **7**. In addition, the reactions yielded hydantoins **8** as by-products, which were formed from the carbonium cation **C** as a precursor. Hence, the first reaction pathway through the formation of 1-alkyl-4,5-dihydroxyimidazolidin-2-ones **3** seems to be more likely. This conclusion is also indirectly supported by the following facts:

— earlier, we have synthesized 5-substituted arylsulfonyliminoimidazolidin-2-ones by the reaction of 1-alkyl-4,5-dihydroxyimidazolidin-2-ones with arylsulfamides,[17] which confirms higher stability of the carbocation bearing a charge on the carbon atom adjacent to the alkyl-substituted nitrogen atom;

— we have described[24] the regioselective reaction of 1-methylurea with acetaldehyde giving rise to both 2,5,7,8-tetramethyl- and 2,5,7,10-tetramethyl-2,4,8,10-tetraazabicyclo[4.4.0]decane-3,9-diones, which is evidence that not only the NH_2 group but also the H—N—Alk fragment are involved in condensation of 1-methylurea with aldehyde.

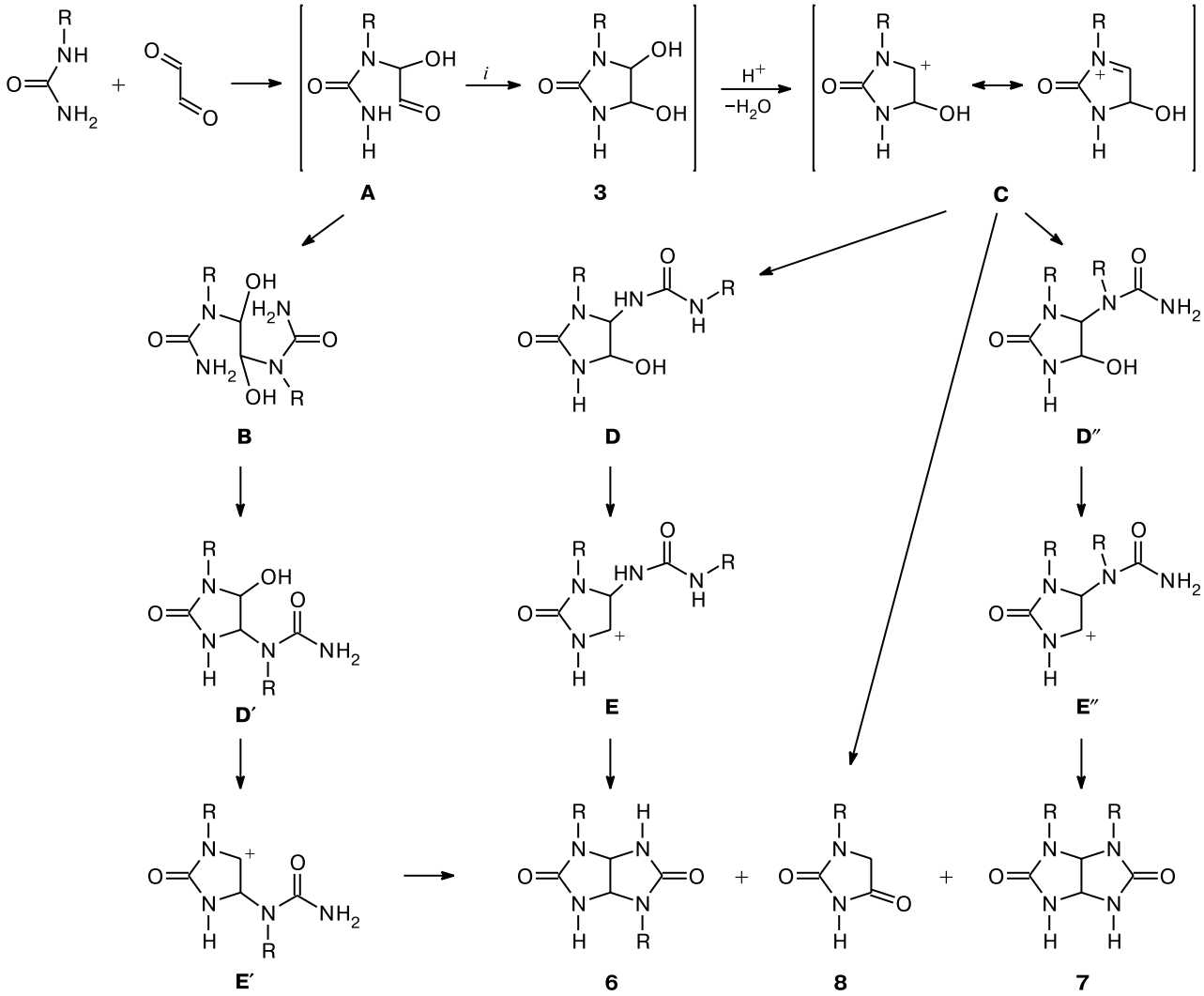
In addition to the sequence of transformations of a particular intermediate shown in Scheme 4, the order in which the NH fragments of the starting 1-alkylurea **2** are involved in condensation with glyoxal is also of fundamental importance for the possible formation of the *trans* or *cis* isomers (2,6- (**6**) or 2,8-dialkylglycolurils (**7**), respectively). It was hypothesized[12,16] that this condensation first occurs at the free NH_2 group of the starting urea **2**. If this is the case, the reactions would always afford only the *trans* isomers, *viz.*, 2,6-dialkylglycolurils **6**, in accordance with Scheme 4. The formation of 2,8-dialkylglycolurils **7** along with glycolurils **6** is indicative of the possible condensation of glyoxal with the H—N—Alk fragment of urea **2**.

To elucidate the possible direction of the first step of condensation of glyoxal with 1-alkylureas **2**, we calculated the three-dimensional and electronic structures of compounds **2a,b,e,g,h** by semiempirical quantum-chemical methods (MNDO and PM3) using the MOPAC and WinMOPAC program packages. The results of calculations are given in Table 1. Analysis of the charge distributions showed that the more negative charge is always localized on the nitrogen atom of the NH—Alk fragments. The dipole moments of the compounds under study depend only slightly on the length of the alkyl fragment, whereas the enthalpies of formation are indicative of an increase in thermochemical stability with increasing length of the alkyl chain. These data confirm our hypothesis that the reaction of glyoxal with ureas occurs at the NH—Alk fragment.

To elucidate the factors responsible for the fact that cyclization follows the first pathway, the three-dimensional and electronic structures of the intermediates (**D**, **D´**, and **DI″**) and the corresponding cations

* The synthesis of hydantoins will be published elsewhere, and here we do not report their physicochemical characteristics.

Scheme 4



i. Rapidly.

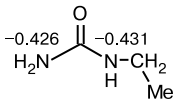
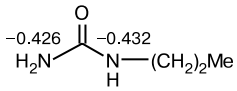
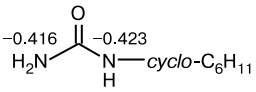
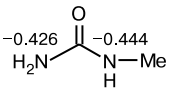
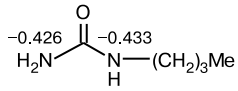
(**E**, **E′**, and **E″**) were calculated by the quantum-chemical MNDO method. The results of calculations are given in Table 2.

Analysis of the results of calculations demonstrated that the isomer **D** is the thermochemically most stable compound, which is characterized by the deepest minimum on the potential energy surface ($E = -2735.292$ eV), whereas the isomer **D′** is the least stable compound ($E = -2734.887$ eV).

A comparison of the stabilities of the corresponding cations shows that the cation **E** is the most stable species (the total energy of the molecule was −2392.762 eV), whereas the cation **E′** is the least stable species and has the energy of −2392.351 eV. The cation **E** is characterized by the highest positive charge on the cationic C center (0.437), whereas the cation **E′** is characterized by the lowest positive charge on the C atom (0.406). As for the ionization potentials, the cations **E** and **E′** are characterized by the lowest and highest potentials (10.617 and 10.778 eV, respectively). These data suggest that cyclization occuring through the formation of the intermediates **D** and **E** is most favorable both in the orbital- and charge-controlled reactions, resulting in the formation of *trans*-glycolurils, whereas cyclization through the intermediates **D′** and **E′** is least favorable. Hence, the formation of *cis*-glycolurils can occur, although it is less probable.

Therefore, both the calculated and experimental data demonstrate that the regioselectivity of the formation of bicyclic compounds **6** or **7** is virtually independent of the length of the alkyl chain or the volume of the substituent in 1-alkylureas **2**.

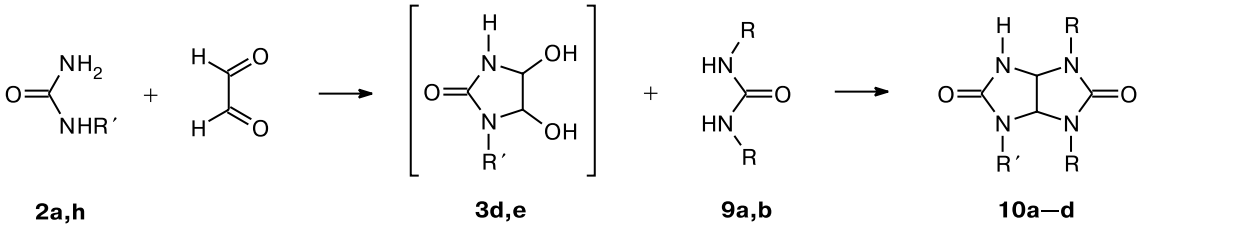
Table 1. Calculated characteristics of the electronic structures of 1-alkylureas **2**

Compound	Charges on atoms (MNDO)	Molecular formula (M)	μ/D[a]		PI[b] /eV		E_{HOMO}/E_{LUMO} ($E_{LUMO} - E_{HOMO}$)/eV		$-\Delta H_f^{\circ}$ [c] /kcal mol^{-1}	
			MNDO	PM3	MNDO	PM3	MNDO	PM3	MNDO	PM3
2a		$C_3H_8N_2O$ (88.109)	3.79	3.63	10.269	9.548	−10.269/ 1.824 (11.509)	−9.548/ 1.146 (10.693)	45.33	48.819
2b		$C_4H_{10}N_2O$ (102.136)	3.77	3.61	10.265	9.553	−10.265/ 1.831 (12.096)	−9.553/ 1.136 (10.690)	50.05	54.03
2e		$C_7H_{14}N_2O_2$ (142.200)	3.95	4.14	10.216	9.581	−10.216/ 1.784 (12.000)	−9.581/ 1.239 (10.821)	54.91	62.406
2h		$C_2H_6N_2O$ (74.082)	3.83	3.64	10.305	9.604	−10.305/ 1.882 (12.187)	−9.604/ 1.154	40.32	42.62
2g		$C_5H_{12}N_2O$ (116.163)	3.79	3.60	10.261	9.553	−10.261/ 1.825 (11.510)	−9.553/ 1.131 (10.685)	54.71	59.46

[a] The dipole moment.
[b] The ionization potential.
[c] The enthalpy of formation.

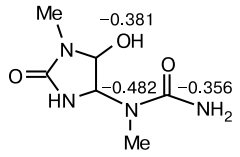
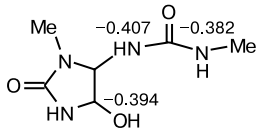
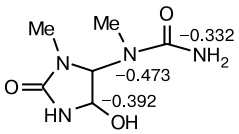
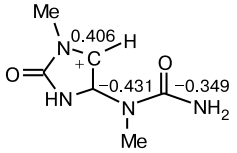
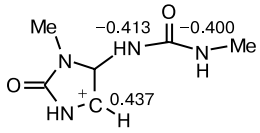
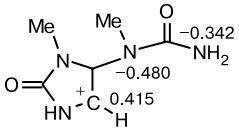
Earlier, we have demonstrated[21] that tri-*N*-alkylglycolurils can be synthesized according to two procedures: (1) by the reaction of 1,3-dialkyl-4,5-dihydroxyimidazolidin-2-ones (**3b**,**c**) (which were synthesized by the reactions of the corresponding ureas with glyoxal)[10,17] with 1-alkylureas **2a**,**h** or (2) by the one-pot reaction of 1-alkyl-4,5-dihydroxyimidazolidin-2-ones **3d,e** (which were synthesized by the reactions of 1-alkylureas **2a**,**h** with glyoxal) with 1,3-dialkylureas **9a**,**b** (Scheme 5). We used both these approaches to synthesize tri-*N*-alkylglycolurils and studied these approaches in more detail. The former reaction was carried out in an aqueous medium by acid catalysis with heating to 90 °C followed by keeping for 1 h. Under these conditions, we prepared

Scheme 5



	2a	**2h**	**3b**	**3c**	**3d**	**3e**	**9a**	**9b**	**10a**	**10b**	**10c**	**10d**
R	—	—	Me	Et	—	—	Me	Et	Me	Et	Me	Et
R^1	Et	Me	—	—	Et	Me	—	—	Et	Et	Me	Me

Table 2. Characteristics of the electronic structures of the compounds calculated by the MNDO method

Compound	Charges on atoms (MNDO)	Molecular formula (M)	μ/D	PI /eV	E_{HOMO}/E_{LUMO} ($E_{LU\ MO} - E_{HOMO}$) /eV	ΔH_f° /kcal mol^{-1}	E_{total}/eV
D′		$C_6H_{12}N_4O_3$ (188.186)	5.25	10.262	−10.262/ 0.948 (11.210)	−141.83	−2734.887
D		$C_6H_{12}N_4O_3$ (188.186)	10.53	10.476	−10.476/ 1.041 (11.517)	−152.51	−2735.292
D″		$C_6H_{12}N_4O_3$ (188.186)	9.89	10.320	−10.320/ 0.742 (11.062)	−144.14	−2734.937
E′		$C_6H_{11}N_4O_2$ (171.179)	7.51	10.778	−10.778/ −1.030 (9.748)	41.836	−2392.351
E		$C_6H_{11}N_4O_2$ (171.179)	13.35	10.617	−10.617/ −0.732 (9.885)	30.07	−2392.762
E″		$C_6H_{11}N_4O_2$ (171.179)	14.12	10.744	−10.744/ −0.866 (9.878)	37.63	−2392.455

the following 2,4,6-trialkylglycolurils: **10a** (44—46%), **10b** (37—39%), **10c** (47—49%), and **10d** (40—42%) (Scheme 5).

The second procedure was carried out using TLC and ^{1}H NMR control of the reaction mixtures. First, we studied the reactions of methyl- and ethylureas **2h**,**a** with glyoxal under the conditions of the reaction giving rise to 4,5-dihydroxyimidazolidin-2-ones (pH 4—5, a 40% aqueous solution of glyoxal, an equimolar reagent ratio, and heating of the reaction mixture at 50 °C).[23] The reaction was monitored based on the disappearance of the signals for the *N*-methyl protons of the starting ureas **2** (at δ 3.72, singlet (**2h**), and at δ 1.00, triplet ^3J = 8 Hz (**2a**)) in the ^{1}H NMR spectra of the reaction mixtures. The results of ^{1}H NMR spectroscopy combined with the TLC control demonstrated that the starting ureas **2h,a** were completely consumed within 2 h, and the ^{1}H NMR spectra showed only signals of 4,5-dihydroxyimidazolidin-2-ones **3d,e**.

These conditions were used in the one-pot synthesis of glycolurils **10a—d**. First, we synthesized **3d,e** by the reaction of **2a,h** with glyoxal and used these compounds (without isolation) in the reactions with 1,3-dimethyl(diethyl)ureas **9a,b**; pH was changed to 1, and the reaction mixture was kept at 90 °C for 1 h. The yields of the target glycolurils were as follows: **10a**, 50—52%; **10b**, 37—39%; **10c**, 32—35%; and **10d**, 60—61%. A comparative analysis demonstrated that the first reaction is a method of choice for the synthesis of compound **10c**, whereas compounds **10a,d** are more convenient to prepare according to the second procedure. Both methods are suitable for the synthesis of compound **10b**, because these methods afforded **10b** in nearly equal yields. The physicochemical characteristics of glycolurils **10** have been described in detail in our earlier publication.[21]

Earlier, we have established the structure of glycoluril **10a** by X-ray diffraction and demonstrated that crystalli-

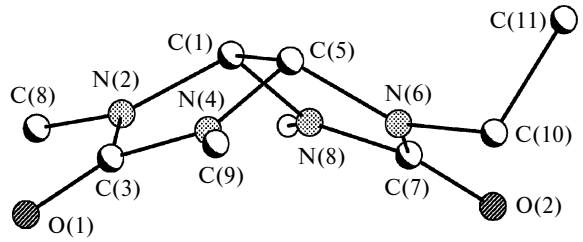
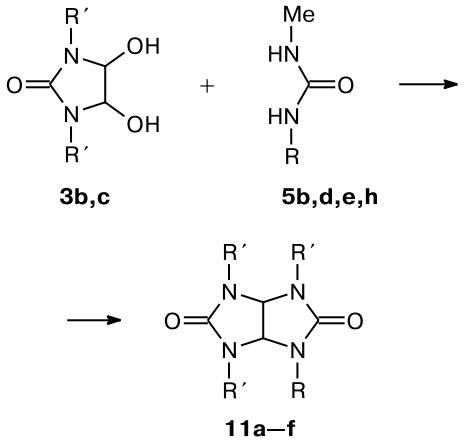


Fig. 3. Overall view of molecule **10a**.

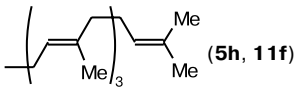
zation of the racemate is accompanied by the spontaneous enantiomeric separation. Compound **10a** crystallizes in the space group $P\bar{1}$ with four independent molecules per asymmetric unit. Molecules **10a** have no symmetry elements and exist as one of the possible enantiomers.[25] The presence of four independent molecules per asymmetric unit suggests that other polymorphs can exist along with the above-considered crystal modification. Because of this, we repeated X-ray diffraction analysis of compound **10a** (Fig. 3), which unexpectedly demonstrated that **10a** crystallizes in the centrosymmetric space group $P\bar{1}$ with two independent molecules and the identical unit cell parameters (see Ref. 25 and Table 6). Therefore, the spontaneous separation of **10a** was not observed and the earlier X-ray diffraction data are incorrect. The main geometric parameters, including the conformation of molecule **10a**, are similar to the previous data.[25] In the crystal, the independent molecules are linked to each other by N—H...O hydrogen bonds (2.865(3)—2.888(3) Å) to form dimers. Other contacts in the crystal of **10a** belong to usual van der Waals interactions.

Only one procedure for the synthesis of chiral tetraalkylglycolurils was described in the literature.[7,22] This procedure is based on alkylation of 2,6-dialkylglycolurils **6**. In the present study, we synthesized chiral tetraalkylglycolurils **11** and **12** using two procedures: (1) cyclocondensation of 1,3-dimethyl(diethyl)-4,5-dihydroxyimidazolidin-2-ones **3b,c** with 1-alkyl-3-methylureas **5b,d,e,h** or (2) the reaction of **5d,e** with glyoxal. In both cases, the reactions were carried out in isopropanol at 80—82 °C using acid catalysis (in the latter case, glyoxal was used as trimeric dihydrate). The reactions of compounds **3b,c** with 1-alkyl-3-methylureas afforded tetraalkylglycolurils **11** in 57—72% yields (Scheme 6). The reactions of dialkylureas **5d,e** with glyoxal occurred regioselectively to give *trans*-tetraalkylglycolurils **12** as the major products. The reactions also produced isomeric *cis*-tetraalkylglycolurils **13** and hydantoins **14** and **15** (Scheme 7), which was confirmed by ^{1}H NMR spectroscopy of the reaction mixtures concentrated to dryness. Hydantoins **14** and **15** were not isolated, but the ^{1}H NMR spectra showed the signals for their protons: two singlets of the CH_2 groups at δ 3.9—4.1, whose integral intensities correspond to the intensities of the signals for other groups of protons of hydantoins **14** and **15**. Glycolurils **12d** and **13d** were isolated by fractional crystallization. Glycolurils **12e** and **13e** were isolated by preparative column chromatography on SiO_2. Compounds **12** and **13** were synthesized in 32—39 and 24—28% yields, respectively. Evidently, the regioselective formation of compounds **12** is controlled by the steric factors.

Scheme 6



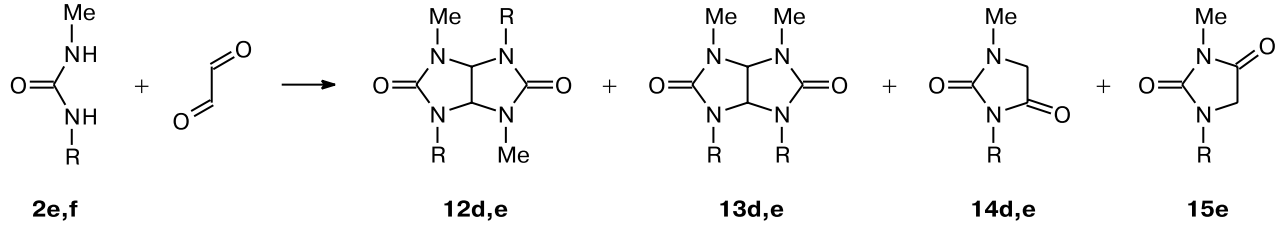
R = Pr (**5b**, **11a**), Bu^t (**5d**, **11b,d**), *cyclo*-C_6H_{11} (**5e**, **11c,e**),



(**5h**, **11f**)

R′ = Me (**3b**, **11a,b,c,f**); Et (**3c**, **11d,e**)

Scheme 7



R = Bu^t (**d**), *cyclo*-C_6H_{11} (**e**)

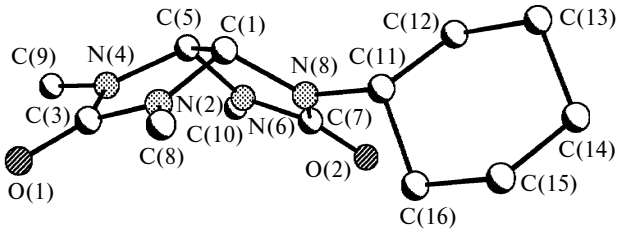


Fig. 4. Overall view of molecule **11c**.

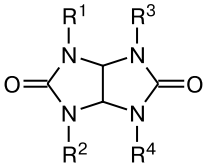
The structure of one of the resulting tetraalkylglycolurils was established by X-ray diffraction analysis. The single-crystal investigation of **11c** demonstrated that this compound crystallizes in the racemic space group as a hydrate (Fig. 4). The bond lengths and bond angles in **11c** are close to the corresponding values in alkyl derivatives of glycolurils studied earlier.[7—9] The hydrogen atoms at the C(1) and C(5) atoms are in the *cis* arrangement. The five-membered rings adopt an envelope conformation with the C(1)/C(5) atoms deviating by 0.11 Å. The angle between the planes of the five-membered rings is 123°. The nitrogen atoms in the ring are planar with the maximum deviation observed for the N(8) atom (the deviation of the C(1), C(7), and C(11) atoms from the plane is 0.12 Å), which is, apparently, associated with the presence of the cyclohexane ring.

Analysis of the crystal packing showed that molecules **11c** are linked to each other to form dimers by medium-strength O—H...O hydrogen bonds (O...O, 2.842 Å) involving the water solvate molecule located at the inversion center.

Most of the chiral glycolurils synthesized in the present study have not been described in the literature. The yields, melting points, elemental analysis data, and spectroscopic characteristics, which confirmed the structures of all these compounds, are given in Tables 4 and 5.

Experiments on crystallization of compounds **1**, **4**, **6**, **7**, and **10—13** allowed us to grow high-quality crystals of only compounds **10a** and **11c**, whereas crystals of the other compounds are unsuitable for X-ray diffraction study. Hence, the separation of racemic mixtures presents a special problem.

To solve this problem, we examined, for the first time, the possibility of using chiral HPLC for the enantiomeric separation of racemates of chiral *N*-alkyl-substituted glycolurils 2-Me-,[10] 2-Et- (**1a**), 2-Pr- (**1b**), 2-Bu^t-4-Me- (**4d**), 2,6-Et_2- (**6a**), 2,6-Bu_2- (**6g**), 2,6-*cyclo*-C_6H_{11}- (**6e**), 2,6-Me_2- (**6h**), 2,4,6-Et_3- (**10b**), 2,4,6-Me_3-8-Pr- (**11a**), 2,4,6-Me_3-8-*cyclo*-C_6H_{11}-glycolurils (**11c**), and "albicar" (2,6-Me_2-4,8-Et_2-glycoluril). The aims were to evaluate the prospects of the preparative separations and develop convenient procedures for the enantiomeric analysis of chiral products. A series of commercial chiral HPLC columns, primarily, based on cellulose and amylose derivatives, were tested. However, nonpolar eluents, for example, mixtures of hexane and isopropanol, were recommended for most of these columns. In these media, the solubility of glycolurils is too low, whereas these compounds are poorly retained on most of chiral phases in polar media (mixtures of water and acetonitrile). A Chirobiotic TAG column (250×4 mm) (Advanced Separation Technologies Inc.), in which the macrocyclic antibiotic Teicoplanin Aglycone containing eight chiral centers covalently bound to silica gel served as the sorbent, proved to be a column of choice. On this column, glycolurils were retained for a rather long period of time with the use a 50% aqueous MeOH solution as the standard eluent (an UV detector, 206 nm). Of the twelve racemates under study, five compounds showed a satisfactory enantiomeric separation in this eluent. Selected results are given in Table 3. For seven racemates, the peaks of enantiomers overlap to a substantial extent, and an improvement of separation requires further optimization of the conditions. When examining the possibility of the separation of the racemate of "albicar" (after preliminary preclinical studies), in spite of a poor peak resolution (R_s = 1.2), we succeeded in isolating individual enantiomers for a more detailed investigation by repeated chromatography on an analytical column. We performed the successful enantiomeric separation of 2-Et- (**1a**), 2-Pr^n- (**1b**), 2-Bu^t-4-Me- (**4d**), and 2,6-Me_2-substituted glycolurils (**6h**).



Compound	R^1	R^2	R^3	R^4
"Albicar"	Me	Et	Et	Me
1a	Et	H	H	H
1b	Pr	H	H	H
4d	Me	Bu^t	H	H
6h	Me	H	H	Me

To summarize, we developed two general procedures for the synthesis of previously unknown chiral mono-, 2,4-; 2,6-di-, 2,4,6-tri-, and tetraalkylglycolurils by the

Table 3. Results of enantiomeric separation of glycolurils by HPLC on a Chirobiotic TAG column (250×4 mm)

Compound	k_1	k_2	α	R_s
"Albicar"	1.32	1.57	1.19	1.2
1a	1.05	2.0	1.91	3.5
1b	1.29	1.65	1.28	1.5
4d	1.71	3.39	1.98	3.7
6h	0.74	0.85	1.15	0.8

Note. k_i is the retention factor, α is the separation factor, and R_s is the peak resolution.

reactions of the corresponding monoalkyl- and 1-alkyl-3-methylureas with glyoxal or 4,5-dihydroxyimidazolidin-2-ones in water or isopropanol using acid catalysis, which substantially extends the range of chiral glycolurils containing alkyl substituents at the nitrogen atoms. When studying the reactions of monoalkyl- and 1-alkyl-3-methylureas with glyoxal, we observed the regioselectivity of the formation of 2,6-dialkyl- and 2,6-dialkyl-4,8-dimethylglycolurils. The mechanism of formation of dialkylglycolurils was proposed based on experimental data and results of quantum-chemical calculations. We demonstrated for the first time that chiral glycolurils can be separated into enantiomer by analytical chiral-phase HPLC.

Experimental

Commercial (Acros) urea, dimethylurea, diethylurea, a 40% aqueous glyoxal solution, and glyoxal trimeric dihydrate were used. 1-Alkylureas **2a—h** and 1-alkyl-3-methylureas **5a—g** were synthesized by the reactions of the corresponding amines with KOCN and MeNCO.[26,27] 4,5-Dihydroxyimidazolidin-2-ones **3** were prepared by the reactions of the corresponding ureas with glyoxal according to procedures described earlier.[17,23,28]

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 in the δ scale relative to Me_4Si as the internal standard. The mass spectra were obtained on a Varian MAT CH-6 mass spectrometer (70 eV). The melting point was determined on a GALLENKAMP instrument (Sanyo). The enantiomeric analysis of compounds **1a,b, 4d**, and **6h** and "albicar" was carried out by HPLC on a Chirobiotic TAG (250×4 mm) column (Advanced Separation Technologies Inc.), in which the macrocyclic antibiotic Teicoplanin Aglycone containing eight chiral centers covalently bound to silica gel was used as the sorbent (50% aqueous MeOH solution as the eluent, an UV detector, 206 nm).

Synthesis of chiral glycolurils: 2-ethyl- (1a), 2-propyl- (1b), 2-*sec*-butyl- (1c), 2-*tert*-butyl- (1d), 2-cyclohexyl- (1e), 2-dodecyl- (1f), 4-ethyl-2-methyl- (4a), 2-methyl-4-propyl- (4b), 2-*sec*-butyl-4-methyl- (4c), 2-*tert*-butyl-4-methyl- (4d), 4-cyclohexyl-2-methyl- (4e), 2-butyl-4-methyl- (4f), 6-ethyl-2,4-dimethyl- (10a), 2,4,6-triethyl- (10b), 2,4-ethyl-6-methyl- (10d), 2,4,6-trimethyl-8-propyl- (11a), 2-*tert*-butyl-4,6,8-trimethyl- (11b), 8-cyclohexyl-2,4,6-trimethyl- (11c), 2-*tert*-butyl-6,8-diethyl-4-methyl- (11d), 4-cyclohexyl-6,8-diethyl-2-methyl- 11(e), and 2-[(2*E*,6*E*,10*E*)-3,7,11,15-tetramethylhexadeca-2,6,10,14-tetraenyl]-4,6,8-trimethyl-2,4,6,8-tetraazabicyclo[3.3.0]octane-3,7-dione (11f) (general procedure). Concentrated hydrochloric acid (0.2 mL) was added (in an aqueous medium to pH of 1) to a solution of the corresponding urea **2** (**2a,b—f**, **5a—h**) (0.02 mol) and 1,3-H-, 1,3-Me_2-, or 1,3-Et_2-4,5-dihydroxyimidazolidin-2-one (**3a—c**) (0.02 mol) in the minimum amount of water or isopropanol (depending on the solubility of the starting compounds). In the synthesis of compounds **1a—c,f**, **4a—c,f**, **10a,b,d**, and **11a—f**, the reaction mixture was kept at reflux temperature for 1 h. In the synthesis of compounds **1d,e** and **4d,e** the reaction mixture was kept at reflux temperature for 1.5 h. Then the reaction mixture (**1a—c**, **4a—c,f**, **10a,b,d**, and **11a,b,d,f**) was concentrated to one-half of the initial volume and kept in a refrigerator for 12 h. The precipitate that formed (**1a—c**, **4a—c,f**, or **11a,b,d**) was filtered off and recrystallized from water. Compounds **10a,b,d** were extracted ten times with chloroform (the volumes were equal to the volumes of the evaporated reaction mixtures). The chloroform extracts were concentrated to dryness and the residues were recrystallized from dioxane. In the case of compounds **1d,e**, **4d,e**, and **11c**, the reactions afforded precipitates, which were filtered off and recrystallized from MeOH.

In the case of compound **1f**, water was evaporated *in vacuo* until an oily residue formed. The latter was triturated in a 1 : 3 acetone—diethyl ether mixture (10 mL). The precipitate of **1f** that formed was filtered off and recrystallized from MeOH. The yields and physicochemical characteristics of compounds **1a—f**, **4a—f**, and **11a—f** are given in Tables 4 and 5.

Synthesis of 2,4,6-trimethyl-2,4,6,8-tetraazabicyclo[3.3.0]octane-3,7-dione (10c). A 20% aqueous NaOH so-

Table 4. Yields and selected physicochemical characteristics of mono-, di-, tri-, and tetraalkylglycolurils

Compound	Yields (%)	M.p. /°C	Found / Calculated (%)			Molecular formula
			C	H	N	
1a	68—70	278—280	42.27 42.35	5.97 5.92	33.10 32.92	$C_6H_{10}N_4O_2$
1b	60—63	250—252	45.22 45.64	6.32 6.57	30.98 30.42	$C_7H_{12}N_4O_2$
1c	70—72	303—305	48.43 48.47	7.15 7.12	27.99 28.26	$C_8H_{14}N_4O_2$
1d	89—91	279—280	48.53 48.47	7.18 7.12	28.31 28.26	$C_8H_{14}N_4O_2$
1e	87—90	300—303	53.49 53.56	7.30 7.19	25.07 24.98	$C_{10}H_{16}N_4O_2$

(*to be continued*)

Table 4 (*continued*)

Compound	Yields (%)	M.p. /°C	Found / Calculated (%)			Molecular formula
			C	H	N	
1f	78—80	255—256	61.81 61.90	9.53 9.74	17.89 18.05	$C_{16}H_{30}N_4O_2$
4a	75—77	248—250	45.75 45.64	6.68 6.57	30.55 30.42	$C_7H_{12}N_4O_2$
4b	86—88	270—272	48.37 48.47	7.14 7.12	28.12 28.26	$C_8H_{14}N_4O_2$
4c	85—86	274—276	50.87 50.93	7.57 7.60	26.31 26.40	$C_9H_{16}N_4O_2$
4d	85—86	264—266	50.85 50.93	7.71 7.60	26.37 26.40	$C_9H_{16}N_4O_2$
4e	90—92	256—258	55.51 55.44	7.64 7.61	23.46 23.51	$C_{11}H_{18}N_4O_2$
4f	88—89	238—240	51.04 50.93	7.68 7.60	26.52 26.40	$C_9H_{16}N_4O_2$
6a	48—50	292—294	48.44 48.47	7.09 7.12	28.31 28.26	$C_8H_{14}N_4O_2$
6b	53—55	293—295	53.11 53.08	7.95 8.02	24.81 24.76	$C_{10}H_{18}N_4O_2$
6d	40—42	340—341	56.74 56.67	8.75 8.72	21.97 22.03	$C_{12}H_{22}N_4O_2$
6e	61—63	365—367	62.68 62.72	8.56 8.55	18.32 18.29	$C_{16}H_{26}N_4O_2$
6g	42—44	319—322	31.27 31.31	2.58 2.63	24.27 24.35	$C_6H_6N_4O_6$
7a	16—18	300—301	48.52 48.47	7.15 7.12	28.21 28.26	$C_8H_{14}N_4O_2$
7b	12—14	287—289	53.00 53.08	7.98 8.02	24.81 24.76	$C_{10}H_{18}N_4O_2$
7d	15—17	332—335	56.70 56.67	8.69 8.72	22.07 22.03	$C_{12}H_{22}N_4O_2$
7e	18—20	355—357	62.73 62.72	8.52 8.55	18.30 18.29	$C_{16}H_{26}N_4O_2$
7g	20—22	312—314	56.61 56.67	8.75 8.72	22.06 22.03	$C_{12}H_{22}N_4O_2$
11a	57—59	126—128	51.00 50.93	7.58 7.60	26.45 26.40	$C_9H_{16}N_4O_2$
11b	63—65	118—120	55.01 54.98	8.40 8.39	23.27 23.32	$C_{11}H_{20}N_4O_2$
11c	70—72	120—122	58.65 58.62	8.30 8.33	21.05 21.04	$C_{13}H_{24}N_4O_2$
11d	59—61	138—140	58.22 58.18	9.04 9.01	20.95 20.88	$C_{13}H_{22}N_4O_2$
11e	65—66	131—135	61.18 61.20	8.94 8.90	18.99 19.03	$C_{15}H_{26}N_4O_2$
11f	60—61	286—287	70.51 70.55	9.59 9.56	12.65 12.66	$C_{26}H_{42}N_4O_2$
12d	32—35	248—250	59.48 59.55	9.27 9.28	19.82 19.84	$C_{14}H_{26}N_4O_2$
12e	37—39	260—262	64.71 64.64	9.08 9.04	16.73 16.75	$C_{18}H_{30}N_4O_2$
13d	24—25	239—241	59.61 59.55	9.23 9.28	19.83 19.84	$C_{14}H_{26}N_4O_2$
13e	26—28	254—256	64.63 64.64	9.07 9.04	16.72 16.75	$C_{18}H_{30}N_4O_2$

Table 5. Spectroscopic characteristics of mono-, di-, tri-, and tetraalkylglycolurils

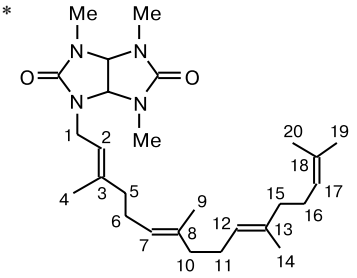
Glycoluril	MS m/z (I (%))	^{1}H NMR (δ, (DMSO-d_6), J/Hz)
1a	170 (43), 155 (100), 126 (10), 112 (22), 85 (13)	1.03 (t, 3 H, CMe, J = 7.1); 2.98 (m, 1 H, CH_2); 3.22 (m, 1 H, CH_2); 5.19, 5.28 (both d, 1 H each, CHCH, J = 8.5); 7.28 (s, 2 H, 2NH); 7.45 (s, 1 H, NH)
1b	184 (23), 155 (61), 112 (100), 86 (10), 84 (10), 82 (10), 73 (10), 69 (52)	0.80 (t, 3 H, CMe, J = 7.3); 1.45 (m, 2 H, CH_2); 2.92, 3.10 (both m, 1 H each, NCH_2); 5.19, 5.26 (both d, 1 H each, 2 CH, J = 6.8); 7.26 (s, 2 H, 2 NH); 7.42 (s, 1 H, NH)
1c		0.79, 1.11 (both m, 3 H each, Me); 1.46 (m, 2 H, CH_2); 3.59 (m, 1 H, CH); 5.24 (m, 2 H, 2 CH); 7.20 (s, 1 H, NH); 7.25 (s, 1 H, NH); 7.33 (s, 1 H, NH)
1d		1.31 (s, 9 H, 3 Me); 5.10, 5.45 (both d, 1 H each, 2 CH, J = 8.1); 7.03 (br.s, 2 H, 2 NH); 7.23 (br.s, 1 H, NH)
1e		1.18 (m, 4 H, 2 CH_2); 1.60 (m, 6 H, 3 CH_2); 3.38 (m, 1 H, N—CH); 5.24, 5.32 (both d, 1 H each, 2 CH, J = 7.7); 7.18, 7.22 7.32 (s, 1 H, NH)
1f		0.87 (m, 3 H, CMe); 1.26 (br.s, 18 H, 9 CH_2); 1.45 (m, 2 H, CH_2); 2.95, 3.17 (both m, 1 H each, NCH_2); 5.19, 5.24 (both d, 1 H each, 2 CH, J = 8.3); 7.09 (br.s, 2 H, 2 NH); 7.30 (br.s, 1 H, NH)
4a		0.96 (m, 3 H, Me); 2.52 (s, 3 H, NMe); 2.98 (m, 2 H, CH_2); 5.12, 5.23 (both d, 1 H each, 2 CH, ^3J = 8.5); 7.58 (br.s, 2 H, 2 NH)
4b	169 (59), 126 (10), 113 (15), 112 (100), 85 (23), 84 (27), 71 (12), 69 (35)	0.80 (t, 3 H, CMe, J = 6.6); 1.45 (m, 2 H, CH_2); 2.62 (s, 3 H, NMe); 3.00 (m, 2 H, NCH_2); 5.10, 5.21 (both d, 1 H each, 2 CH, ^3J = 8.5); 7.50 (br.s, 2 H, 2 NH)
4c		0.78 (m, 3 H, $CH_2\underline{CH_3}$); 1.10 (d, 3 H, $CH\underline{CH_3}$, J = 7.3); 1.49 (m, 2 H, CH_2); 2.61 (s, 3 H, NMe); 3.56 (m, 1 H, NCH); 5.19, 5.73 (both d, 1 H each, 2 CH, J = 8.6); 7.39 (s, 1 H, NH); 7.50 (br.s, 1 H, NH)
4d	198 (15), 197 (95), 156 (10), 154 (13), 141 (10), 140 (100), 114 (25), 113 (13), 112 (13), 98 (10), 97 (22), 84 (38), 71 (17), 67 (12), 59 (19)	1.30 (s, 9 H, 3 CMe), 2.59 (s, 3 H, NMe); 4.97, 5.40 (both d, 1 H each, 2 CH, J = 7.9); 7.42, 7.52 (both s, 1 H each, NH)
4e	183 (100), 140 (26), 126 (77), 84 (16), 83 (31), 73 (10), 71 (11), 70 (17), 69 (11)	1.11 (m, 4 H, 2 CH_2); 1.62 (m, 6 H, 3 CH_2); 2.58 (s, 3 H, NMe); 3.43 (m, 1 H, CH); 4.94, 5.37 (both d, 1 H each, 2 CH, J = 8.2); 7.33, 7.48 (both s, 1 H each, NH)
4f		0.86 (m, 3 H, CMe); 1.23, 1.39 (both m, 2 H each, CH_2); 2.62 (s, 3 H, NMe); 3.08 (m, 2 H, NCH_2); 5.10, 5.21 (both d, 1 H each, 2 CH, J = 7.9); 7.5 (br.s, 2 H, 2 NH)
6a		1.03 (t, 6 H, 2 Me, J = 7.1); 3.00, 3.21 (both m, 2 H each, 2 CH_2); 5.23 (s, 2 H, CHCH); 7.48 (br.s, 2 H, 2 NH)
6b		0.81 (m, 6 H, 2 Me); 1.50 (m, 4 H, 2 CCH_2); 2.98, 3.17 (both m, 1 H each, NCH_2); 5.18 (s, 2 H, CHCH); 8.00 (br.s, 2 H, 2 NH)
6d		1.31 (s, 18 H, 6 Me); 5.24 (s, 2 H, CHCH); 8.08 (br.s. 2 H, 2 NH)
6e	225 (14), 220 (10), 167 (15), 166 (100), 163 (12), 142 (12), 141 (22), 138 (12), 112 (10), 99 (12), 98 (12), 84 (36), 83 (16), 81 (12), 73 (10), 71 (16), 69 (22), 67 (17)	1.16 (m, 8 H, 4 CH_2); 1.55 (m, 12 H, 6 CH_2); 3.38 (m, 2 H, CH); 5.27 (s, 2 H, CHCH); 7.36 (br.s, 2 H, 2 NH)
6g		0.89 (m, 6 H, 2 Me); 1.32, 1.45 (both m, 4 H each, 2 CH_2); 2.98 (m, 2 H, CH_2); 3.28 (m, 2 H, CH_2); 5.26 (s, 2 H, CHCH); 7.51 (br.s, 2 H, 2 NH)
7a		0.95 (m, 6 H, 2 Me); 2.97, 3.29 (both m, 2 H each, 2 CH_2); 5.15, 5.35 (both d, 2 H each, CHCH, J = 8.3)
7b		0.82 (m, 6 H, 2 Me); 1.51 (m, 4 H, 2 CH_2); 3.10 (m, 2 H, CH_2); 3.29 (m, 2 H, NCH_2); 5.17, 5.32 (both d, 2 H each, CHCH, J = 7.7); 7.83 (br.s, 2 H, 2 NH)

(*to be continued*)

Table 5 (*continued*)

Glycoluril	MS *m/z* (*I* (%))	^{1}H NMR (δ, (DMSO-d_6), *J*/Hz)
7d		1.22 (s, 9 H, 3 CMe); 5.06, 5.41 (both d, 2 H each, CHCH, *J* =8.1); 7.32 (br.s, 2 H, 2 NH)
7e		1.12 (m, 8 H, 4 CH_2); 1.65 (m, 12 H, 6 CH_2); 2.88 (m, 2 H, 2 CH); 5.15, 5.33 (both d, 2 H each, CHCH, *J* = 7.9); 7.28 (br.s, 2 H, 2 NH)
7g		0.94 (m, 6 H, 2 Me); 1.35 (m, 4 H, 2 CH_2); 1.47 (m, 4 H, 2 CH_2); 3.11 (m, 2 H, CH_2); 3.37 (m, 2 H, CH_2); 4.99, 5.39 (both d, 2 H each, CHCH, *J* = 7.4); 7.62 (br.s, 2 H, 2 NH)
11a		0.82 (t, 3 H, CMe, *J* = 7.6); 1.42 (m, 2 H, CH_2); 2.76 (s, 6 H, 2 Me); 2.88 (s, 3 H, Me); 2.94, 3.12 (both m, 1 H each, NCH_2); 5.19, 5.26 (both d, 1 H each, 2 CH, *J* = 7.0)
11b		1.35 (s, 9 H, 3 Me); 2.83 (s, 6 H, 2 Me); 2.85 (s, 3 H, Me); 5.41, 5.84 (both d, 1 H each, CHCH, *J* = 7.3)
11c		1.13 (m, 4 H, 2 CH_2); 1.71 (m, 6 H, 3 CH_2); 2.85 (s, 6 H, 2 Me); 2.91 (s, 3 H, Me); 3.47 (m, 2 H, 2 CH); 5.39, 5.44 (both d, 1 H each, CHCH, *J* = 8.0)
11d		1.00, 1.11 (both t, 3 H each, 2 Me, *J* = 6.7); 2.71 (s, 3 H, NMe); 1.37 (s, 9 H, 3 Me); 3.05 (m, 2 H, CH_2); 3.40 (m, 2 H, CH_2); 5.46, 5.90 (both d, 1 H each, CHCH, *J* = 7.6)
11e		1.04 (m, 6 H, 2 CMe); 1.21 (m, 4 H, 2 CH_2); 1.67 (m, 6 H, 3 CH_2); 2.75 (s, 3 H, NMe); 3.14 (m, 3 H, 2 NCH_2); 3.35 (m, 3 H, 2 NCH_2); 5.13, 5.28 (both d., 1 H each, CHCH, *J* = 8.6)
11f*		1.58 (br.s, 6 H, 3 CH_2(9,14,20)); 1.85 (s, 3 H, CH_3(4)); 1.87 (br.s, 1 H, C(19)H); 2.02 (m, 12 H, C(5)H_2, C(6)H_2, C(10)H_2, C(11)H_2, C(15)H_2, C(16)H_2); 2.79 (s, 6 H, 2 NMe); 2.93 (s, 3 H, NMe); 3.74 (m, 3 H, C(1)H_3); 5.09 (m, 5 H, C(7)H, C(12)H, C(17)H, CHCH); 5.20 (m, 3 H, C(2)H_3)
12d		1.35 (s, 18 H, 6 CMe); 2.80 (s, 6 H, NMe); 5.26 (s, 2 H, CHCH)
12e	334 (12), 252 (19), 180 (95), 170 (27), 127 (13), 113 (19), 99 (12), 98 (100), 85 (10), 83 (10), 82 (12), 69 (17)	1.21 (m, 8 H, 4 CH_2); 1.62 (m, 12 H, 6 CH_2); 2.75 (s, 6 H, 2 Me); 3.27 (m, 1 H, CH); 3.37 (m, 1 H, CH); 5.14 (s, 2 H, CHCH)
13d		1.21 (s, 18 H, 6 CMe); 2.72 (s, 6 H, NMe); 4.99, 5.39 (both d, 1 H each, CHCH, *J* = 8.2)
13e		1.19 (m, 8 H, 4 CH_2); 1.72 (m, 12 H, 6 CH_2); 2.80 (s, 6 H, 2 Me); 3.79 (m, 1 H, CH); 3.85 (s, 1 H, CH); 4.98, 5.25 (both d, 1 H each, CHCH, *J* = 8.4)

*



lution was added to a solution of methylurea **2h** (0.02 mol) in 40% aqueous glyoxal (0.02 mol) to pH 4—5 (a universal indicator). The reaction mixture was heated at 50 °C for 2 h. Then pH of the reaction mixture was brought to 1 (with 18% aqueous HCl) at the same temperature, 1,3-dimethylurea (0.02 mol) was added, and the reaction mixture was kept at 90 °C for 1 h. Then the reaction mixture was cooled to room temperature and extracted with $CHCl_3$ (0.5 volume of the reaction mixture was added 10 times). The combined portions were concentrated to an oily consistency and triturated with a mixture of diethyl ether and ethyl acetate (in a ratio of 2 : 1). The precipitate of compound **10c** was recrystallized from dioxane.

Synthesis of chiral glycolurils, *viz.*, 2,6-diethyl- (6a), 2,6-dipropyl- (6b), 2,6-di-*tert*-butyl- (6d), 2,6-dicyclohexyl- (6e), 2,6-dibutyl- (6g), 2,6-dimethyl- (6h), 2,6-di-*tert*-butyl-4,8-dimethyl- (12d), and 4,8-dicyclohexyl-2,6-dimethyl-2,4,6,8-tetraazabicyclo[3.3.0]octane-3,7-dione (12e), and achiral glycolurils, *viz.*, 2,8-diethyl- (7a), 2,8-propyl- (7b), 2,8-di-*tert*-butyl- (7d), 2,8-dicyclohexyl- (7e), 2,8-dibutyl- (7g), 2,8-dimethyl- (7h), 2,8-di-*tert*-butyl-4,6-dimethyl- (13d), and 4,6-dicyclohexyl-2,8-

Table 6. Selected crystallographic characteristics and parameters of structure refinement of **10a** and **11c**

Parameter	**10a**	**11c**
Molecular formula	$C_8H_{14}N_4O_2$	$C_{13}H_{22}N_4O_2 \cdot 1/2H_2O$
M	198.23	275.35
T/K	298	120
Diffractometer	Siemens P3/PC	Smart CCD
Crystal system	Triclinic	Monoclinic
Space group	$P\bar{1}$	$C2/c$
Z (Z')	4 (2)	8 (1)
a/Å	8.544 (2)	16.922 (3)
b/Å	9.723 (2)	12.187 (2)
c/Å	12.994 (3)	15.793 (3)
α/deg	78.43 (3)	—
β/deg	79.74 (3)	119.520 (3)
γ/deg	71.37 (3)	—
V/Å^3	994.6 (3)	2834.2 (8)
d_{calc}/g cm^{-3}	1.324	1.291
μ/cm^{-1}	0.98	0.91
F(000)	424	1192
$2\theta_{max}$/deg	54	60
Scanning mode	θ/2θ	ω
Number of measured reflections	4600	8637
(R_{int})	(0.0494)	(0.0206)
Number of independent reflections	4311	4065
Number of observed reflections	1706	2920
Number of parameters in refinement	268	269
R_1	0.0418	0.0518
wR_2	0.1875	0.1276
GOOF	0.870	1.007
Residual electron density (e_{max}/e_{min})/e Å^{-3}	−0.118/0.112	−0.279/0.338

dimethyl-2,4,6,8-tetraazabicyclo[3.3.0]octane-3,7-dione (13e) (general procedure). Concentrated hydrochloric acid (0.2 mL; in aqueous medium, pH 1) was added to a solution of the corresponding urea **2** (**2a,b,d,e,g,h**) (0.02 mol) in water or isopropanol (depending on the solubility) and 40% aqueous glyoxal (0.01 mol) (in the synthesis of **12d,e** and **13d,e**, glyoxal dihydrate (trimer) was added). The reaction mixture was kept with stirring at 80—90 °C for 1 h. After cooling, the reaction mixture was kept in a refrigerator for 48 h. Compound **6a** (**6b,d,e,g,h**) that precipitated was filtered off and recrystallized from water. In all cases, the filtrate was concentrated to one-half of the initial volume and cooled at +4 °C for 12 h. The crystalline precipitate of the corresponding compound **7** (**7a,b,d,e,g,h**) was filtered off and recrystallized from a mixture of methanol and water (5 : 2). Compounds **6** (**6a,b,d,e,g,h**) and **7** (**7a,b,d,g,h**) were recrystallized from water.

Compounds **12d,e** and **13d,e** precipitated as mixtures, and individual isomers were isolated by column chromatography on SiO_2 (100×160) using a 10 : 1 $CHCl_3$—CH_3OH mixture. The fractions of compounds **12d** (R_f = 0.66), **13d** (R_f = 0.48), **12e** (R_f = 0.56), and **13e** (R_f = 0.49) concentrated to dryness were recrystallized from methanol.

X-ray diffraction study of compounds 10a and 11c. Selected crystallographic parameters and characteristics of the structure refinement are given in Table 6. The structures were solved by direct methods. The positions of the hydrogen atoms in the structure of **10a** were calculated geometrically. The hydrogen atoms in the structure of **11c** were revealed from difference Fourier syntheses. All calculations were carried out using the SHELXTL PLUS 5.0 program package.[29]

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