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Novel synthesis of 1,6- and 1,4-dialkyl glycolurils and their supramolecular organization

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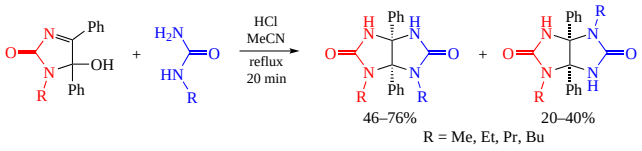
New regioselective reaction of 1-alkyl-5-hydroxy-4,5-diphenyl-1*H*-imidazol-2(5*H*)-one with alkylureas gives predominantly 1,6-dialkyl-3a,6a-diphenylglycolurils along with minor quantities of the 1,4-isomers. In case of propyl homologues, co-crystal of 1,6/1,4-dipropyl glycolurils would precipitate. Based on the analysis of the crystal packing of the products, new type of supramolecular chains for 1,4-disubstituted glycolurils has been identified.



Keywords: glycolurils, 1-alkylimidazolones, 1-alkylureas, supramolecular organization, regioselective condensation, X-ray.

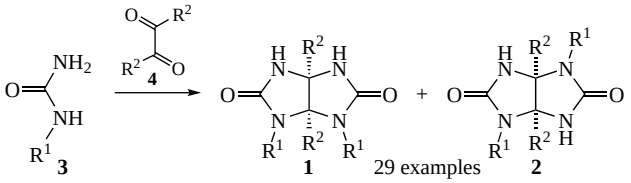
Glycolurils and their analogues including 1,6- and 1,4-disubstituted glycolurils (**1** and **2**, respectively) attract an attention as promising substrates in organic and supramolecular chemistry.[1–9] Based on 1,6-disubstituted glycolurils **1**, molecular receptors,[10,11] self-assembled molecular capsules[12] and dimers[13] have been obtained. Glycolurils **1** have been used to study mechanisms of formation of cucurbiturils[14,15] and as molecular templates for the intramolecular Claisen-type condensation.[16] The self-organization of 3a,6a-diphenylglycolurils was studied and their hydrophobic properties were demonstrated.[7]

Synthesis of compounds **1**,**2** is usually carried out by the reaction of 1-substituted ureas **3** with α-dicarbonyl compounds **4** (Scheme 1).[7,10,18,19] The regioselectivity of the formation of glycolurils **1** and **2** depends on both α-dicarbonyl compound **4** and urea **3** structures.[10]

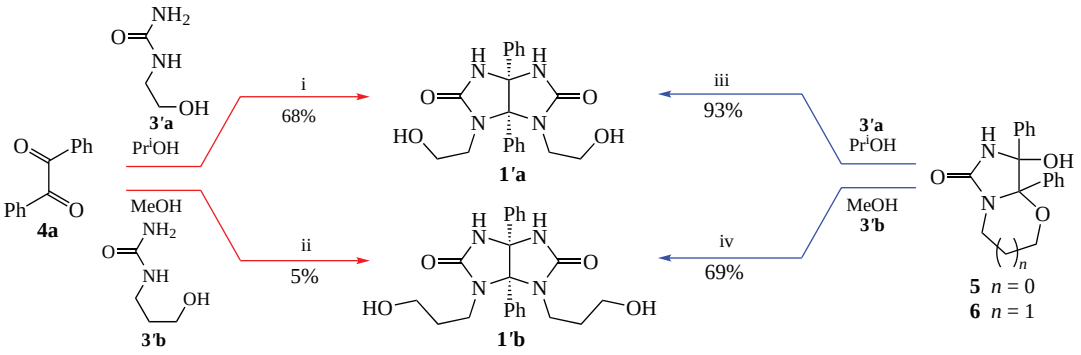
1,6-Bis(hydroxyalkyl)-3a,6a-diphenylglycolurils **1′a**,**b** are obtained by the reaction of (hydroxyalkyl)ureas **3′a**,**b** with either benzil **4a** or with bicyclic compounds **5**, **6** with high regioselectivity (Scheme 2).[20]

In this work, we studied in detail the reactions of 1-alkylureas **3a–d** with benzil **4a** (approach 1) or with 1-alkyl-5-hydroxyimidazolones **5a–d** (approach 2) to access 1,4- and 1,6-dialkyl-3a,6a-diphenylglycolurils **1a–d** and **2a–d**. The first approach involving benzil **4a** is outlined in Scheme 3 (the conditions such as HCl, MeCN, 6 h reflux were taken from ref. 7). The ratios of products **1a–d**/**2a–d** were determined from the ratios of integral intensities of signals for the Ph groups protons in the ^{1}H NMR spectrum [6.70–6.85 (2 H, Ph for **1a–d**) and 6.90–7.20 (8 H, Ph for **1a–d** + 10 H, Ph for **2a–d**)] (Figure 1).

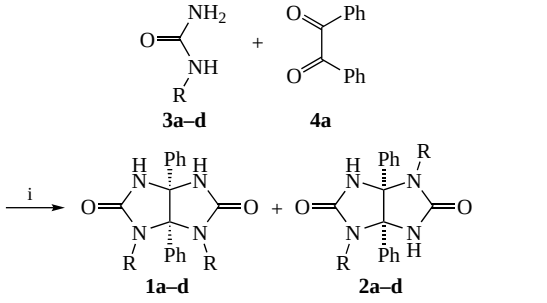
It was established that the selectivity of the formation of 1,6-isomers **1a–d** decreased with the lengthening of alkyl



Scheme 1



Scheme 2 *Reagents and conditions*: i, HCl, Pr^{i}OH, reflux, 2 h; ii, HCl, MeOH, reflux, 2 h; iii, HCl, Pr^{i}OH, reflux, 20 min; iv, HCl, MeOH, reflux, 8 h.



a R = Me (**1a**, 48%; **2a**, 24%) **c** R = Pr (**1c**, 5%; **2c**, 37%)
b R = Et (**1b**, 32%; **2b**, 20%) **d** R = Bu (**1d**, 15%; **2d**, 15%)

Scheme 3 *Reagents and conditions*: i, HCl, MeCN, reflux, 6 h.

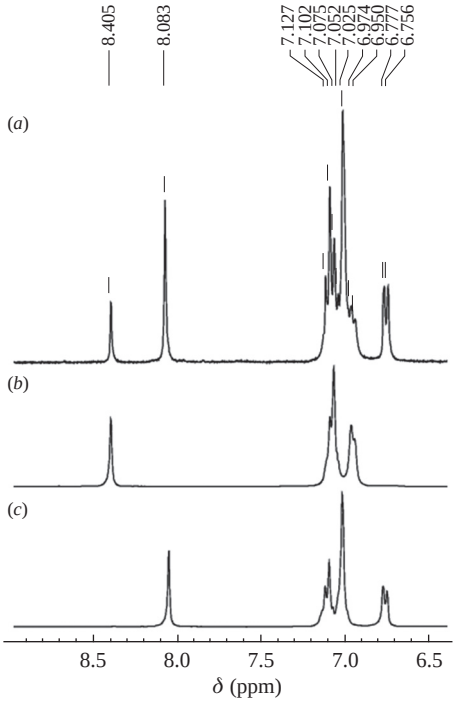
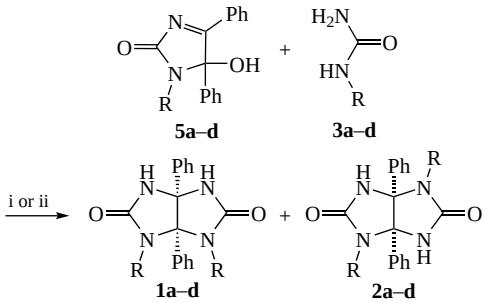


Figure 1 A fragment of the ^{1}H NMR spectrum of (*a*) the reaction mixture while the preparation of compounds **1a** and **2a**, (*b*) compound **2a** and (*c*) compound **1a**.

substituents in ureas **3a–d** (Me > Et > Pr > Bu) and completely disappeared when R was butyl. The ratio of the target glycolurils **1a–d**/**2a–d** ranged from 1.1 : 1 to 1.9 : 1 (1.9 : 1 for R = Me, 1.6 : 1 for R = Et, 1.1 : 1 for R = Pr and 1 : 1 for R = Bu). In addition, new co-crystal **1c** · **2c** (1 : 1) was isolated.

For studying the reaction of ureas **3a–d** with 1-alkyl-5-hyroxyimidazolones **5a–d** (Scheme 4) we used the conditions (HCl, Pr^{i}OH, reflux, 20 min) that we previously developed for the preparation of 1,6-disubstituted glycoluril **1′a** from 1-(2-hydroxyethyl)urea and bicyclic compound **5**.[11] Substrates **5a–d** were synthesized according to the literature.[12] The target glycolurils **1a–d** (32–41%) and **2a–d** (9–27%) were formed selectively with the predominant formation of 1,6-dialkyl glycolurils **1a–d**. The ratios of products **1a**/**2a**, **1b**/**2b**, **1c**/**2c**, **1d/2d** ranged from 1.4 : 1 to 3 : 1 (1.5 : 1 for R = Me, 2.8 : 1 for R = Et, 1.4 : 1 for R = Pr and 3 : 1 for R = Bu). Moderate yields of products **1a–d** and **2a–d** may be explained by hydrolysis of imidazolones **5a–d** to benzil and ureas **3a–d**.

When using another solvent (MeCN), the selectivity for the formation of glycolurils **1** increases. The ratios of products **1a**/**2a**, **1b**/**2b**, **1c**/**2c** and **1d**/**2d** ranged from 2 : 1 to 4 : 1 (2 : 1 for R = Me, 2.8 : 1 for R = Pr, 3.3 : 1 for R = Et, 4 : 1 for R = Bu). The yields of glycolurils **1a–d** and **2a–d** were 61–76 and 20–31%, respectively. It is obvious that approach 2 (conditions ii) is more



a R = Me [**1a**: 41% (i), 61% (ii); **2a**: 27% (i), 31% (ii)]
b R = Et [**1b**: 32% (i), 68% (ii); **2b**: 9% (i), 20% (ii)]
c R = Pr [**1c**: 6% (i), 46% (ii); **2c**: 2% (ii); **1c**·**2c**: 26% (i), 40% (ii)]
d R = Bu [**1d**: 34% (i), 76% (ii); **2d**: 10% (i), 20% (ii)]

Scheme 4 *Reagents and conditions*: i, Pr^{i}OH, reflux, 20 min; ii, MeCN, reflux, 20 min.

selective for the synthesis of 1,6-disubstituted glycolurils **1** than approach 1.

Self-organization of glycolurils **2c**,**d** and co-crystal **1c** · **2c** (1 : 1) grown from acetonitrile was studied by X-ray diffraction (Figure 2).† It was found that the self-organization of molecules in crystals of 1,4- and 1,6-disubstituted 3a,6a-diphenylglycolurils demonstrated new examples of supramolecular synthons with $R_2^2(8)$ motif[22] based on an N–H···O=C hydrogen bond at room temperature.

Co-crystal **1c** · **2c** exists in the monoclinic space group *C*2/*c*, the N–H···O=C hydrogen bonds [N···O 2.8307(19)–2.899(2) Å, NHO 161.17(10)–167.04(10)°] produce zig-zag chain along the

† *Crystal data for* **2c**. $C_{22}H_{26}N_4O_2$, F_w = 378.47, triclinic, a = 8.8234(7), b = 14.8956(11) and c = 16.1940(12) Å, α = 75.029(2), β = 87.532(2) and γ = 84.045(2)°, V = 2044.7(3) Å^3, space group $P\bar{1}$, Z = 4, d_{calc} = 1.229 g cm^{-3}, $F(000)$ = 808, $\mu(MoK_\alpha)$ = 0.81 cm^{-1}. Total of 23655 reflections (unique 9868, R_{int} = 0.0334) were measured on a Bruker APEX II CCD diffractometer, using graphite monochromated MoK_α radiation (λ = 0.71073 Å) at 120 K. The final residuals were: R_1 = 0.0457 for 7800 reflections with $I > 2\sigma(I)$ and wR_2 = 0.1224 for all data and 513 parameters. GoF = 1.027.

Crystal data for **2d**. $C_{24}H_{30}N_4O_2$, F_w = 406.52, monoclinic, a = 16.322(3), b = 17.694(4) and c = 16.240(3) Å, α = 90, β = 103.85(3) and γ = 90°, V = 4553.5(17) Å^3, space group $P2_1/c$, Z = 8, d_{calc} = 1.186 g cm^{-3}, $F(000)$ = 1744, $\mu(MoK_\alpha)$ = 0.77 cm^{-1}. Total of 46362 reflections (unique 12097, R_{int} = 0.0488) were measured on a Bruker APEX II CCD diffractometer, using graphite monochromated MoK_α radiation (λ = 0.71073 Å) at 120 K. The final residuals were: R_1 = 0.1117 for 9038 reflections with $I > 2\sigma(I)$ and wR_2 = 0.2416 for all data and 569 parameters. GoF = 1.186.

Crystal data for **1c** · **2c**. $C_{44}H_{52}N_8O_4$, F_w = 756.93, monoclinic, a = 22.830(2), b = 13.5162(14) and c = 27.293(3) Å, α = 90, β = 107.361(2) and γ = 90°, V = 8038.4(14) Å^3, space group *C*2/*c*, Z = 8, d_{calc} = 1.251 g cm^{-3}, $F(000)$ = 3232, $\mu(MoK_\alpha)$ = 0.82 cm^{-1}. Total of 31198 reflections (unique 10635, R_{int} = 0.0520) were measured on a Bruker APEX II CCD diffractometer, using graphite monochromated MoK_α radiation (λ = 0.71073 Å) at 120 K. The final residuals were: R_1 = 0.0557 for 7012 reflections with $I > 2\sigma(I)$ and wR_2 = 0.1249 for all data and 509 parameters. GoF = 1.032.

Using Olex2,[23] the structures were solved with the ShelXT structure solution program[24] using Intrinsic Phasing and refined with the XL refinement package[25] using Least-Squares minimization against F_{hkl}^2 in anisotropic approximation for non-hydrogen atoms. Hydrogen atoms of the NH groups of the target compounds were found from difference Fourier synthesis while the positions of others were calculated, and they all were refined in isotropic approximation within the riding model.

Crystal data and structure refinement parameters are given in Table S1 (see Online Supplementary Materials).

CCDC 2344098 (**2c**), 2344099 (**2d**) and 2344092 (**1c** · **2c**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* https://www.ccdc.cam.ac.uk.

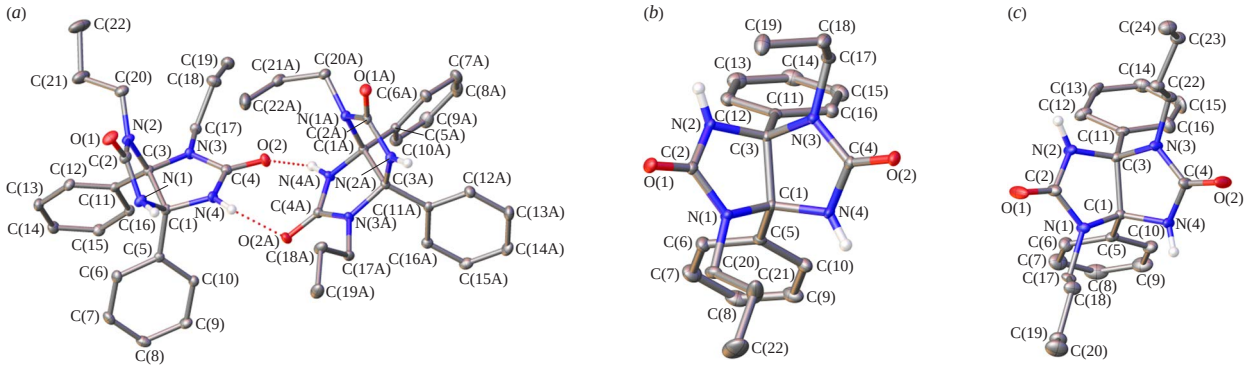


Figure 2 General view of (*a*) crystal **1c**·**2c**, (*b*) crystal **2c** and (*c*) crystal **2d** at 120 K. Only hydrogen atoms at the nitrogen atoms are shown, and other atoms are drawn as thermal ellipsoids at 30% probability level. The minor components of the disorder alkyl groups are omitted.

crystallographic axis *b* made of alternating molecules of the two glucoluryls with *cis*- and *trans*-disposition of *n*-propyl groups (Figure 3).

Individual compound **2c** crystalizes in the triclinic space group *P*1 with the *R*,*R* and *S*,*S* isomers alternating in heterochiral zig-zag chains along the crystallographic diagonal *b*0*c* [Figure 4(*a*),(*c*)] formed by N–H···O=C hydrogen bonds [N···O 2.7647(18)–2.8972(17) Å, NHO 169.77(7)–174.35(8)°]. In the crystal of 1,4-dibutyl homologue **2d**, which belongs to the monoclinic space group $P2_1/c$, there are also both *R*,*R* and *S*,*S* isomers which are held together by N–H···O=C hydrogen bonds [N···O 2.820(4)–2.836(4) Å, NHO 175.1(2)–175.3(2)°] to produce heterochiral zig-zag chains along the crystallographic diagonal *a*0*c* [Figure 4(*b*),(*d*)]. In these chains, however, the alternating units are not the molecules of each isomer, as in **2c**, but their centrosymmetric dimers are hydrogen-bonded into a $R_2^2(8)$ motif. Interestingly, in the discovered chains of a new type, elements consisting of two hydrogen-bonded molecules of one and two hydrogen-bonded molecules of another isomer **2d** are repeated (see parts *b* and *d*).

In conclusion, the condensation of 1-alkylureas with benzyl (approach 1) or with 1-alkyl-5-hydroxy-4,5-diphenyl-1*H*-imidazol-2(5*H*)-ones (approach 2) gives mixtures of 1,6- and 1,4-dialkyl-3a,6a-diphenylglycolurils; the approach 2 is more selective and effective towards 1,6-isomers. Self-organization of glycolurils **2c**,**d** and co-crystal **1c**·**2c** (1 : 1) studied by X-ray diffraction revealed that the compounds studied tend to self-organize into chains due to N–H···O=C hydrogen bonds with $R_2^2(8)$ motif. A new type of supramolecular chains for 1,4-disubstituted glycolurils has been identified.

X-ray diffraction data were collected using the equipment of Center for molecular composition studies of INEOS RAS by S. A. Aksenova with the financial support from Ministry of Science and Higher Education of the Russian Federation (contract/agreement no. 075-00277-24-00).

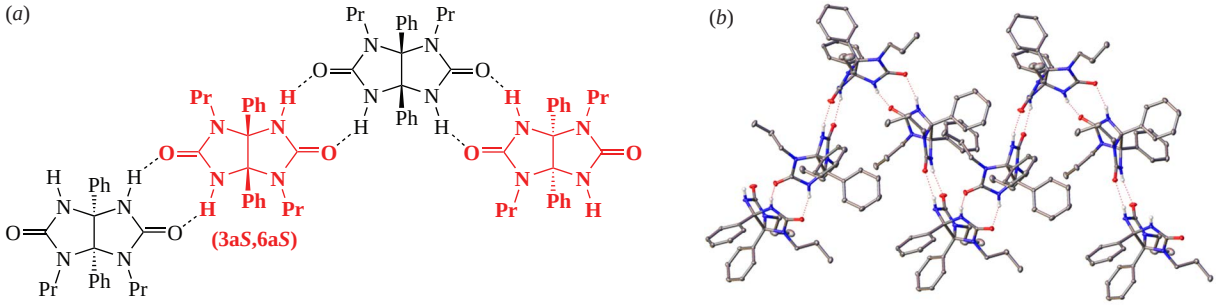


Figure 3 (*a*) Schematic representation and (*b*) a fragment of zig-zag chain in glucoluryl co-crystal **1c**·**2c**.

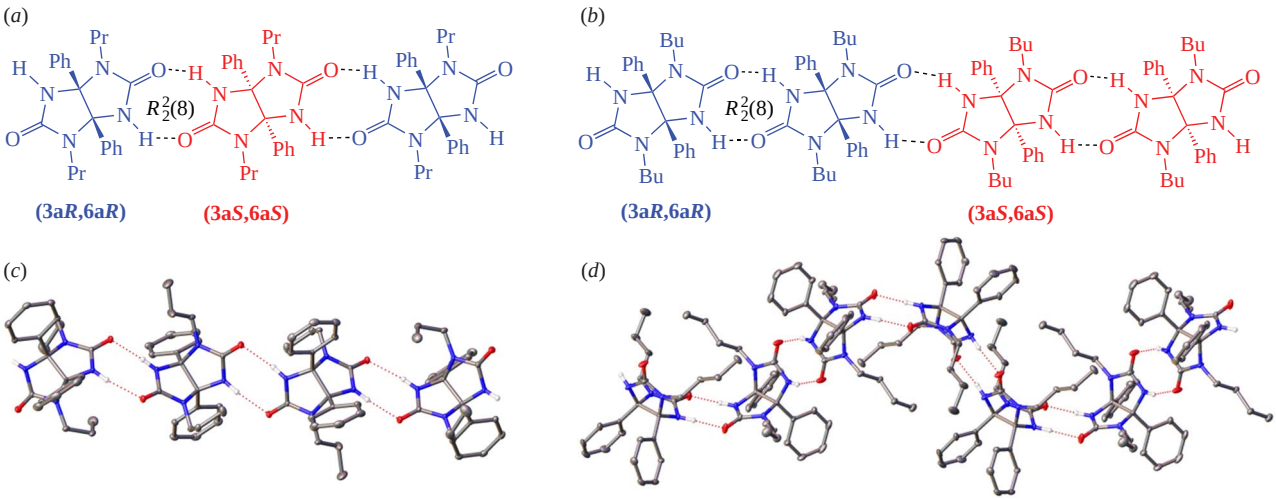


Figure 4 Schematic representations and fragments of the crystal packing in (*a*), (*c*) compound **2c** and (*b*), (*d*) compound **2d**.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2024.10.032.

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