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Highly regioselective synthesis and structure of 1-substituted 3a,6,6a-triphenylglycolurils

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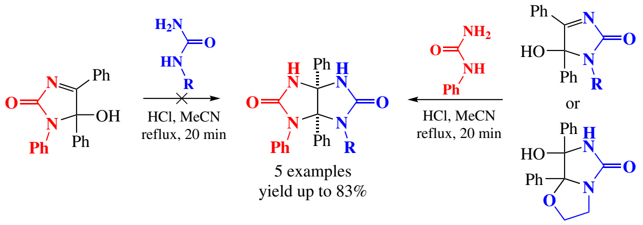
The reactions of 1-alkyl-5-hydroxy-4,5-diphenyl-1,5-dihydro-2*H*-imidazol-2-ones or 7-hydroxy-7,7a-diphenyltetrahydroimidazo[5,1-*b*][1,3]oxazol-5(6*H*)-one with 1-phenylurea selectively afford new 1-substituted 3a,6,6a-triphenylglycolurils. Crystals of four representatives were studied by X-ray diffraction when the formation of two conglomerates was discovered.

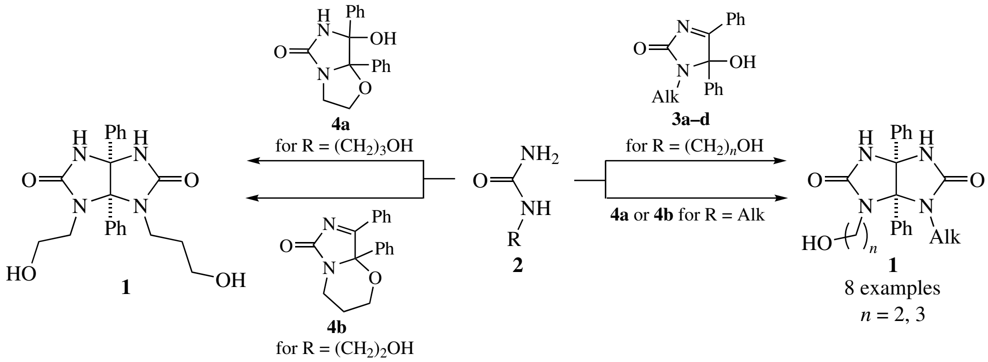


Keywords: glycolurils, 1-alkylimidazolones, tetrahydroimidazo[5,1-*b*][1,3]oxazol-5(6*H*)-one, 1-phenylurea, supramolecular organization, regioselective condensation, X-ray.

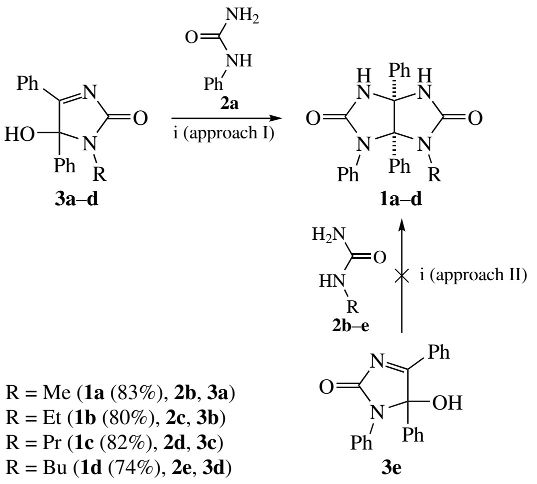
The chemistry of glycolurils is progressing in different directions[1–22] including the construction of self-assembling molecular entities such as clips,[18,19] capsules[20] and supramolecular coordination-bonded systems based on cucurbiturils.[21,22] The study of crystallization leading to self-organizing crystalline systems is an important aspect of expanding knowledge about nature-like processes and materials.[23] In particular, 1,6-disubstituted glycolurils turned out to be promising objects capable of crystallizing in the form of conglomerates,[24] co-crystals,[24] and also forming supramolecular assemblies of varying complexity.[24–32] Recently, the generation of chirality in crystals was established for achiral 1,6-disubstituted 3a,6a-diarylglycolurils.[25,33] The above facts relate mainly to the symmetrically 1,6-disubstituted glycolurils since methods for the synthesis of non-symmetrically 1,6-disubstituted glycolurils are not sufficiently developed.[1,2] The examples of the straightforward preparation of non-symmetrically 1,6-disubstituted 3a,6a-diphenylglycolurils **1** (Scheme 1) involve the condensation of 1-(ω-hydroxyalkyl)ureas **2** with imidazolone derivatives **3a–d** or **4a** with imidazooxazine **4b** as well as reactions of 1-alkylureas **2** with compounds **4a**,**b**.[33–35]

In this report, the reactions of 1-phenylurea with 1-alkyl-5-hydroxy-4,5-diphenyl-1,5-dihydro-2*H*-imidazol-2-ones or their bicyclic analogues were studied, which gave 1-alkyl(2-hydroxyethyl)-3a,6,6a-triphenylglycolurils **1a–e**. Crystals of four target compounds were obtained, and the formation of two conglomerates was confirmed by X-ray diffraction.

Two approaches for the synthesis of 3a,6,6a-triphenylglycolurils **1a–d** were used, namely, condensation of 1-alkyl-containing dihydroimidazolones **3a–d** with 1-phenylurea **2a** (Scheme 2, approach I) and the reaction of 1-phenyl-containing dihydroimidazolone **3e** with 1-substituted ureas **2b–e** (approach II). Using the first approach, previously unavailable glycolurils **1a–d** were prepared. The conditions for this synthesis (MeCH, HCl, reflux, 20 min) were previously employed for the preparation of analogous 1,4(6)-dialkyl-3a,6a-diphenylglycolurils.[32,34] The herein studied reactions proceed with high



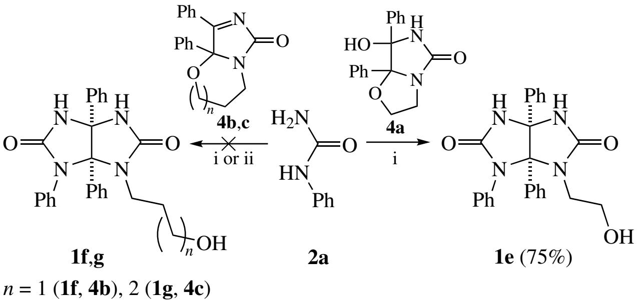
Scheme 1



Scheme 2 *Reagents and conditions*: i, HCl, MeCN, reflux, 20 min.

regioselectivity towards products **1a–d** (yields 74–83%). However, the reaction between 1-phenylimidazolone **3e** and 1-alkylureas **2b–e** (approach II) did not occur and the starting compounds were fully recovered.

The reaction of 1-phenylurea **2a** with tetrahydroimidazo-oxazole **4a** leads to the target 1-(2-hydroxyethyl)-3a,6,6a-triphenylglycoluril **1e** (Scheme 3). A study of the reaction of urea **2a** with polyhydro imidazo-fused oxazine **4b** or oxazepine **4c** under both conditions (i) and conditions (ii)[35] showed that the corresponding glycolurils **1f**,**g** were not formed, and the starting compounds were isolated unchanged.



Scheme 3 *Reagents and conditions*: i, HCl, MeCN, reflux, 20 min; ii, HCl, MeCN, reflux, 8 h.

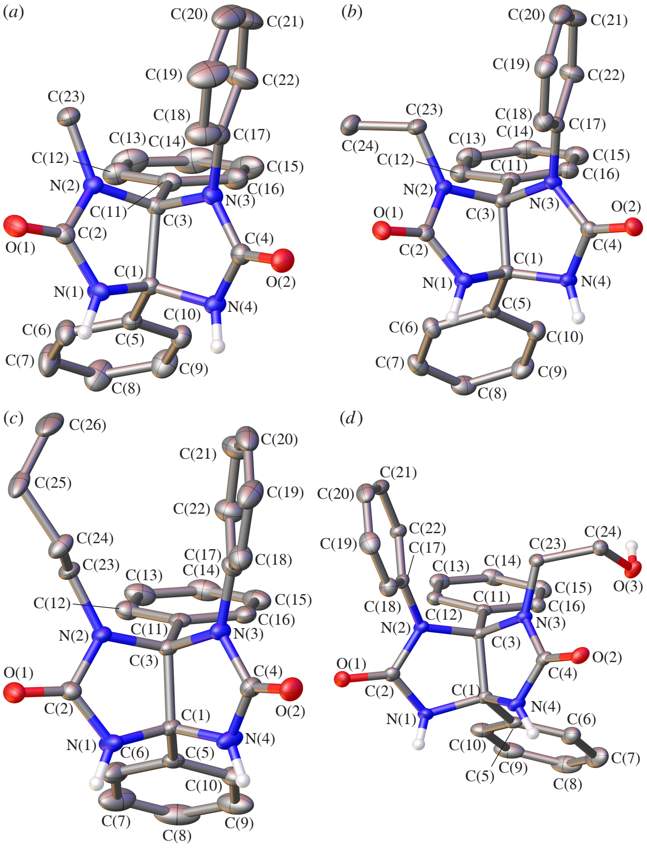


Figure 1 General view of (*a*) compound **1a**, (*b*) compound **1b**, (*c*) compound **1d** and (*d*) compound **1e**. Hereafter, only hydrogen atoms at the nitrogen and oxygen atoms are shown, and other atoms are drawn as thermal ellipsoids at 45% probability level. The minor components of the disorder butyl group are omitted.

The crystals of glycolurils **1a**,**b**,**d**,**e** were grown from MeCN and studied by X-ray diffraction (Figure 1).† Glycoluril **1a** crystallizes in non-centrosymmetric $P2_12_12_1$ space group with the formation of the heterochiral zig-zag chains along the crystallographic axis *a* (Figure 2) *via* N–H···O=C hydrogen bonds [N···O 2.753(2)–3.051(2) Å, NHO 164.55(10)–167.38(10)°] with $R_2^2(8)$ motif.[36] In these chains, two enantiomers of **1a** alternate in a head-to-tail manner (the head and tail contain alkyl and phenyl groups, respectively). A similar pattern of supramolecular assembly has also been observed previously in other glycoluril derivatives.[25,26,28,32]

1-(2-Hydroxyethyl)-3a,6,6a-triphenylglycoluril **1e** also crystallizes in $P2_12_12_1$ space group with another structure of the supramolecular ensemble. In this case, the heterochiral zig-zag chain formed is based on hydrogen bonds between C=O and NH groups [N···O 2.9596(17) Å, NHO 158.5(1)°] and OH group with NH [N···O 2.7826(17) Å, NHO 170.52(9)°] and C=O

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† *Crystal data for* **1a**. $C_{23}H_{20}N_4O_2$, $M = 384.43$, orthorhombic, $a = 7.4907(8)$, $b = 14.4336(14)$ and $c = 18.5675(19)$ Å, $\alpha = \beta = \gamma = 90°$, $V = 2007.5(4)$ Å^3, space group $P2_12_12_1$, $Z = 4$, $d_{calc} = 1.229$ g m^{-3}, $F(000) = 808$, $\mu(\mathrm{MoK}_\alpha) = 0.84$ cm^{-1}. Total of 11786 reflections (unique 5322, $R_{int} = 0.0226$) were measured. The final residuals were: $R_1 = 0.0403$ for 4750 reflections with $I > 2\sigma(I)$ and $wR_2 = 0.0992$ for all data and 263 parameters. GoF = 1.034.

Crystal data for **1b**. $C_{24}H_{22}N_4O_2$, $M = 398.45$, monoclinic, $a = 11.9188(9)$, $b = 8.6408(6)$ and $c = 21.0884(15)$Å, $\alpha = \gamma = 90°$, $\beta = 96.378(2)°$, $V = 2158.4(3)$ Å^3, space group $P2_1/c$, $Z = 4$, $d_{calc} = 1.226$ g cm^{-3}, $F(000) = 840$, $\mu(\mathrm{MoK}_\alpha) = 0.8$ cm^{-1}. Total of 17292 reflections (unique 5736, $R_{int} = 0.0487$) were measured. The final residuals were: $R_1 = 0.0501$ for 3978 reflections with $I > 2\sigma(I)$ and $wR_2 = 0.1286$ for all data and 272 parameters. GoF = 1.017.

Crystal data for **1d**. $C_{26}H_{26}N_4O_2$, $M = 426.51$, monoclinic, $a = 14.8551(12)$, $b = 8.0851(7)$ and $c = 18.4823(16)$ Å, $\alpha = \gamma = 90°$, $\beta = 99.081(2)°$, $V = 2192.0(3)$ Å^3, space group $P2_1$/c, $Z = 4$, $d_{calc} = 1.292$ g cm^{-3}, $F(000) = 904$, $\mu(\mathrm{MoK}_\alpha) = 0.84$ cm^{-1}. Total of 17599 reflection (unique 5813, $R_{int} = 0.0445$) were measured. The final residuals were: $R_1 = 0.0560$ for 4057 reflections with $I > 2\sigma(I)$ and $wR_2 = 0.1536$ for all data and 301 parameters. GoF = 1.009.

Crystal data for **1e**. $C_{24}H_{22}N_4O_3$, $M = 414.45$, orthorhombic, $a = 8.8829(3)$, $b = 13.3240(4)$ and $c = 17.6994(6)$ Å, $\alpha = \beta = \gamma = 90°$, $V = 2094.83(12)$ Å^3, space group $P2_12_12_1$, $Z = 4$, $d_{calc} = 1.314$ g cm^{-3}, $F(000) = 872$, $\mu(\mathrm{MoK}_\alpha) = 0.89$ cm^{-1}. Total of 17434 reflections (unique 5569, $R_{int} = 0.0219$) were measured. The final residuals were: $R_1 = 0.0322$ for 5253 reflections with $I > 2\sigma(I)$ and $wR_2 = 0.0824$ for all data and 280 parameters. GoF = 1.025.

Data were acquired on a Bruker APEX II CCD diffractometer, using graphite monochromated MoK_α radiation ($\lambda = 0.71073$ Å) at 120 K. The structures were solved by direct methods and refined by the Least-Squares minimization using Olex2 program[37] in anisotropic approximation over F^2_{hkl} for non-hydrogen atoms. Hydrogen atoms of the NH and OH groups were found from difference Fourier synthesis, 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.

CCDC 2363535 (**1a**), 2363536 (**1b**), 2363537 (**1d**) and 2363538 (**1e**) 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.

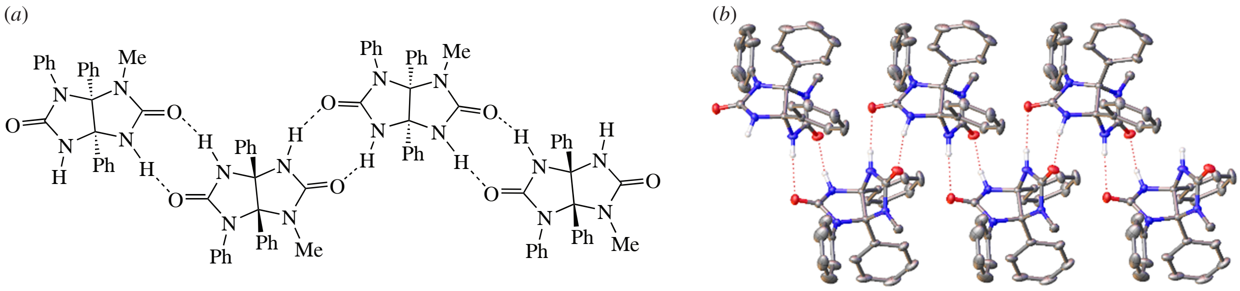

Figure 2 (*a*) Schematic representation and (*b*) a fragment of the crystal packing in compound **1a**. Hereafter, the dashed lines stand for hydrogen bonds.

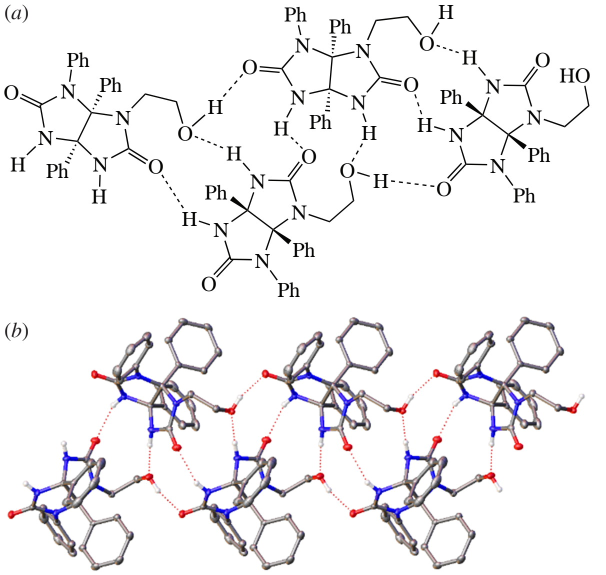

Figure 3 (*a*) Schematic representation and (*b*) a fragment of the crystal packing in compound **1e**.

groups [O···O 2.6519(16) Å, OHO 162.43(8)°] (Figure 3). Enantioselective self-assembly is provided by hydrogen bonds in a head-to-head and head-to-tail mode along the crystallographic axis *a*.

Compounds **1b** and **1d** crystallize in the monoclinic centrosymmetric space group $P2_1/c$, which indicates that they cannot be spontaneously divided into enantiomers. In both cases the molecules form zig-zag chains based on hydrogen bonds between NH and C=O groups [NH···O 2.8263(16)–2.8803(15) Å and 2.784(2)–3.029(2) Å, NHO 164.42(9)–170.71(9)° and 171.45(10)–172.57(10)° for **1b** and **1d**, respectively] along the crystallographic axis *b* with $R_2^2(8)$ motif in a head-to-tail mode (Figure 4).

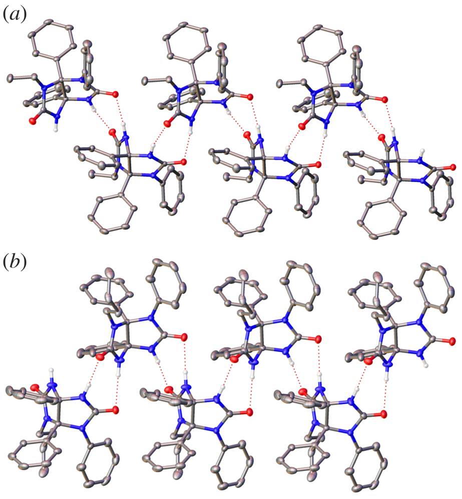

Figure 4 A fragment of crystal packing of (*a*) **1b** and (*b*) **1d**.

X-ray diffraction studies made it possible to detect new conglomerates (**1a**,**e**) and a new structure of the supramolecular ensemble in the crystal of glycoluril **1e**.

In summary, the condensation of 1-phenylurea **2a** with 1-alkyl-substituted dihydroimidazolones **3a–d** or their bicyclic synthetic equivalents **4a–c** proceeds with high regioselectivity and leads only to 1-alkyl(2-hydroxyethyl)-3a,6,6a-triphenylglycolurils **1a–e**. Based on the X-ray crystal study of four compounds, new conglomerates (**1a**,**e**) and a new structure of the supramolecular ensemble in the crystal of glycoluril **1e** were revealed. This fact indicates that the obtained glycolurils can be promising objects of supramolecular chemistry.

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 The Ministry of Science and Higher Education of the Russian Federation (contract/agreement no. 075-00277-24-00).

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.71267/mencom.7564.

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