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New cage-fused polyaza polycyclic systems based on thioglycolurils and alkanediamines

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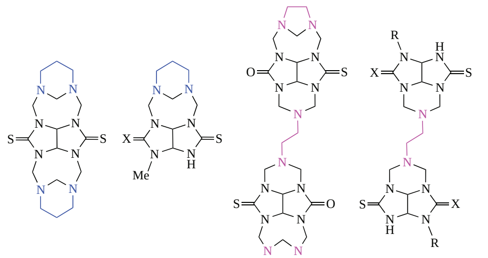
New aspects of multicomponent condensation reactions of ethylene/propylenediamine, formaldehyde and unsubstituted and 1-methyl substituted semithio- and dithioglycolurils have been examined. Ethylene-linked 2,3a,4a,6,9,10a,11a-heptaaza-6,9-methanobenzo[*cd*]cyclonona[*gh*]pentalene and 2,6:10,14-dimethano-2,6,7a,8a,10,14,15a,16a-octaazadicyclodeca[*cd,gh*]pentalene as well as their simpler analogues were synthesized, and their structures were proved by 1D and 2D NMR spectroscopy, HRMS and X-ray analysis.



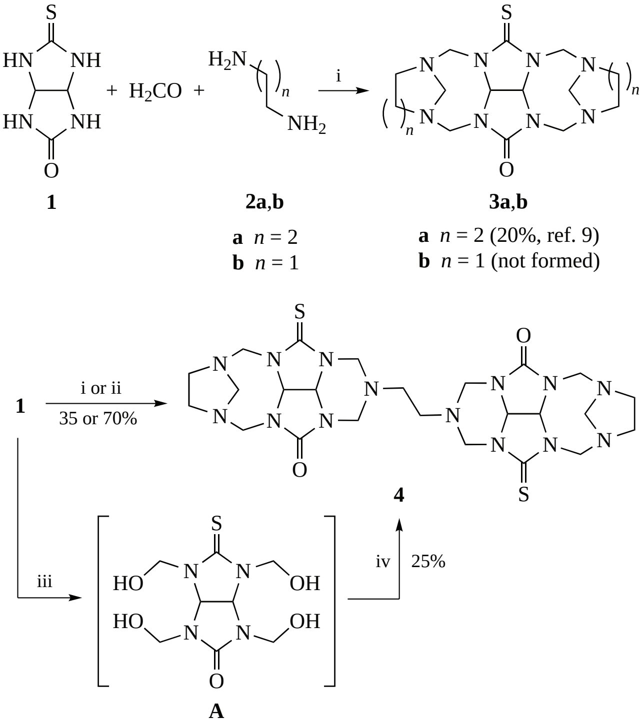
X = O, S; R = H, Me

Keywords: thioglycolurils, multicomponent reactions, diamines, polyheterocycles, formaldehyde, aminals.

Polyheterocyclic (tri-, tetra-, and pentacyclic) compounds obtained by condensation of glycolurils, formaldehyde, and various amines, amino acids, ureas, and sulfonamides have been widely studied.[1–3] The similar reaction was extended onto relative 5-thioxohexahydroimidazo[4,5-*d*]imidazol-2(1*H*)-one (semithioglycoluril) and 3a,6a-diphenyltetrahydroimidazo-[4,5-*d*]imidazole-2,5(1*H*,3*H*)-dithione (dithioglycoluril).[4–8] Such compounds are used as photostabilizers of polymers, molecular clips, starting material in the synthesis of new energetic materials, building blocks for supramolecular chemistry and have shown neuroprotective properties and suppressed multidrug resistance of various cancer cells, viruses, fungi and bacteria.[1,4,5] The reaction of glycolurils with formaldehyde and di(poly)amines has hardly been studied, although these reactions would lead to other types of polyhetero- and macrocycles (see Online Supplementary Materials, Figure S1).[9–12] Reaction between semithioglycoluril **1**, 1,3-propylenediamine **2a** and formaldehyde afforded hexacyclic compound **3a** as the only product (Scheme 1).[9]

In the present study, we investigated new reactions for ethylene- and propylenediamines, formaldehyde and the most accessible thioglycolurils, and synthesized new polyheterocyclic compounds.

Performing the reaction between semithioglycoluril **1**, formaldehyde and 1,2-ethylenediamine **2b**, we anticipated to obtain compound **3b** analogous to previously reported[9] derivative **3a** comprising moiety of lower homologous diamine **2b** (see Scheme 1). The condensation was processed under the same conditions,[9] namely, **1**/H_2CO/**2b** ratio of 1 : 6 : 2 and 12 h reflux in MeOH were used. To our surprise, we isolated a new polyheterocyclic compound **4** (yield 35%) in which ethylene fragments were present both in imidazolidine cycles and between decahydro-1*H*-2,3a,4a,6,9,10a,11a-heptaaza-6,9-methanobenzo[*cd*]cyclonona[*gh*]pentalene cores. This type of embedding of diamines in polyheterocyclic compounds has not yet been



Scheme 1 *Reagents and conditions*: i, **1**/CH_2O/**2b** (1 : 6 : 2), MeOH, reflux, 12 h; ii, **1**/CH_2O/**2b** (2 : 10 : 3), MeOH, reflux, 12 h; iii, CH_2O (5 equiv.), Et_3N, H_2O, reflux, 2 h; iv, **2b** (1.5 equiv.), 40 °C, 30 min, then room temperature, 12 h.

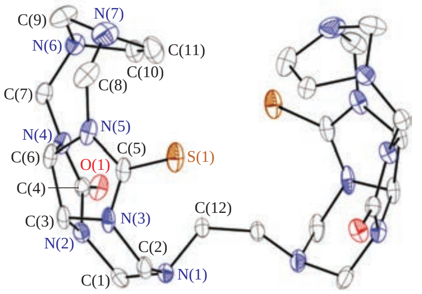


Figure 1 General view of molecule **4** in crystal. Anisotropic displacement parameters are drawn at 30% probability level; hydrogen atoms are omitted for clarity.

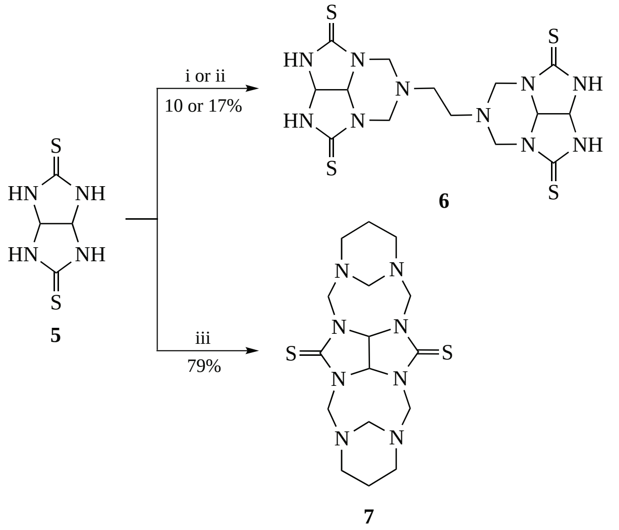
known, although diamines have been used in reactions with formaldehyde and glycolurils,[9–12] urea[13,14] and thiourea.[14–16] To improve the yield of compound **4**, we changed the ratio of the reactants **1**/H_2CO/**2b** to 2 : 10 : 3, which resulted in the product yield increase to 70%. It was not possible to identify other products in filtrates evaporated to resin using ^1H NMR spectra as well as to isolate them in individual states.

Interesting, two-step one-pot reaction of semithioglycoluril **1** with formaldehyde and ethylenediamine **2b** without isolation of the intermediate thioglycoluril's tetrahydroxy derivative **A** under conditions similar to those providing 2,6-disubstituted 4-thioxo-2,3a,4a,6,7a,8a-hexaazaperhydrocyclopenta[*def*]fluoren-8-ones,[4] also led to compound **4** in a lower (25%) yield.

Crystals of **4** suitable for X-ray diffraction studies were grown from water. Molecule of **4** (Figure 1)[†] contains a number of chiral centers and the compound crystallizes in an enantiomorphic space group $C222_1$ thus being a conglomerate. With the refined Flack parameter equal to 0.43(2), we cannot exclude that the structure is a pseudoracemate (solid solution of two enantiomers); however, the presence of only two heavy sulfur atoms is insufficient to draw such a conclusion. The whole molecule lies on a two-fold axis with only a half being crystallographically independent.

Both polycyclic fragments connected by an ethylene bridge adopt the same bowl-like conformation stabilized by stereoelectronic interactions, mainly between a lone pair of nitrogen atoms [N(1), N(6), N(7)] and anti-bonding orbitals of the adjacent C–N bonds. As a result, these anomeric effects force disposition of the atoms C(10), C(11) and C(12) above the heterocyclic core. It is interesting that two polycyclic parts of the molecule in the crystal are folded [the torsion angle N(1)–C(12)–C(12A)–N(1A) is 92.2(4)°] in a claw-like particles. The outer side of these particles does not contain atoms available for strong intermolecular interactions. The molecules form layers coplanar to the crystallographic *ac*-plane. These layers alternate with layers of completely disordered water molecules.

To expand the boundaries of the detected phenomenon, a three-component condensation of dithioglycoluril **5** with formaldehyde and ethylenediamine **2b** was performed (Scheme 2). In our hands, the only compound **6** in which the ethylene fragment was located between heterocycles could be isolated. Varying reactant ratios and reaction times showed that only at the **5**/CH_2O/**2b** ratio of 1 : 6 : 2 the yield of compound **6** approached 10%. We managed to increase this yield to 17% when that ratio was 2 : 4 : 1, while other reaction products were not identified in ^1H NMR spectra and were not isolated from resin-like residues. Apparently, the presence of the second C=S group not only reduces the reactivity of compound **6** but also prevents the embedding of imidazolidine cycles present in compound **4**.



Scheme 2 *Reagents and conditions*: i, **5**/H_2CO/**2b** (1 : 6 : 2), MeOH, reflux, 12 h; ii, **5**/H_2CO/**2b** (2 : 4 : 1), MeOH, reflux, 12 h; iii, **5**/H_2CO/**2a** (1 : 6 : 2), MeOH, reflux, 12 h.

A different result was obtained in the reaction between dithioglycoluryl **5**, formaldehyde and propylenediamine **2a** (see Scheme 2) with the reactant ratio **5**/H_2CO/**2a** of 1 : 6 : 2. Polyheterohexacyclic compound **7** in which propylenediamine moiety was included into pyrimidine cycles was isolated in a yield of 79% (the analogue of structure **IV**, see Online Supplementary Materials, Figure S1).

For the targeted synthesis of new polycyclic compounds with an ethylene fragment between cycles, a multicomponent one-pot condensation of 1-methylthioglycolurils **8** and **9** with formaldehyde and ethylenediamine **2b** was performed (Scheme 3, the ratio of **8** or **9**/H_2CO/**2b** was 2 : 4 : 1). As a result, new compounds **10** (yield 65%) and **11** (yield 38%) were obtained. When performing condensation of 1-methylthioglycolurils **8** and **9** with formaldehyde and propylenediamine **2a** (the ratio of **8** or **9**/H_2CO/**2a**, 1 : 3 : 1), new polyheterocycles **12** and **13**, derivatives of novel decahydro-1*H*-2,3,4a,6,10,11a-hexaaza-6,10-methanocyclodeca[*cd*]pentalene system, were obtained in 40 and 25% yields, respectively (see Scheme 3).

The structure of the obtained compounds was proved by ^1H and ^{13}C NMR spectroscopy including NOESY, COSY, HSQC and HMBC experiments, as well as by high-resolution mass spectrometry.

In general, different chemical behaviour of ethylene- and propylenediamines in the studied reactions with formaldehyde

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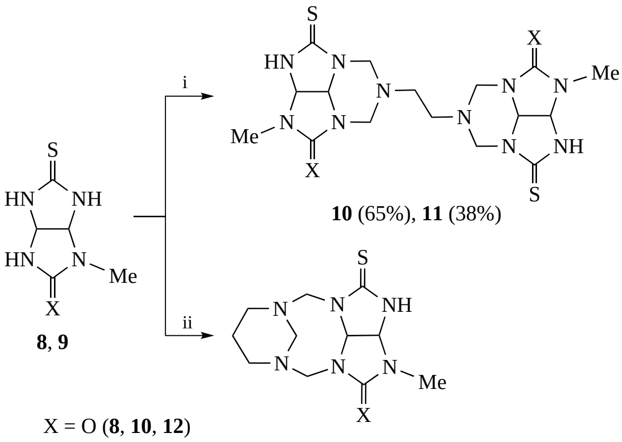
[†] *Crystal data for* **4**. Colorless crystals of $C_{24}H_{36}N_{14}O_2S_2$ (+ solvent) [$M = 616.79$ (+ solvent)] at 120 K are orthorhombic, space group $C222_1$, $a = 9.3771(4)$, $b = 22.3405(13)$ and $c = 17.9322(8)$ Å, $V = 3756.6(3)$ Å^3, $Z = 4$ ($Z' = 0.5$), $d_{\mathrm{calc}} = 1.091$ g cm^{-3}, μ(MoKα) = 1.81 cm^{-1} (last two values calculated without solvent). Data collection was performed on a Bruker SMART APEX II diffractometer [λ(MoKα) = 0.71073 Å, ω-scans, $2\theta < 61.1°$]. A semiempirical absorption correction was applied with the SADABS[20] program using the intensity data of equivalent reflections. Intensities of 5752 independent reflections ($R_{\mathrm{int}} = 0.0313$) out of 25136 collected were used in structure solution and refinement. The structure was solved using the dual-space approach with SHELXT program[21] and refined by the full-matrix least-squares technique against F^2_{hkl} in anisotropic approximation for non-hydrogen atoms with SHELXL[22] program. The contribution of heavily disordered water molecules to the diffraction was modeled with SQUEEZE method implemented in PLATON program.[23] The refinement converged to $R_1 = 0.0512$ [calculated for 4779 observed reflections with $I > 2\sigma(I)$], $wR_2 = 0.1379$ and GOF = 1.030 for all the independent reflections.

CCDC 1991290 contains supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk.



8, **9**

10 (65%), **11** (38%)

12 (40%), **13** (25%)

X = O (**8**, **10**, **12**)
X = S (**9**, **11**, **13**)

Scheme 3 *Reagents and conditions*: i, **8** or **9**/H_2CO/**2b** (2 : 4 : 1), MeOH, reflux, 12 h; ii, **8** or **9**/H_2CO/**2a** (1 : 3 : 1), MeOH, reflux, 12 h.

and thioglycolurils **1**, **5**, **8**, **9** was revealed, which led to polyheterocyclic compounds **3**, **6**, **7**, **10–13** of different structure types. Based on data on various forms produced in the reactions of ethylene-and propylenediamines **2a**,**b** with formaldehyde[17,18] and related processes[1–12,19] we would propose the multistage mechanism for the formation of new polyheterocycles (see Online Supplementary Materials, Scheme S1). It consists of a set of individual acts of aminal formation (azaacetalization), whose final direction is determined by the profitability of the final structure.

In conslusion, we have accomplished new multicomponent one-pot condensations of unsubstituted and 1-methyl substituted semithio- and dithioglycolurils, ethylene- and propylenediamines and formaldehyde, which led to various new polyheterocyclic compounds, including derivatives of two new polyheterocyclic systems, namely, decahydro-1*H*-2,3a,4a,6,9,10a,11a-heptaaza-6,9-methanobenzo[*cd*]cyclonona[*gh*]pentalene and decahydro-1*H*-2,3,4a,6,10,11a-hexaaza-6,10-methanocyclodeca[*cd*]pentalene. 1D and 2D NMR spectroscopy, HRMS and X-ray were used to prove the structure of the new compounds. Polycycle **4** crystallizes from H_2O in an enantiomorphic space group $C222_1$.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2020.07.024.

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