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Tetrakis(hydroxymethyl)glycoluril in *N*-methylenation reactions with arylamines

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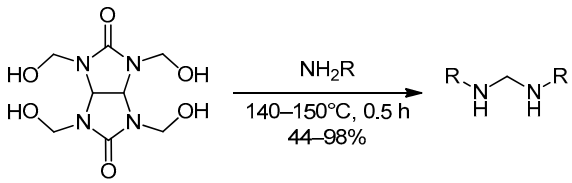


This work shows for the first time the use of tetrakis(hydroxymethyl)glycoluril in the melt *N*-methylenation reactions of arylamines, based on the ability of tetrakis(hydroxymethyl)glycoluril to eliminate a formaldehyde molecule. It was shown by HPLC that tetrakis-(hydroxymethyl)glycoluril under the studied conditions is subject to dehydroxymethylation processes.

Keywords: aminals, arylamines, formaldehyde, tetrakis(hydroxymethyl)glycoluryl, dehydroxymethylation, HPLC.

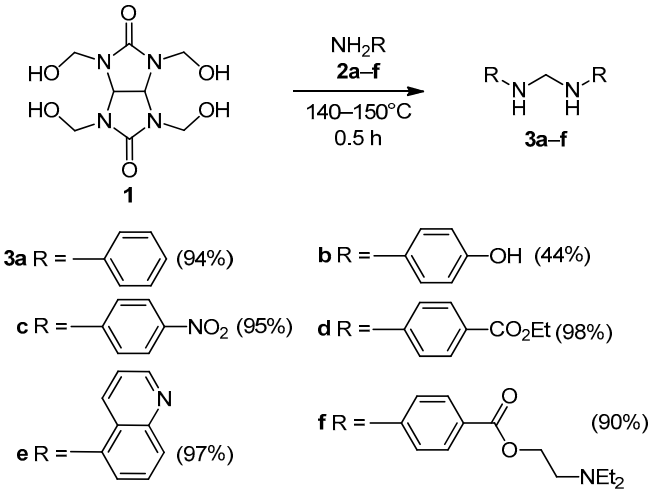
In recent years, there has been a steady upward trend in the number of studies on the synthesis and properties of bicyclic bisureas, among which *N*-tetrakis(hydroxymethyl)-glycoluril (2,4,6,8-tetramethylol-2,4,6,8-tetraazabicyclo-[3.3.0.]octane-3,7-dione (THGU) (**1**)) is of particular interest. Due to its unique properties and structural features, THGU (**1**) has found wide practical application as a crosslinking agent in the creation of macroporous polymers based on methyl methacrylate and acrylamide,[1] as a stabilizer for hardness of wood products,[2] and as a stabilizer of water-based dyes.[3] Solubility in H_2O and the presence of four highly reactive hydroxyl groups makes THGU (**1**) an extremely attractive reagent for the synthesis of novel heterocyclic structures and the creation of various macro- and supramolecular systems,[4] formation of which occurs at low pH; in particular, THGU (**1**) is a precursor in the synthesis of cucurbiturils.[5,6]

An analysis of the literature on the chemical properties of THGU (**1**) showed that it is most often used in Mannich-type condensation reactions with amines.[7] These reactions were mainly carried out in various solvents (H_2O, MeOH, MeOH–H_2O, MeOH–C_7H_{16}, EtOH, MeCN, H_2O–*i*-PrOH (2:3), *i*-PrOH, *i*-BuOH) in an alkaline medium and culminated in the formation of macroazacyclic heterostructures based on THGU (**1**). A number of patents report the ability of THGU (**1**) to eliminate a formaldehyde molecule (dehydroxymethylation).[8–11] This property was exploited using THGU (**1**) as a biocidal additive Protectol TD.[11]

However, the ability of THGU (**1**) to eliminate the formaldehyde molecule has not yet been used to study its reactions with amines that do not result in hetero-cyclization. The purpose of our work was to study the reaction of THGU (**1**) with aromatic amines in the absence of direct acid-base catalysis and solvent (Scheme 1).

In the course of the study, we found that the reactions of aromatic amines **2a**–**f** with THGU (**1**) in the melt (Scheme 1) do not lead to the formation of polyheterocyclic nitrogen-containing compounds, as was reported earlier,[7] but to bisamine coupling products **3a**–**f** with yields of 44–98%, which are derivatives of amines **2a**–**f** linked by methylene bridges. As can be seen in Scheme 1, THGU (**1**) does not act as a frame-forming substrate during reactions in the melt,[7] but manifests itself as a donor of the methylene group. In other words, THGU (**1**) eliminates formaldehyde under the found conditions, which, through a preliminary step of reaction with aromatic amines **2a**–**f** and subsequent

Scheme 1. Reaction of THGU (**1**) with aromatic amines



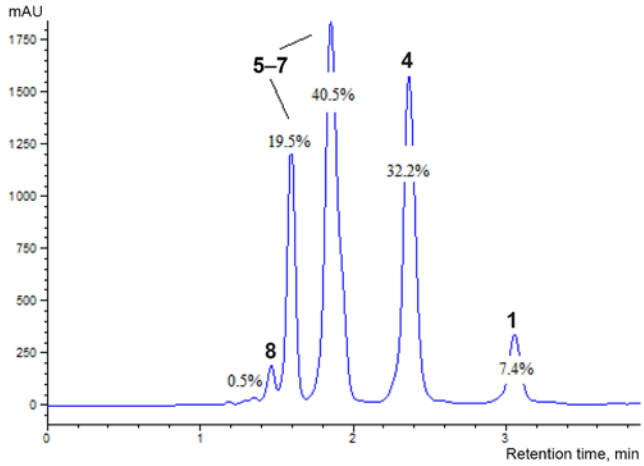


Figure 1. The HPLC result of the aqueous extract after *N*-methylenation in the synthesis of compound **3d**.

condensation with another amine molecule, ultimately leads to the formation of aminals **3a**–**f**.

Aminals **3a**,**c**,**d** were previously accessed *via* the reaction of the corresponding amine **2a**,**c**,**d** with aqueous formaldehyde and were considered the primary products in the process of polycondensation in a neutral or slightly alkaline medium.[12,13] Their identification was difficult due to the large number of accompanying oligomeric products, especially when using aromatic amines with alkyl, halide, cyano, amino, and alkoxy substituents resulting in the formation of trimeric and tetrameric oligomers.[13] The process of condensation of formaldehyde and aniline **2a** proceeds uncontrollably, and to slow down the secondary oligomerization processes, compound **3a** was obtained at a temperature of –60°C.[12] Paraformaldehyde was used to selectively form aminals **3a**,**c**,**d**; however, to obtain compound **3a**, the presence in the reaction mixture of Na_2CO_3 as a catalyst was required.[13] In addition, it is noted that some strongly electron-withdrawing substituents in the benzene ring prevent the formation of oligomeric products. However, a correlation between the electronic properties of the starting substrate and the reaction conditions has not been established.[13]

Syntheses carried out by us for the preparation of aminals **3a**–**f** using THGU (**1**) did not require any special precautions and culminated in *N*-monomethylenation of amines **2a**–**f** with high yields of products **3a**–**f** (90–98%), with the exception of compound **3b** (44%). The relatively low yield of compound **3b** is probably due to the fact that oligomerization processes with the formation of products such as phenol formaldehyde resins prevail during the reaction of *p*-aminophenol **2b** and THGU (**1**), as is known for the reactions of phenols with formaldehyde.[14] Also, the low yield of product **3b** is effected by the fact that aminophenol **2b** has a melting point of 186°C, which is higher than the reaction temperature. Apparently, in the absence of a solvent, the mixture of compounds **1** and **2b** is heterogeneous. In all other cases the reaction mixture was homogeneous.

Aminal **3d**, the synthesis of which was monitored by TLC for the disappearance of the spot of amine **2d**, is poorly soluble in H_2O. A separate part of the reaction mixture was treated with H_2O, where product **3d** was filtered off and washed with cold H_2O. The aqueous filtrate was further analyzed by HPLC. According to the HPLC data of the aqueous extract (Fig. 1, Scheme 2), in accordance with the previously described data,[15] it was found that the analyzed sample contains compounds **4**–**7** (19.5–40.5%) and compound **8** (0.5%, Table 1), and it was shown that THGU (**1**) almost completely undergoes degradation processes (its remaining content in the reaction mixture was 7.4%).

The employed HPLC system provides group selectivity for compounds **5**–**7**.

In the course of individual model reactions of aromatic amines with formaldehyde in melt and in solution, we found that in this case the formation of compounds **3a**–**f** is nonselective, since macrocyclic compounds of an unknown structure prevail in the reaction products.

To conclude, we demonstrated for the first time the use of tetrakis(hydroxymethyl)glycoluryl as a mild and selective *N*-methylenating reagent for the synthesis of arylamines. HPLC results indicate the conversion of tetrakis-(hydroxymethyl)glycoluryl to its dehydroxymethylated derivatives under the developed conditions.

Scheme 2. Dehydroxymethylation products of THGU (**1**)

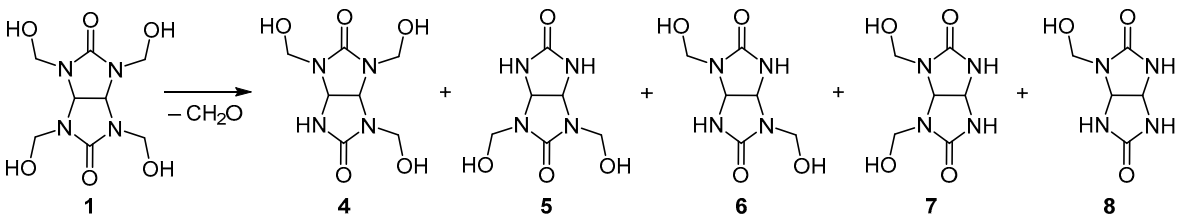


Table 1. The content of THGU (**1**) dehydroxymethylation products according to HPLC ($n = 3$, $p = 0.95$) in the synthesis of compound **3d**

THGU (**1**) dehydroxymethylation products	Reaction time, min	Content (internal normalization), %
8	1.4	0.5
5–**7**	1.6	19.5
	1.8	40.5
4	2.4	32.2
1	3	7.4

Experimental

IR spectra were registered on a FTIR Bruker Alpha spectrometer in KBr in 400–4000 cm^{-1} range. ^1H and ^{13}C NMR spectra were acquired on a Bruker Avance III HD spectrometer (400 and 100 MHz, respectively) in DMSO-d_6, with TMS as internal standard. HPLC was performed on a chromatograph using a PerfectSil Target ODS-3 HD 5 μ, 250 × 4.6 mm (MZ-Analysentechnik) column thermostatat temperature of +40°C and 1.5 ml/min flow rate. Run time 10 min, mobile phase H_2O, injection volume 10 μl. The aqueous extract of the reaction mixture of the synthesis of compound **3d** was used for HPLC analysis of compounds **1**, **4**–**8**, where product **3d** was filtered off, and the filtrate was used for chromatographic analysis. Elemental analysis was performed on an Euro Vector EA-3000 CHNS-analyzer. Melting points were determined on a Buchi apparatus. Monitoring of the reaction progress and assessment of the purity of compounds were done by TLC on Silufol UV-254 plates by disappearance of the respective amine, eluent PhH–EtOH, 8:2, visualization with iodine vapors or under UV light (254 nm).

Synthesis of compounds 3a–**f** (General method). Aniline **2a**–**f** (0.73 ml, 8 mmol) and tetrakis(hydroxymethyl)glycoluril **1** (1.05 g, 4 mmol) were placed in a 100-ml round-bottom flask equipped with a temperature-resistant stirrer. The mixture was heated to 140–150°C and stirred until complete conversion of the starting amine and the mixture becoming turbid due to precipitation (0.5 h). The mixture was treated with Me_2CO, and residual methylol glycolurils were filtered off. H_2O was added dropwise to the filtrate, and the mixture was kept overnight. The formed crystals were filtered off, washed with H_2O, and air-dried.

***N*,*N*'-Diphenylmethanediamine (3a)**. Yield 0.74 g (94%), white crystals, mp 63°C (mp 64–65°C[12]). IR spectrum, ν, cm^{-1}: 3376 (NH), 2884 (CH_2). ^1H NMR spectrum, δ, ppm: 4.90 (2H, s, NHC<u>H</u>$_2$NH); 6.77–6.80 (2H, m, H Ph); 6.98–7.02 (2H, m, 2NH); 7.06–7.08 (4H, m, H Ph); 7.16–7.20 (4H, m, Ph). ^{13}C NMR spectrum, δ, ppm: 67.4 (CH_2); 117.3; 120.3; 129.4; 148.7 (12C Ph). Found, %: C 78.70; H 7.15; N 14.15. $C_{13}H_{14}N_2$. Calculated, %: C 78.75; H 7.12; N 14.13.

4,4'-(Methanediyldiimino)diphenol (3b). Yield 0.40 g (44%), light-beige crystals, mp 230°C (decomp.). IR spectrum, ν, cm^{-1}: 3194 (NH), 3033–2684 (OH). ^1H NMR spectrum, δ, ppm (*J*, Hz): 4.42 (2H, t, *J* = 8.0, NHC<u>H</u>$_2$NH); 6.53 (2H, s, 2NH); 6.61–6.64 (4H, m, H Ph); 6.89–6.92 (4H, m, H Ph); 8.98 (2H, s, OH). ^{13}C NMR spectrum, δ, ppm: 65.8 (CH_2); 116.0 (4C Ph); 120.5 (4C Ph); 139.4 (2CNH Ph); 152.2 (2COH). Found, %: C 67.31; H 6.30; N 12.38; O 14.01. $C_{13}H_{14}N_2O_2$. Calculated, %: C 67.81; H 6.13; N 12.17; O 13.90.

***N*,*N*'-Bis(4-nitrophenyl)methanediamine (3c)**. Yield 2.19 g (95%), bright-yellow crystals, mp 232°C (decomp.) (mp 237–239°C[16] (decomp.)). IR spectrum, ν, cm^{-1}: 3374 (NH), 3083 (CH), 1604, 1530, 1500, (NO_2), 1373 (CN). ^1H NMR spectrum, δ, ppm (*J*, Hz): 4.70 (2H, t, *J* = 5.8, NHC<u>H</u>$_2$NH); 6.79 (4H, d, *J* = 8.0, H Ph); 7.98 (2H, t, *J* = 5.8, 2NH); 8.03 (4H, d, *J* = 8.0, H Ph). ^{13}C NMR spectrum, δ, ppm: 51.4 (CH_2); 112.1 (4C Ph); 126.5 (4C Ph); 137.2 ($2CNO_2$); 153.7 (2CNH Ph). Found, %: C 54.13; H 4.21; N 19.39; O 22.27. $C_{13}H_{12}N_4O_4$. Calculated, %: C 54.17; H 4.20; N 19.44; O 22.20.

Diethyl 4,4'-(methanediyldiimino)dibenzoate (3d). Yield 2.68 g (98%), white crystals, mp 190–193°C (mp 193–194°C[17]). IR spectrum, ν, cm^{-1}: 3224 (NH), 2980 (CH_3), 1690 (C=O), 1274 (COC). ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.27 (6H, t, *J* = 7.1, CH_3); 4.21 (4H, q, *J* = 7.1, C<u>H</u>$_2$CH$_3$); 4.58 (2H, t, *J* = 5.6, NHC<u>H</u>$_2$NH); 6.74 (4H, d, *J* = 8.9, H Ph); 7.27 (2H, t, *J* = 5.8, 2NH); 7.71 (4H, d, *J* = 8.9, H Ph). ^{13}C NMR spectrum, δ, ppm: 14.8 (CH_3); 51.7 (CH_2); 60.1 (CH_2); 112.0 (4C Ph); 117.4 (2C-4 Ph); 131.3 (4C Ph); 152.0 (2CNH Ph); 166.3 (C=O). Found, %: C 66.54; H 6.59; N 8.16; O 18.71. $C_{19}H_{22}N_2O_4$. Calculated, %: C 66.65; H 6.48; N 8.18; O 18.69.

***N*,*N*'-Di(quinolin-5-yl)methanediamine (3e)**. Yield 2.33 g (97%), beige crystals, mp 175°C. IR spectrum, ν, cm^{-1}: 3210 (NH), 2926 (CH), 1584 (C=N). ^1H NMR spectrum, δ, ppm (*J*, Hz): 4.94 (2H, t, *J* = 5.2, NHC<u>H</u>$_2$NH); 7.08 (2H, d, *J* = 7.8, H Ar); 7.27 (2H, dd, *J* = 7.8, *J* = 4.0, H Ar); 7.27 (2H, t, *J* = 5.2, 2NH); 7.41 (2H, dd, *J* = 8.5, *J* = 4.2, H Ar); 7.54 (2H, t, *J* = 8.0, H Ar); 8.64 (2H, d, *J* = 8.6, H-4 Ar); 8.77 (2H, dd, *J* = 4.2, *J* = 1.4, H-2 Ar). ^{13}C NMR spectrum, δ, ppm: 53.4 (CH_2); 104.7; 117.1; 118.3; 119.6; 130.6; 130.7 (C Ar); 143.8 (CN); 149.2 (CN); 150.3 (CN). Found, %: C 76.02; H 5.35; N 18.63. $C_{19}H_{16}N_4$. Calculated, %: C 75.98; H 5.37; N 18.65.

(Diethylamino)ethyl 4,4'-(methanediyldiimino)dibenzoate (3f). Yield 3.48 g (90%), white crystals, mp 240°C (decomp.). IR spectrum, ν, cm^{-1}: 3208 (NH), 2981 (CH_3), 1684 (C=O), 1281 (COC). ^1H NMR spectrum, δ, ppm (*J*, Hz): 0.95 (12H, t, *J* = 8.0, 4NCH$_2$C<u>H</u>$_3$); 2.51 (8H, q, *J* = 8.0, 4NC<u>H</u>$_2$CH$_3$); 2.70 (4H, t, *J* = 6.0, 2C<u>H</u>$_2$N); 4.19 (4H, q, *J* = 6.0, 2OCH$_2$); 4.57 (2H, t, *J* = 5.7, NHC<u>H</u>$_2$NH); 6.74 (4H, d, *J* = 8.8, H Ar); 7.30 (2H, t, *J* = 5.7, 2NH); 7.69 (4H, d, *J* = 8.6, H Ar). ^{13}C NMR spectrum, δ, ppm: 12.5 (CH_3); 47.5 (<u>C</u>H$_2$CH$_3$); 51.2 (CH$_2$N); 62.7 (NHCH$_2$NH); 65.1 (OCH$_2$); 113.1; 117.3; 131.3 (C Ph), 152.0 (CN Ph); 166.3 (C=O). Found, %: C 66.87; H 8.38; N 11.49; O 13.26. $C_{27}H_{40}N_4O_4$. Calculated, %: C 66.91; H 8.32; N 11.56; O 13.20.

Supplementary information file containing ^1H and ^{13}C NMR spectra of all synthesized compounds, as well as

HPLC data of aqueous extract after *N*-methylenation is available at the journal website at http://link.springer.com/journal/10593.

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