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Efficient synthesis of *N*,*N*′-methylenebisglycolurils

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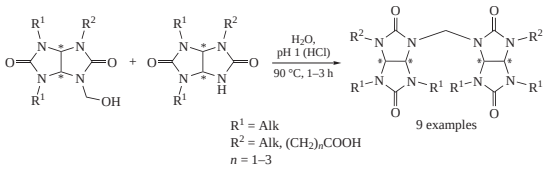
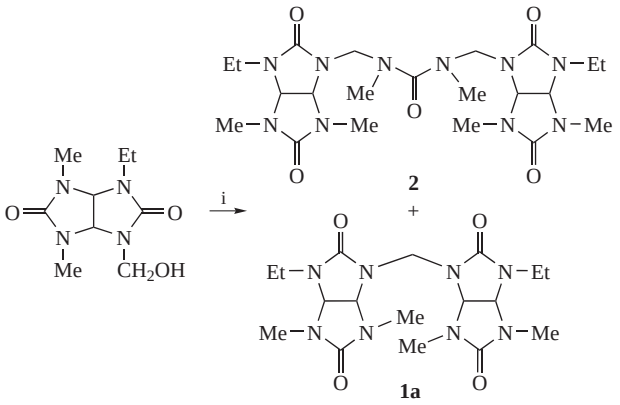
Coupling of 6-(carboxy)alkyl-2,4-dialkylglycolurils with *N*-(hydroxymethyl)glycolurils gives *N*,*N*′-methylenebisglycolurils totally substituted at the nitrogen atoms, which are formed mostly as racemate diastereomers.



Glycolurils constitute a new promising class of pharmacologically active compounds.[1] One of them, 2,4,6,8-tetramethylglycoluril (Mebicar, Mebix or Adaptol), has already been introduced into medical practice as a daytime tranquillizer.[1(*a*)]

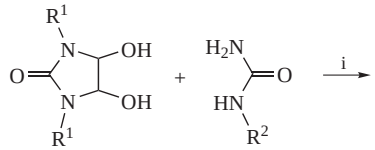
In this work we suggest a simple and efficient approach to the previously unknown derivatives in which two glycoluril moieties with different combinations of substituents are bound by nitrogen atoms through a methylene bridge, *viz.*, *N*,*N*′-methylenebisglycolurils **1a–i**. Only two examples of *N*,*N*′-bisglycolurils **1a** and **2** have been described so far, which were obtained as a mixture in an attempt to synthesize compound **2** (Scheme 1).[2]



Scheme 1 *Reagents and conditions*: i, *N*,*N*′-dimethylurea, 80–90 °C, pH 1 (HCl), 2 h.

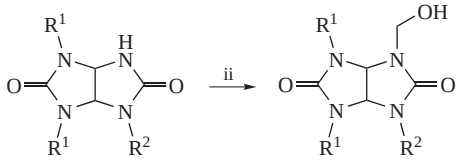
In order to develop a general method for synthesizing methylene-linked derivatives **1a–g** we studied the α-ureidoalkylation of 6-(carboxy)alkyl-2,4-dialkylglycolurils **3a–g** with *N*-(hydroxymethyl)glycolurils **4a–g**. Compounds **4a–g** were obtained either as individual compounds or in a one-pot variant in reactions of glycolurils **3a–g** with formaldehyde.

The starting glycolurils **3a–g** were prepared using known techniques[3,4] by condensation of ureas **5a–e** with dihydroxyimidazolidinones **6a**,**b** (Scheme 2). *N*-(Hydroxymethyl)glycolurils **4a–d** were synthesized by the treatment of glycolurils **3a–d** with formaldehyde[5] in the presence of catalytic amounts of $NaHCO_3$ (pH 8–9) in 83–95% yields.



6a R^1 = Me
6b R^1 = Et

5a R^2 = Et
5b R^2 = Me
5c R^2 = CH_2COOH
5d R^2 = $(CH_2)_2COOH$
5e R^2 = $(CH_2)_3COOH$



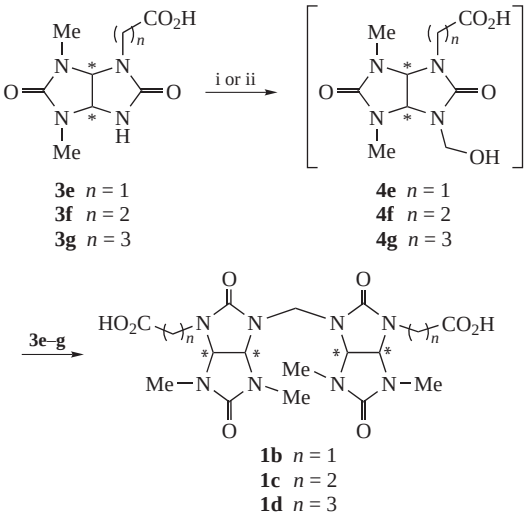
3a–g **4a–d**

3, **4**: **a** R^1 = Me, R^2 = Et
b R^1 = R^2 = Me
c R^1 = Et, R^2 = Me
d R^1 = R^2 = Et
e R^1 = Me, R^2 = CH_2COOH
f R^1 = Me, R^2 = $(CH_2)_2COOH$
g R^1 = Me, R^2 = $(CH_2)_3COOH$

Scheme 2 *Reagents and conditions*: i, H_2O, 90 °C, pH 1 (HCl), 1 h (for **3a–d**); 85 °C, pH 1 (HCl), 3 h (for **3e**,**g**) and 2 h (for **3f**); ii, CH_2O, H_2O, 60 °C, pH 8–9, 1 h.

Similar reactions of *N*-(carboxyalkyl)glycolurils **3e–g** with formaldehyde have not previously been studied. We could not isolate the expected derivatives **4e–g** from the reactions of equimolar amounts of formaldehyde with glycolurils **3e–g** under the conditions used to synthesize compounds **4a–d**. Acidification of the reaction mixture to pH 2 and heating while removing water gave methylenebisglycolurils **1b–d** in 30–40% yields. Changing the glycoluril : formaldehyde molar ratio from 1:1 to 2:1 and pH to 1 raised the yields of compounds **1b–d** to 79–85% within 2 h (Scheme 3).

The structures of *N*,*N*′-methylenebisglycolurils **1b–d** were determined using a combination of spectral characteristics, data of elemental analysis and high resolution mass spectra (HRMS).[†] In particular, HRMS spectra contained peaks of molecular mass ions $[M+H]^+$. As it could be expected, compounds **1b–d** are



Scheme 3 *Reagents and conditions*: i, CH_2O, H_2O, pH 8–9, 90 °C, 3 h, then HCl, heating; ii, CH_2O, H_2O, pH 1, 90 °C, 2 h.

formed as a mixture of diastereomers, which is confirmed by ^{1}H NMR spectra. In the case of compound **1b**, a racemate (**1b**′) and a *meso*-form (**1b**″) (Figure 1) were characterized by spectral data. The ratio of integral intensities of CH_2 group protons in the ^{1}H NMR spectrum of the diastereomer mixture indicates that the racemate (**1b**′) and the *meso*-form (**1b**″) are formed in 1:1 ratio. Assignment of the methylene protons signals to **1b**′ or **1b**″ was made as follows: in **1b**′, the protons of the CH_2 linker are equivalent and appear as a singlet at 4.66 ppm; in **1b**″, such protons are diastereotopic and observed as AB system at 4.63 and 4.71 ppm (2 d, ^2J 6.8 Hz). Furthermore, the ^{1}H NMR spectra show doubling of signals from protons in the N–Me groups (singlets at δ ~2.8) and bridging CH–CH protons, which manifest themselves as a broadened singlet or an AB system.†

Compounds **1c**,**d** were isolated only as racemates **1c**′,**d**′ (yields 79–82%), since the protons of the methylene group binding the bicycles manifest themselves as singlets at δ 4.82 and 4.83 in the ^{1}H NMR spectra. *meso*-Forms **1c**″,**d**″, which are formed in small amounts (^{1}H NMR spectra of the evaporated reaction mixture) were not isolated.

Two approaches were used to obtain symmetrically substituted *N*,*N*′-methylenebisglycolurils **1a**,**e**–**g** with the same glycoluril moieties: α-ureidoalkylation of glycolurils **3a**–**d** with the corresponding *N*-(hydroxymethyl)glycolurils **4a**–**d** (method A) and condensation of glycolurils **3a**–**d** with formaldehyde when the corresponding *N*-(hydroxymethyl)glycolurils are formed *in situ* (method B). The reactions were carried out in water under acid

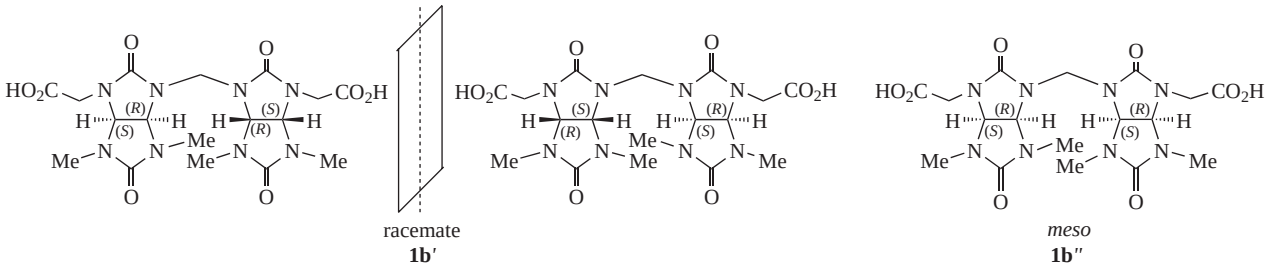


Figure 1 Racemate (**1b**′) and *meso*-form (**1b**″) of *N*,*N*′-methylenebisglycoluril **1b**.

† *N*-(Carboxyalkyl)glycolurils **3e**–**g**, 2,4,6-trialkylglycolurils **3a**–**d** and their hydroxymethyl derivatives **4a**–**d** were obtained using the techniques reported previously.[3–5] Ureas **5a**,**b** and *N*-carbamoylamino acids **5c**–**e** were synthesized by KOCN N-carbamoylation of methyl- or ethylamine or amino acids (Gly, β-Ala and GABA).[6] 1,3-Dialkyl-4,5-dihydroxyimidazolidin-2-ones **6a**,**b** were prepared using reported procedures.[7,8] Glyoxal (40% aqueous solution), formaldehyde (30% aqueous solution) and amino acids were purchased from Acros.

2,2′-Methylenebis[6,8-dialkyl-4-(carboxyalkyl)glycolurils] **1b**–**d** *(general procedure)*. Glycoluril **3e** (**3f** or **3g**) (5 mmol) and concentrated hydrochloric acid (to pH 1) were added to aqueous solution of formaldehyde (30%, 2.5 mmol). The resulting mixture was stirred for 2 h at 90 °C and concentrated in a rotary evaporator. The oil residues were treated with acetone (5 ml). The obtained precipitates of **1b** (**1c** or **1d**) were filtered, dried and stored in a desiccator with $CaCl_2$.

2,2′-Methylenebis(6,8-dimethyl-3,7-dioxo-2,4,6,8-tetraazabicyclo-[3.3.0]octane-4-acetic acid) **1b** (*meso*-form **1b**′ + racemate **1b**″, ratio 1:1). Yield 85%, mp 198–200 °C (decomp.). ^{1}H NMR (DMSO-d_6) δ: for *meso*-form **1b**′: 2.74 (s, 6 H, 2 Me), 2.80 (s, 6 H, 2 Me), 3.83–4.14 (m, 4 H, 2 CH_2), 4.63 (d, 1H, CH_2, ^2J 6.7 Hz), 4.71 (d, 1H, CH_2, ^2J 6.8 Hz), 5.19 (d, 2 H, 2 CH, ^3J 8.5 Hz), 5.30 (d, 2 H, 2 CH, ^3J 8.5 Hz), 12.03 (br. s, 2 H, COOH); for racemate **1b**″: 2.75 (s, 6 H, 2 Me), 2.81 (s, 6 H, 2 Me), 4.66 (s, 2 H, CH_2), 5.24 (br. s, 4 H, 4 CH), 12.03 (br. s, 2 H, COOH). HRMS, *m*/*z*: 469.1798 $[M+H]^+$ ($C_{17}H_{24}N_8O_8$, Δ = 1.7 ppm). Found (%): C, 43.64; H, 5.19; N, 23.89. Calc. for $C_{17}H_{24}N_8O_8$ (%): C, 43.59; H, 5.16; N, 23.92.

*(1*R*,*1′*R*,*5*S*,*5′*S*)*-2,2′-Methylenebis(6,8-dimethyl-3,7-dioxo-2,4,6,8-tetraazabicyclo[3.3.0]octane-4-propionic acid)* **1c**′ (racemate). Yield 82%, mp 208–209 °C (decomp.). ^{1}H NMR (DMSO-d_6) δ: 1.70–1.83 (m, 4 H, 2 CH_2), 2.84 (s, 12 H, 4 Me), 3.19–3.42 (m, 4 H, 2 CH_2), 4.82 (s, 2 H, NCH_2), 5.10 (d, 2 H, 2 CH, ^3J 7.5 Hz), 5.19 (d, 2 H, 2 CH, ^3J 7.5 Hz), 12.08 (br. s, 2 H, COOH). HRMS, *m*/*z*: 497.2106 $[M+H]^+$ ($C_{19}H_{28}N_8O_8$, Δ = 0.6 ppm). Found (%): C, 45.93; H, 5.69; N, 22.60. Calc. for $C_{19}H_{28}N_8O_8$ (%): C, 45.97; H, 5.68; N, 22.57.

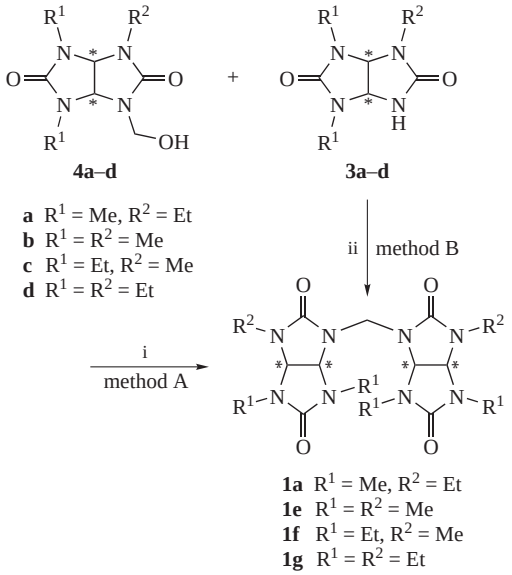
2,2′-Methylenebis-4,6,7-trialkylglycolurils **1a**,**e**–**g** *(general procedure). Method A.* Concentrated hydrochloric acid was added dropwise to a solution of *N*-(hydroxyalkyl)glycoluril **4a** (**4b**, **4c** or **4d**) (10 mmol) and glycoluril **3a** (**3b**, **3c** or **3d**, respectively) (10 mmol) in water (10 ml) to reach pH 1 and the reaction mixture was stirred for 1 h at 90 °C. The solvent was distilled off in a rotary evaporator until a precipitate of the corresponding methylene-bis-product **1a** (**1e**, **1f** or **1g**) formed, which was then filtered after cooling.

Method B. Concentrated hydrochloric acid was added dropwise to a solution of glycoluril **3a** (**3b**, **3c** or **3d**) in 30% aqueous formaldehyde (5 mmol) to reach pH 1 and the reaction mixture was stirred for 1.5 h at 90 °C. The solvent was distilled off in a rotary evaporator. The formed precipitate of the corresponding product **1a** (**1e**, **1f** or **1g**) was filtered after cooling.

*(1*R*,*1′*R*,*5*S*,*5′*S*)*-2,2′-Methylenebis(4-ethyl-6,8-dimethyl-2,4,6,8-tetraazabicyclo[3.3.0]octane-3,7-dione)* **1a**′ (racemate): yield 68%, mp 235–238 °C. ^{1}H NMR ($CDCl_3$) δ: 1.20 (t, 6 H, 2 CMe, ^3J 7.1 Hz), 2.96 (s, 6 H, 2 NMe), 3.11 (s, 6 H, 2 NMe), 3.29 (m, 2 H, NCH_2), 3.64 (m, 2 H, NCH_2), 4.89 (s, 2 H, NCH_2N), 5.05 (d, 2 H, 2 CH, ^3J 8.5 Hz), 5.31 (d, 2 H, 2 CH, ^3J 8.5 Hz). ^{13}C NMR (DMSO-d_6) δ: 13.14 (CMe), 29.85, 30.24 (both NMe), 37.27 (NCH_2), 50.83 (NCH_2N), 69.21, 70.01 (both CH), 158.16, 158.74 (both C=O). HRMS, *m*/*z*: 431.2121 $[M+Na]^+$ ($C_{17}H_{28}N_8O_4$, Δ = 1.2 ppm). Found (%): C, 49.91; H, 6.92; N, 27.36. Calc. for $C_{17}H_{28}N_8O_4$ (%): C, 49.99; H, 6.91; N, 27.43.

*(1*R*,*1′*S*,*5*S*,*5′*R*)*-2,2′-Methylenebis(4-ethyl-6,8-dimethyl-2,4,6,8-tetraazabicyclo[3.3.0]octane-3,7-dione)* **1a**″ (*meso*-form): yield 10%, mp 175–178 °C. ^{1}H NMR ($CDCl_3$) δ: 1.11 (t, 3 H, CMe, ^3J 7.0 Hz), 1.12 (t, 3 H, CMe, ^3J 6.9 Hz), 2.92 (s, 6 H, 2 NMe), 2.95 (s, 6 H, 2 NMe), 3.31 (m, 2 H, NCH_2), 3.54 (m, 2 H, NCH_2), 5.06 (d, 2 H, 2 CH, ^3J 8.5 Hz), 5.08 (d, 1H, NCH_2N, ^3J 14 Hz), 5.14 (d, 1H, NCH_2N, ^3J 14 Hz), 5.24 (dd, 2 H, 2 CH, ^3J 8.5 Hz). HRMS, *m*/*z*: 431.2129 $[M+Na]^+$ ($C_{17}H_{28}N_8O_4$, Δ = 0.7 ppm). Found (%): C, 49.87; H, 6.90; N, 27.39. Calc. for $C_{17}H_{28}N_8O_4$ (%): C, 49.99; H, 6.91; N, 27.43.

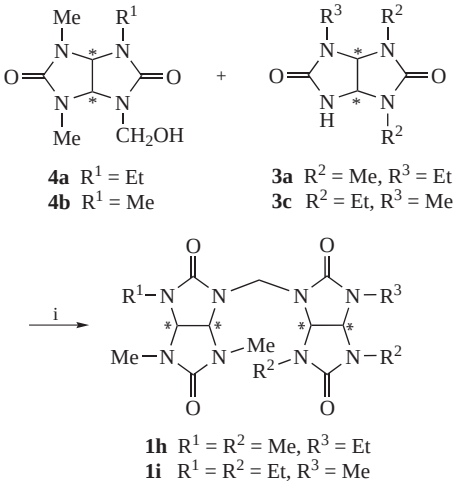
catalysis conditions with addition of hydrochloric acid and heating at 90 °C for 1 h (in method A) or 1.5 h (in method B). Method B provided products **1a**,**e**–**g** in low yields (15–17%), whereas higher yields (62–78%) were achieved in method A on using preliminary synthesized **4a**–**d** (Scheme 4).



Scheme 4 *Reagents and conditions*: i, H_2O, pH 1 (HCl), 90 °C, 1 h; ii, H_2O, CH_2O, pH 1, 90 °C, 1.5 h.

More efficient method A was applied to the preparation of non-symmetrically substituted *N*,*N*′-methylenebisglycolurils. Compounds **1h**,**i** were obtained by reactions **4b** + **3a** and **4a** + **3c**, respectively, in low (17–20%) yields (Scheme 5). The ^{1}H NMR spectra of the crude materials also contained signals of the corresponding symmetrical analogues **1a**,**e**,**f**.

Alkyl-substituted *N*,*N*′-methylenebisglycolurils **1a**,**f**,**g** were also formed as mixtures, racemate and *meso*-diastereomers. Compounds **1a**,**f** were isolated by fractional crystallization from $CHCl_3$ as individual racemates **1a**′ and **1f**′ (yields 68 and 60%, respectively) and *meso*-forms **1a**″ and **1f**″ (yields 10 and 6%, respectively). In the ^{1}H NMR spectra of racemates **1a**′ and **1f**′ the protons of the CH_2 linker resonate as singlets, whereas those of *meso*-forms **1a**″ and **1f**″ as AB systems. For compound **1g**, the CH_2 signals could not be assigned to a racemate or a *meso*-form, since they are located in the range of multiplet signals of bridging CH–CH moiety protons. Compound **1e** was isolated as a predominant racemate **1e**′ in 70% yield. Compounds **1h**,**i** were isolated as single predominant 'racemates' of the two possible. Since the protons of their CH_2 linkers are non-equivalent, they appear as an AB system with a small coupling constant (^2J 2.5 Hz) in ^{1}H NMR spectra. The second racemates were formed in trace amounts.



Scheme 5 *Reagents and conditions*: i, H_2O, pH 1 (HCl), 90 °C, 1 h.

Compounds **1h**,**i** were obtained as above (method A). The reaction mixture was concentrated in a rotary evaporator to give an oil, which was triturated with acetone after cooling. The precipitated solids were filtered.

For characteristics of compounds **1d**′, **1e**′, **1f**′, **1f**″ and **1g**–**i**, see Online Supplementary Materials.

In addition to ^{1}H and ^{13}C NMR spectra, the structure and purity of the compounds synthesized were confirmed in all cases by a combination of data of elemental analyses and HRMS.†

In conclusion, we studied coupling of NH-glycolurils with $N(CH_2OH)$-glycolurils leading to CH_2-linked bisglycolurils. Symmetrical bisglycolurils can also be obtained by linking of two molecules of NH-glucoluril with formaldehyde. Compounds synthesized seem promising for biological testing.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2016.03.018.

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