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Synthesis of 2,4,6-trialkyl-8-(2,3-epoxypropyl)glycolurils

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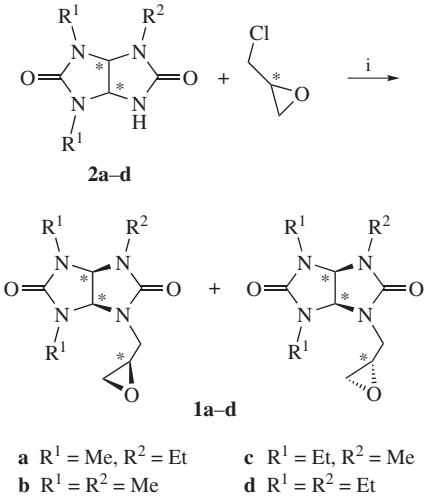
Reaction of 2,4,6-trialkylglycolurils with epichlorohydrin under phase-transfer conditions affords the title compounds as diastereomeric mixtures.

The functionalization of glycolurils is of considerable practical importance.[1–7] Hydroxymethylglycolurils are synthons in supramolecular chemistry.[1] 2,8-Bis(carboxymethyl)glycolurils were transformed into amides, which found use as anion receptors.[2] {(1*R**,5*S**)-6,8-Dimethyl(3,7-dioxo-2,4,6,8-tetraazabicyclo-[3.3.0]oct-2-yl)}butyric acid manifests anxiolytic, sedative and nootropic action,[3] and 2-(2-acetylaminoethyl)-4-methylglycoluril exhibits nootropic activity, which is an advantage over pyracetam.[4]

The epoxy derivatives of glycolurils, namely, 2,3-epoxypropyl ones, were patented as starting compounds for the synthesis of cytostatic agents.[5–7] Hovewer, the experimental details were insufficient for the reproduction of their synthesis. Moreover, the individual *N*-(2,3-epoxypropyl)glycolurils were not isolated and characterized.

In this work, we studied reactions of 2,4,6-trialkylglycolurils with epichlorohydrin in detail, isolated and characterized the target 2,3-epoxypropyl derivatives **1a–d** (Scheme 1). Based on patent data,[5–7] the reaction was carried out under the conditions of phase-transfer catalysis. The starting compounds **2a–d** were prepared according to previously developed procedures.[8] Of them, compounds **2a**,**c**,**d** were obtained by the interaction of 1-methyl(ethyl)urea and 1,3-diethyl(dimethyl)-4,5-dihydroxyimidazolidin-2-ones, respectively, which were accessible from reaction between the corresponding 1,3-dialkylureas and glyoxal.[9,10] Glycoluril **2b** was synthesized by the one-pot condensation between 1,3-dimethylurea and 1-methyl-4,5-dihydroxyimidazolidin-2-one, which was prepared in the same vessel from 1-methylurea and glyoxal.

Epoxypropylation of glycolurils was developed using 2,4-dimethyl-6-ethylglycoluril **2a** as an example (see Scheme 1).† For optimization, we tested various solvents (C_8H_{18}, CH_2Cl_2 and Et_2O), varied amounts of epichlorohydrin (from 6 to 10 mol per mole of glycoluril) and alkali (NaOH or KOH), reaction temperature (20, 40, 60, 80, 90 and 115 °C) and its duration (15, 30 and 60 min) and tried different phase-transfer catalysts [benzyltriethylammoniun chloride (BTEAC), tetrabutylammonium bromide (TBAB) and trimethylphenylammonium iodide]. The course



Scheme 1 *Reagents and conditions*: i, epichlorohydrin (solvent), KOH, BTEAC, 80 °C, 15 min.

† *4,6,8-Trialkyl-2-(2,3-epoxypropyl)glycolurils* **1a–d** *(general procedure).* Epichlorohydrin (0.06 mol), KOH (0.01 mol) and 0.01% BTEAC (relative to glycoluril) were added to tri-*N*-alkylglycoluril **2a–d** (0.01 mol) and the mixture was stirred at 80 °C for 15 min, cooled and filtered. The filtrate was evaporated in a vacuum. Residual epichlorohydrin was extracted from the resulting oily liquid with diethyl ether (2×20 ml). The etheral solution was discarded, and the oily layer was pumped. Crude products **1a–d** (R_f = 0.45, 0.35, 0.46 and 0.57, respectively) were purified by column chromatography on silica gel L 100/160 in the $CHCl_3$–MeOH system (10 : 1) to remove starting compounds **2a–d** (with R_f = 0.34, 0.26, 0.32 and 0.41, respectively). The proper fractions were kept in a vacuum to a constant refractive index.

1a′ + 1a″: yield 87%; n_D^{20} = 1.5078; R_f = 0.45. ^{1}H NMR, δ: 1.12–1.28 [m, 6H, Me (**1a′ + 1a″**)], 2.52–2.60 [m, 2H, *cis*-H of OCH_2 (**1a′ + 1a″**)], 2.70–2.83 [m, 2H, *trans*-H of OCH_2 (**1a′ + 1a″**)], 2.91–3.02 [m, 12H, NMe (**1a′ + 1a″**)], 3.12–3.35 [m, 6H, OCH (**1a′ + 1a″**) + C*H*$_2$Me (**1a″ + 1a″**)], 3.48–3.71 [m, 7H, C*H*$_2$Me (**1a′ + 1a″**) + CH_2 (**1a′**) + C*H*H (**1a″**)], 4.22 [m, 1H, CH*H* (**1a″**)], 5.20 and 5.23 [both d, 2H, CH (**1a′ + 1a″**), *J* 8.7 Hz, *J* 8.4 Hz], 5.26 [1H, CH (**1a′**), *J* 8.4 Hz], 5.50 [d, 1H, CH (**1a″**), *J* 8.7 Hz]. Found (%): C, 47.35; H, 7.02; N, 22.15. Calc. for $C_{11}H_{18}N_4O_3$ (%): C, 47.26; H, 7.01; N, 22.35.

1b′ + 1b″: yield 79%; n_D^{22} = 1.5172; R_f = 0.35. ^{1}H NMR, δ: 2.51–2.62 [m, 2H, *cis*-H of OCH_2 (**1b′ + 1b″**)], 2.70–2.82 [m, 2H, *trans*-H of OCH_2 (**1b′ + 1b″**)], 2.92–3.04 [m, 18H, NMe (**1b′ + 1b″**)], 3.06–3.20 [2H, OCH (**1b′ + 1b″**)], 3.50–3.68 [m, 3H, CH_2 (**1b′**) + C*H*H (**1b″**)], 4.22 [m, 1H, CH*H* (**1b″**)], 4.95 and 4.99 [both d, 2H, CH (**1b′ + 1b″**), *J* 8.6 Hz, *J* 8.3 Hz], 5.12 [d, 1H, CH (**1b′**), *J* 8.6 Hz], 5.39 [d, 1H, CH (**1b″**), *J* 8.3 Hz]. Found (%): C, 49.48; H, 6.79; N, 23.31. Calc for $C_{10}H_{16}N_4O_3$ (%): C, 49.59; H, 6.79; N, 23.33.

1c′ + 1c″: yield 86%; n_D^{22} = 1.5075; R_f = 0.46. ^{1}H NMR, δ: 1.14–1.26 [m, 12H, 4Me (**1c′ + 1c″**)], 2.52–2.65 [m, 2H, *cis*-H of OCH_2 (**1c′ + 1c″**)], 2.71–2.80 [m, 2H, *trans*-H of CH_2 (**1c′ + 1c″**)], 2.91 [s, 3H, Me (**1c′**)], 3.00 [s, 3H, Me (**1c″**)], 3.10–3.25 [m, 6H, OCH (**1c′ + 1c″**) + C*H*$_2$Me (**1c′ + 1c″**)], 3.48–3.71 [m, 7H, C*H*$_2$Me (**1c′ + 1c″**) + CH_2 (**1c′**) + C*H*H (**1c″**)], 4.22 [m, 1H, CH*H* (**1c″**)], 5.18 and 5.21 [both d, 2H, CH (**1c′ + 1c″**), *J* 8.3 Hz, *J* 8.5 Hz], 5.32 [d, 1H, CH (**1c′**), *J* 8.3 Hz], 5.47 [d, 1H, CH (**1c″**), *J* 8.5 Hz]. Found (%): C, 53.33; H, 7.50; N, 20.66. Calc. for $C_{12}H_{20}N_4O_3$ (%): C, 53.71; H, 7.51; N, 20.88.

1d′ + 1d″: yield 84%; n_D^{20} = 1.5088; R_f = 0.57. ^{1}H NMR, δ: 1.04–1.25 [m, 18H, Me (**1d′ + 1d″**)], 2.45–2.82 [m, 4H, OCH_2 (**1d′ + 1d″**)], 2.95–3.75 [m, 17H, OCH (**1d′ + 1d″**) + C*H*$_2$Me (**1d′ + 1d″**) + CH_2 (**1d′**) + C*H*H (**1d″**)], 4.22 [m, 1H, CH*H* (**1d″**)], 5.16 and 5.21 [both d, 2H, CH (**1d′ + 1d″**), *J* 8.2 Hz], 5.34 [d, 1H, CH (**1d′**), *J* 8.2 Hz], 5.49 [d, 1H, CH (**1d″**), *J* 8.2 Hz]. Found (%): C, 55.33; H, 7.85; N, 19.25. Calc. for $C_{13}H_{22}N_4O_3$ (%): C, 55.30; H, 7.87; N, 19.64.

of reaction was monitored by TLC on Silufol plates using the $CHCl_3$–MeOH system (10:1).

We found that the maximum yield of epoxypropyl product **1a** (87%) was achieved at reaction temperature of 80 °C, a reaction time of 15 min, and a ratio of 1:1:6 between **2a**, KOH and epichlorohydrin, the latter being both a reactant and a solvent. The amount of BTEAC was 0.01% (relative to glycoluril **2a**). We extended this procedure for epoxypropylation of compounds **2b–d** to synthesize other *N*-(epoxypropyl)glycolurils **1b–d** (yields were 79–86%). The structure of compounds **1a–d** was confirmed by elemental analysis data and ^{1}H NMR spectra [Bruker AM-250 spectrometer (250 MHz); solvent, $CDCl_3$], which indicated that they were the ~1:1 mixtures of diastereomers, each being a racemate (Figure 1). For example, compound **1a** contained 52% of diastereomer **1a′** (integral intensities of signals of the CH–CH bridge, doublets, δ = 5.20 and 5.50 ppm, J 8.7 Hz) and 48% of diastereomer **1a″** (doublets, δ 5.23 and 5.26 ppm, J 8.4 Hz). The oxirane ring in compound **1a** is characterized by the signals of protons as multiplets at δ 3.14 and 3.18 ppm (CH groups of diastereomers), 2.57 ppm (*cis*-oriented to the N–CH_2 substituent) and 2.80 ppm (*trans*-oriented to the N–CH_2 substituent). Note that the protons of the methylene groups of the oxirane ring of diastereomers differ in chemical shifts and spin–spin coupling constants (SSCCs): the *cis*-oriented protons coincide in terms of chemical shifts and SSCCs, and the *trans*-oriented protons of the oxirane ring of diastereomers are characterized by equal chemical shifts but different SSCCs. The diastereotopic protons of the N–CH_2 group form two AMX systems. Diastereotopic *N*-methylene protons in the stereoisomer with a smaller concentration are non-equivalent.

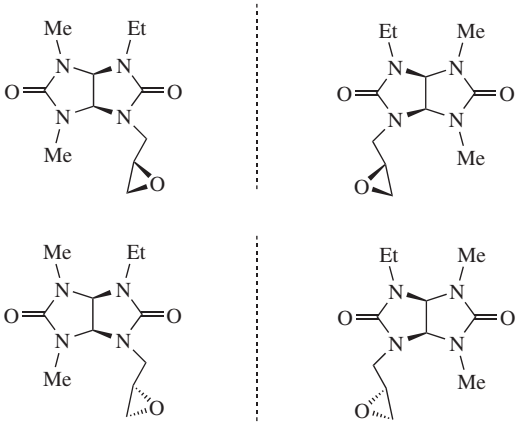


Figure 1 Structures of racemic diastereomers **1a′** + **1a″**.

In summary, we developed a simple procedure for the synthesis of the *N*-(2,3-epoxypropyl) derivatives of tri-*N*-alkylglycolurils **1a–d**, which can be further transformed into other valuable functionalized glycolurils.

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