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Dimeric molecular clips based on glycoluril†

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Glycoluril dimers **4a** and **4b** were prepared and successfully transformed to glycoluril dimeric clips **7a** and **7b**. ^{1}H NMR spectroscopy was used to reveal that the dimeric clip **7b** with methyl substituents in its structure exists as a mixture of two distinct conformers in D_2O at ambient temperature, while **7a** possesses only one stable conformer under the same conditions due to its bulky phenyl substituents. The coalescence temperatures for **7b** and its precursor **5b** were determined. Both dimeric clips **7a** and **7b** formed complexes with methylviologen in D_2O in which each of two clip-binding sites was occupied by one molecule of the guest. Thus, this study uncovers possible use of glycoluril dimers **4a** and **4b** as general building blocks for glycoluril-based supramolecular host molecules with two binding sites in their structure.

Introduction

Cucurbiturils are an important class of supramolecular host molecules that are prized for their ability to strongly and selectively bind organic molecules in water.[1–6] These macrocycles consist of glycoluril units connected by methylene bridges. Recent progress in the chemistry of cucurbiturils enables the preparation of their functionalized derivatives,[7–13] which can be covalently attached to various substrates and thus can be used for real applications. Along with the synthesis of cucurbituril derivatives, other supramolecular hosts based on glycoluril have been prepared, including anionic receptors – bambusurils[14–16] – and acyclic glycoluril oligomers.[17–19] The latter group of compounds features high affinities toward anaesthetics, nitrosamines and various drugs.[20–22] Despite recent progress in cucurbituril synthesis, there have been only two reported approaches dealing with the preparation of cucurbituril dimers. The first is based on the condensation of acyclic glycoluril hexamers with tetraaldehydes;[23,24] the second relies on the conjugation of two monofunctionalized cucurbiturils.[25] These cucurbituril dimers have been used as building blocks for the construction of supramolecular polymers and oligomers.

We decided to investigate a different approach for the preparation of dimeric cucurbiturils and their acyclic analogs. Our work was inspired by compound **4a** (Scheme 1) previously reported in the literature.[26,27] This compound contains two glycoluril units connected through phenylene links. Therefore, we wanted to investigate whether this structural motif could be suitable for the construction of cucurbituril-based compounds. As a first approximation of a cucurbituril derivative, we selected to prepare dimeric clip **7a**. The successful preparation of this compound should uncover the possibility of attaching methylene bridges to nitrogen atoms of sterically hindered glycoluril units of **4a**.

Results and discussion

The starting building block **4a** for this dimeric clip has already been reported.[26,27] According to the literature, compound **4a** can be prepared by condensation of urea or urea derivative **8** (Fig. 1) with compound **3a** in refluxing formic or acetic acid with a catalytic amount of sulfuric acid. However, when the synthesis was repeated in our laboratory under these conditions, only compound **9** with one glycoluril moiety was formed.

Fortunately, the reaction of urea with **3a** in toluene in the presence of TFA provided dimer **4a** in 95% yield. Compound **4a** was then transformed to cyclic ether **5a** by its reaction with paraformaldehyde in aqueous HCl (Scheme 1). Compound **5a** was further reacted with hydroquinone to provide dimeric molecular clip **6** bearing OH groups on its terminal aromatic walls in 69% yield. Clip **6** was alkylated using 1,3-propanesultone to give water-soluble clip **7a** in 68% yield.

The phenyl substituent present in glycoluril dimer **4a** can be a source of low reactivity and low solubility of this compound, as previously reported on the corresponding glycolurils for cucurbituril syntheses.[8] Thus, we decided to prepare dimer **4b** in which two phenyls are replaced by methyl substituents. The synthesis of **4b** required precursor **3b**, which was not commercially available (unlike **3a**) and had to be prepared from 1,4-diethynylbenzene (**1**) (Scheme 1). Alkyne **1** was deprotonated with

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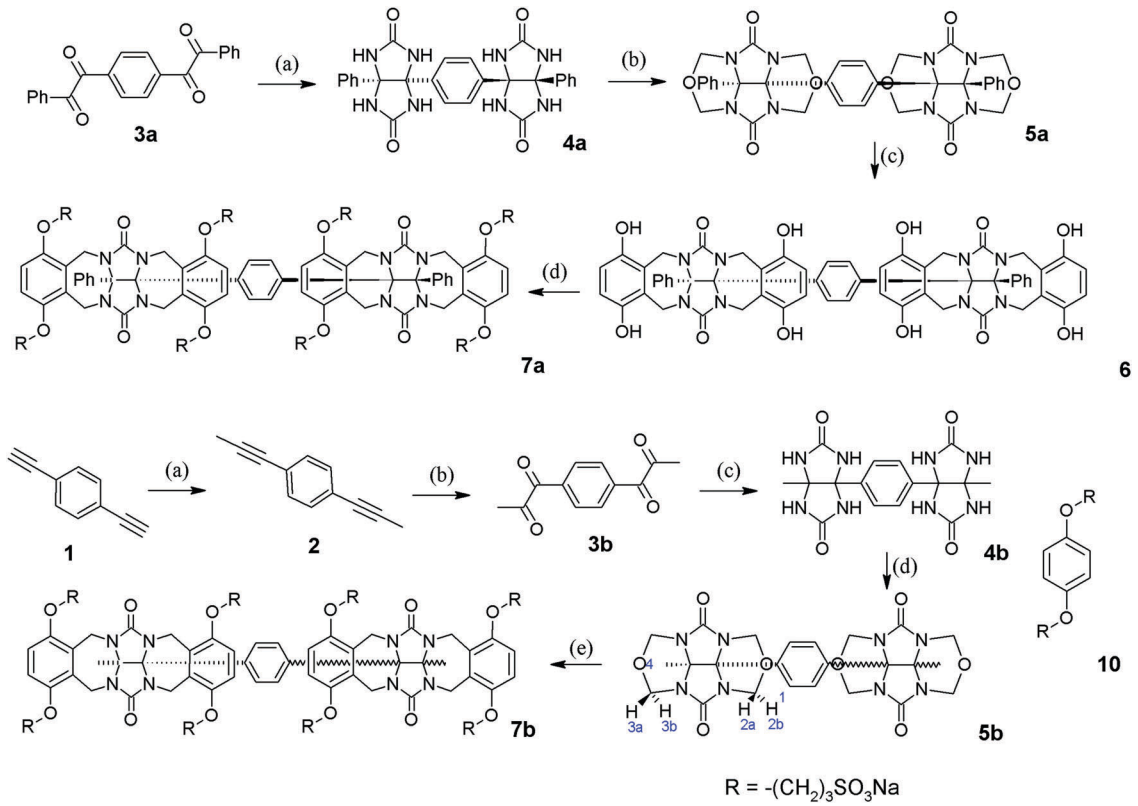
† Electronic supplementary information (ESI) available: ^{1}H NMR spectra of all compounds, NMR titration data, and DFT calculation details (PDF). See DOI: 10.1039/c7nj00969k



Scheme 1 Synthesis of molecular clips **7a** and **7b**. Conditions: (a) urea, PhMe/TFA, reflux, 12 h, 96%; (b) CH_2O, 7 M HCl, reflux, 12 h, 91%; (c) hydroquinone, TFA, reflux, 6 h, 69%; (d) **9**, NaOH, water/dioxane, 25 °C, 12 h, 68%; (e) (1) *n*-BuLi, THF, −78 °C, 1 h, (2) MeI, 0–25 °C, 12 h, 95%; (f) $RuCl_3$, $NaIO_4$, CCl_4/MeCN/water, 25 °C, 2 h, 55%; (g) urea, 0.3 M HCl, 25 °C, 48 h, 77%; (h) CH_2O, 7 M HCl, 25 °C, 36 h, 47%; (i) **10**, TFA/Ac_2O, 95 °C, 3 h, 59%.

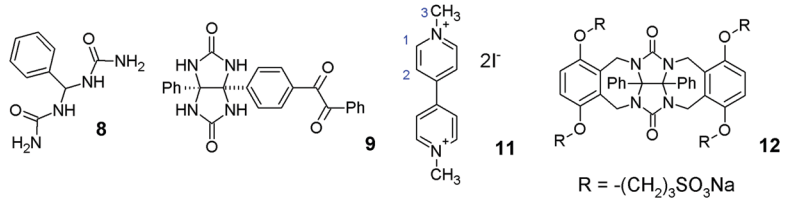


Fig. 1 Structures of selected compounds discussed in this work.

n-butyllithium and subsequently treated with methyl iodide to give **2**. Compound **2** was oxidized to **3b** using an $RuCl_3/NaIO_4$ mixture. Having compound **3b** in our hands, we performed its reaction with urea in an aqueous HCl/CH_2Cl_2 emulsion to obtain glycoluril dimer **4b**, which was transformed into cyclic ether **5b** by its reaction with paraformaldehyde. Each of the glycoluril units of **5b** bears methyl groups in the methine position, which are significantly smaller compared to phenyl groups in **5a**. Cyclic ether **5b** can react directly with compound **10** yielding molecular clip **7b** in 59% yield. This approach was significantly less efficient in the case of **5a** as bulky phenyl groups lower the reactivity of the ether groups towards the aromatic ring. This observation is in agreement with previously reported synthesis.[16]

Conformational properties

When recording the ^{1}H NMR spectra of compounds **5b** and **7b** at 30 °C in DMSO, we observed two signals instead of the expected one signal for each of their protons. These two sets of signals can be attributed to two distinct conformers, which were likely enabled by the rotation of two single C–C bonds connecting the central phenylene group to the glycoluril moieties. The rotation was slow on the NMR timescale at 30 °C; thus, the conformers were distinguished by their unique NMR spectra. Steric hindrance between methyl groups (attached to the methine carbon atoms of the glycoluril units) and the side walls of glycoluril units were likely the reason why the rotation was restricted. We decided to label the first conformer *syn* (the methyl groups located on the same side of the central phenylene group) and second *anti* (the methyl groups on opposite sides) (Fig. 2). Unfortunately, we could not distinguish which set of signals in the NMR spectra belonged to which conformer. Conformers of **5b**, as well as of **7b**, are present in a ratio of 58 : 42, which is based on the integration of the corresponding signals in the NMR spectra. The ratio corresponds to a 0.2 kcal mol^{-1} energy difference (ΔE)

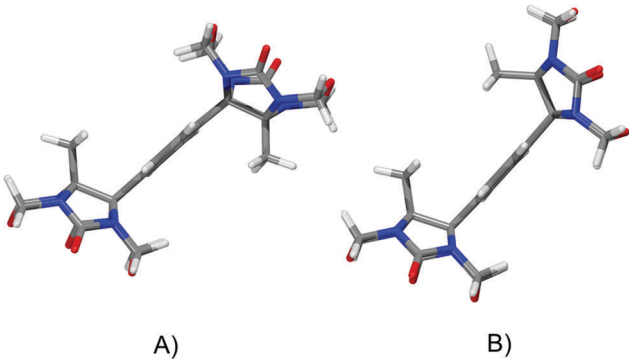


Fig. 2 Optimized structures of *anti* (A) and *syn* (B) conformers of compound **5b** obtained at the B3LYP/6-311G level of theory.

between the two conformers. The situation is different in the case of glycoluril dimer **4b**, which shows only one set of signals under the same conditions. This indicates that the rotation is fast on the NMR timescale as it is not restricted, due to the absence of the methylene side-groups featuring in **5b** and **7b**. Glycoluril dimer **4a** and its derivatives **5a** and **7a** also showed only one set of signals in their NMR spectra. However, these compounds distinguish themselves from **4b**, **5b**, and **7b** by the presence of phenyl instead of methyl groups in the two methine positions of the glycoluril dimer core. We assume that two phenyl groups are too bulky to be fitted in the *syn* conformation. This is why **4a** and its derivatives adopt only the sterically favorable *anti* conformation.

In order to gain information on the energy characteristics of the conformational changes in **5b**, the ^{1}H NMR spectra in DMSO-d_6 with temperature rising to 130 °C were recorded (Fig. 3). It was discovered that some signals in the NMR spectra show coalescence at a different temperature from the others. The coalescence temperature of signals 2b and 4 was 90 °C, while 1, 2a and 3b had already coalesced at 60 °C. The reason why there are two coalescence temperatures observed instead of one may be that compound **5b** possesses two C–C bonds

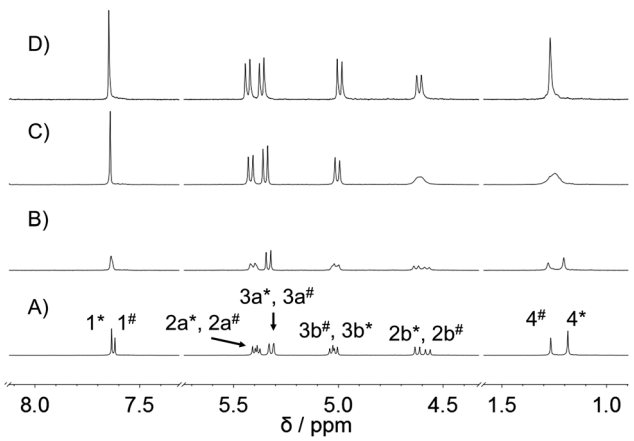


Fig. 3 ^{1}H NMR spectra (500 MHz, DMSO-d_6) of compound **5b** recorded at 30 °C (A), 60 °C (B), 90 °C (C), and 130 °C (D). * denotes the signals of major conformers. # denotes the signals of minor conformers.

Table 1 Determined values of the activation Gibbs energy of the interconversion of conformers

		Compound			
		5b		**7b**	
Signals		1	4	1	4
$\Delta G^{\ddagger}$ (kcal mol^{-1})	Major → minor	18.42	18.95	21.05	21.14
	Minor → major	18.20	18.71	20.81	20.89

around which the rotation occurs. Due to this, there is a possibility of two different kinds of rotational movements: (i) rotation of phenylene with respect to the glycoluril units and (ii) rotation of one glycoluril unit with respect to the other. The signals of protons 1 and 4 were used for the calculation of Gibbs activation energies of both rotations ($\Delta G^{\ddagger}$) using the Eyring equation. The resulting values of $\Delta G^{\ddagger}$ are shown in Table 1. The whole calculation is described in detail in the ESI.†

In contrast to **5b**, dimeric molecular clip **7b** showed only a single coalescence temperature, 110 °C. The values of $\Delta G^{\ddagger}$ of **7b** calculated using singlets 1 and 4 were greater than those of **5b** (Table 1). This means that the xylylene side walls of the clip **7b** are a source of more significant steric hindrance than the cyclic ether groups of **5b**. In the case of compound **4b**, the $\Delta G^{\ddagger}$ might be determined by measurement of the NMR spectra at low temperature. However, compound **4b** was insoluble in common organic solvents including DMF. The only suitable NMR solvent for this compound was DCOOD. The melting point of formic acid is 8.4 °C and therefore we could not measure the low-temperature spectra and determine the $\Delta G^{\ddagger}$ of compound **4b**.

Supramolecular properties

The ability of dimeric clips **7a** and **7b** to act as supramolecular hosts was investigated by ^{1}H NMR spectroscopy. Inclusion complexes between viologens with cucurbiturils as well as their acyclic versions have been previously described. However, interactions of molecular clips resembling those present in dimeric clips **7a** and **7b** with viologen have not been reported. Thus, methylviologen **11** was selected as a suitable guest for supramolecular studies with dimeric clips **7a** and **7b** and their interactions in D_2O (Fig. 4).

The aromatic signals of **11** underwent an upfield shift after addition of clips **7a** and **7b** to the guest solution. This indicates the formation of an inclusion complex between the clips and methylviologen. Since compounds **7a** and **7b** have two sites that could encapsulate guest **11**, it was expected that these compounds would form 1 : 2 complexes, in which each clip arm holds one guest molecule **11**. To prove the expected binding mode, the stoichiometry of the complex was determined by the continuous variation method (Job's plot). The maximum of Job's curve appeared approximately at *x*-coordinate = 0.66 which proves that 1 : 2 complexation is predominant at equilibrium (Fig. S19 and S20, ESI†). This binding mode was further visualized by a model obtained by quantum chemical calculations (Fig. 5).

A plot of the chemical shifts of signals 1 and 2 of the guest was fitted to the binding isotherm of the 1 : 2 binding model to

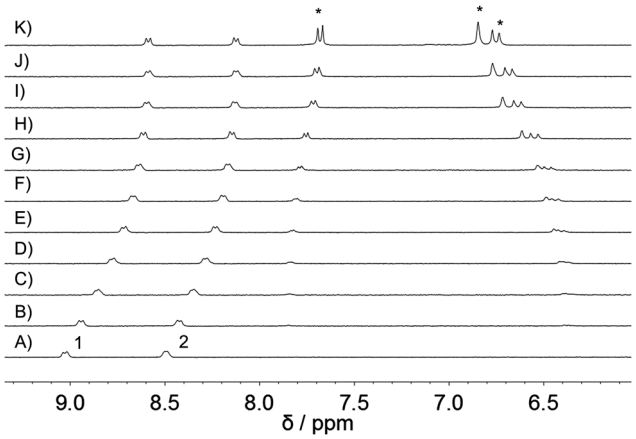


Fig. 4 ^{1}H NMR (300 MHz, D_2O) spectra of **11** in the absence (A) and in the presence of 0.13 equiv. (B), 0.25 equiv. (C), 0.38 equiv. (D), 0.50 equiv. (E), 0.63 equiv. (F), 0.75 equiv. (G), 1.00 equiv. (H), 1.50 equiv. (I), 2.00 equiv. (J), and 3.00 equiv. (K) of **7b**. * denotes the signals of **7b**.

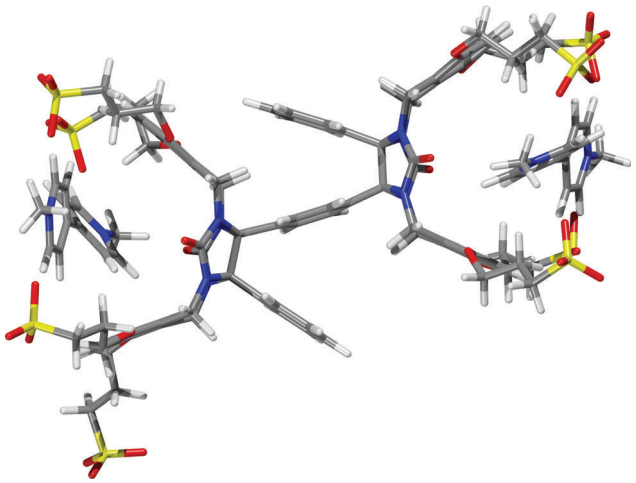


Fig. 5 Optimized structures of the **7a**·**11**$_2$ complex obtained using the PM6 method.

obtain the corresponding association constants (Table 2). Unlike clip **7a**, the situation in the case of clip **7b** was complicated by its ability to adopt two different conformers. In aqueous solution, the conformers were always in a ratio of 58 : 42; the equilibrium was not affected by the presence of guest **11**. We were not able to determine the association constants for separate conformers due to the presence of four binding sites (each conformer has two indistinguishable binding sites) during titration with **11**. However, if the concentration of **11** was kept constant during the titration and the concentration of **7b** was varied, it was possible to use the signals of guest **11** to establish the association constants describing the affinity of **11** towards an equilibrium mixture of both conformers of **7b**. The association constants determined for complexes **7a**·**11**$_2$ and **7b**·**11**$_2$ are summarized in Table 2.

Hosts **7a** and **7b** bind methylviologen **11** with a very similar overall affinity and in both cases the binding is associated with a negative cooperativity. The observed negative cooperativity

Table 2 Association constants of complexes of hosts **7a** and **7b** with **11** determined by NMR titrations in D_2O at 30 °C

Host	β (M^{-2})	K_1 (M^{-1})	K_2 (M^{-1})	4 K_2/K_1
7a	$(2.11 \pm 0.41) \times 10^7$	$(1.28 \pm 0.25) \times 10^4$	$(1.66 \pm 0.34) \times 10^3$	0.52
7b	$(1.31 \pm 0.42) \times 10^7$	$(2.15 \pm 0.19) \times 10^4$	$(6.3 \pm 1.4) \times 10^2$	0.12

can be rationalized by the inclusion of the guest molecule in the first binding side of the dimeric clip which causes conformational changes at the second binding site of the host. However, in our case the binding sites are separated by a rigid phenylene moiety. Therefore, we do not expect that the negative cooperativity is a result of conformational changes. We presume that binding of the first cation **11** affects the distribution of electron density in the host molecule, which makes it less attractive for another guest **11**. Thus, electronic effects, rather than conformational changes, are the reason for the negative cooperativity. Finally, we determined the binding between **11** and model compound **12** to be $(8.82 \pm 0.77) \times 10^3$ M^{-1} which is in good agreement with the values obtained for binding sites in dimeric clips.

Conclusion

We prepared compounds **7a** and **7b** as the first examples of glycoluril-based dimeric molecular clips. Clip **7b**, as well as other compounds derived from glycoluril dimer **4b**, can adopt two different conformations, which can be distinguished by means of NMR. On the other hand, free rotation is forbidden in compounds based on **4a** due to the presence of the bulky phenyl substituent. Both dimeric clips **7a** and **7b** form complexes with methylviologen in a 1 : 2 ratio and with submillimolar stability in water. Our work demonstrated that structural motifs represented by compounds **4a** and **4b** can be converted to supramolecular hosts with two binding sites. Thus, a similar strategy should be applicable to the synthesis of dimers of acyclic glycoluril oligomers or cucurbituril dimers. The syntheses of these compounds are under development in our laboratory.

Experimental section

General methods

Starting materials were purchased from commercial suppliers and used without further purification. NMR spectra were recorded using a Bruker Avance 500 spectrometer operating at frequencies of 500.13 MHz (^{1}H) and 125.77 MHz (^{13}C), and a Bruker Avance 300 spectrometer operating at frequencies of 300.13 MHz (^{1}H) and 75.48 MHz (^{13}C). Both spectrometers were equipped with a BBFO probe. High-resolution mass spectra were recorded on an Agilent 6224 Accurate-Mass TOF LC-MS spectrometer using a multimode ESI/APCI ion source and a KDS Model 100 Series manual pump for sampling.

Synthetic procedures and characterization

Glycoluril dimer (4a). Compound **3a** (2.480 g, 7.43 mmol) was dissolved in toluene (150 mL); urea (8.91 g, 0.149 mol) and trifluoroacetic acid (7.5 mL) were added and the mixture was heated to reflux in a flask equipped with a Dean–Stark trap for 12 h. A precipitate was formed at the bottom of the flask during the reaction. Toluene was then removed by decantation and the precipitate was treated with methanol (200 mL) and sonicated for 30 min. The suspension was filtered and the solid was washed with acetone and dried *in vacuo* to give **4a** as a white powder (3.605 g, 95%). ^{1}H NMR (300 MHz, 96% D_2SO_4, DMSO-d_6 as external reference) δ 6.72 (t, J = 7.2 Hz, 2H), 6.59 (t, J = 7.2 Hz, 4H), 6.53 (s, 4 H), 6.24 (d, J = 7.8 Hz, 4H). ^{13}C NMR (126 MHz, 96% D_2SO_4, DMSO-d_6 as external reference) δ 161.86, 131.69, 130.92, 128.44, 126.85, 126.45, 124.68, 87.26, 85.82.

Cyclic ether (5a). Compound **4a** (3.01 g, 5.89 mmol) was mixed with paraformaldehyde (5.30 g, 0.177 mol); water (48 mL) and 35% HCl (72 mL) were added and the suspension was heated to reflux for 16 h. The suspension was cooled to RT and filtered. The solid material was washed with water and dried *in vacuo* to give **5a** as a white powder (3.64, 91%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.14 (m, 6H), 7.09 (m, 4H), 6.93 (s 4H), 5.43 (m, 8H), 4.56 (d, J = 11.4 Hz, 4H), 4.04 (d, J = 11.4 Hz, 4H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 157.67, 133.50, 132.45, 128.79, 128.38, 128.08, 127.86, 78.79, 78.46, 71.60, 71.54. HR-MS (APCI−): m/z $[C_{32}H_{28}N_8O_7 + Cl]^-$ observed: 713.1884, m/z $[C_{32}H_{28}N_8O_7 + Cl]^-$ calculated: 713.1881.

Dimeric clip (6). Compound **5a** (1.20 g, 1.77 mmol) was dissolved in TFA (15 ml); hydroquinone was added (4.21 g, 38 mmol) and the mixture was heated to reflux for 6 h and then allowed to cool to RT. The product was precipitated with methanol (100 ml) and the precipitate was collected by filtration. The crude product was dissolved in DMSO (15 ml) at 80 °C. Methanol (80 ml) was added to the solution and the mixture was cooled to RT. The precipitate was collected by filtration and washed with methanol and diethyl ether to give **6** as a white powder (1.29 g, 69%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.76 (s, 4H), 8.67 (s, 4H), 7.00 (t, J = 7.9 Hz, 4H), 6.92 (d, J = 7.4 Hz, 4H), 6.79 (t, J = 7.1 Hz, 2H), 6.75 (s, 4H), 6.52 (s, 4H), 6.45 (s, 4H), 5.32 (d, J = 15.9 Hz, 4H), 5.30 (d, J = 15.7 Hz, 4H), 3.53 (d, J = 15.9 Hz, 4H) 3.21 (d, J = 15.7 Hz, 4H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 156.50, 146.93,134.01, 133.83, 128.25, 127.95, 124.89, 124.82, 115.32, 115.19, 84.32, 84.14, 36.48, 36.29.

Dimeric clip (7a). Compound **6** (0.510 g, 0.49 mmol) was dissolved in 2.5 M NaOH (3.5 mL). The solution was treated with 1,3-propanesultone (0.911 g, 7.46 mmol) in dioxane (3.5 mL). The reaction mixture was stirred at RT for 8 h. The resulting precipitate was collected by filtration, washed with methanol and suspended in 2.5 M NaOH (7 mL). The suspension was again treated with 1,3-propanesultone (2.139 g, 17.51 mmol) in dioxane (9 mL). The reaction mixture was stirred at RT for 8 h. The resulting precipitate was collected by filtration and washed with methanol. The crude product was dissolved in water (20 mL) and precipitated with acetone (120 mL). The precipitate was collected by filtration, washed with methanol and diethyl ether and dried *in vacuo* to afford **7a** as a yellowish powder (0.728 g, 68%). ^{1}H NMR (300 MHz, D_2O) δ 7.22 (m, 10H), 7.09 (s, 4H), 7.03 (s, 4H), 6.99 (s, 4H), 5.42 (d, J = 15.9 Hz, 4H), 5.38 (d, J = 15.9 Hz, 4H), 4.18 (m, 16H), 4.00 (d, J = 15.9 Hz, 4H), 3.66 (d, J = 15.9 Hz, 4H), 3.22 (m, 16H), 2.31 (m, 16H). ^{13}C NMR (126 MHz, D_2O, 1,4-dioxane as internal reference) δ 159.82, 150.70,150.68, 134.62, 133.57, 129.51, 129.36, 129.03, 128.28, 127.93, 115.86, 115.72, 86.45, 86.12, 69.48, 69.43, 48.72, 48.65, 37.27, 25.18, 25.10. HR-MS (ESI+): m/z $[C_{82}H_{86}N_8Na_8O_{36}S_8 + 2Na]^{2+}$ observed: 1122.5939, m/z $[C_{82}H_{86}N_8Na_8O_{36}S_8 + 2Na]^{2+}$ calculated: 1122.5953.

1,4-Bis(1,2-dioxopropane-1-yl)benzene (3b). Compound **2**[28] (0.771 g, 5.00 mmol) was dissolved in a mixture of CCl_4 (15.5 mL) and CH_3CN (15.5 mL). A mixture of $NaIO_4$ (6.42 g, 30.02 mmol), $NaHCO_3$ (67.3 mg, 0.80 mmol) and $MgSO_4$ (308.0 mg, 2.56 mmol) in water (20 mL) was added to the solution. Aqueous 0.01 M $RuCl_3$ (4 mL, 0.04 mmol) was added and the reaction mixture was stirred at RT for 1.5 h. The mixture was diluted with ethyl acetate (100 ml) and the organic phase was separated from the precipitated salts by decantation. The organic phase was dried over $MgSO_4$ and the solvents were removed by rotary evaporation. The crude product was dissolved in ethyl acetate and filtered through a plug of silica gel. The solvent was removed by rotary evaporation to give compound **3b** as a yellow solid (0.605 g, 55%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.13 (s, 4H), 2.55 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 199.30, 189.93, 136.15, 130.64, 26.22.

Glycoluril dimer (4b). Compound **3b** (1.42 g, 6.51 mmol) was dissolved in CH_2Cl_2 (20 mL). Urea (5.06 g, 92.7 mmol) was dissolved in 0.3 M HCl (20 mL). The solutions were mixed and stirred together at RT for 2 days. The resulting precipitate was collected by filtration, washed with water and acetone and dried *in vacuo* to give **4b** as a white powder (1.95 g, 77%). ^{1}H NMR (500 MHz, 95% DCOOD) δ 7.80 (s, 4H), 1.22 (s, 6H). ^{13}C NMR (126 MHz, 95% DCOOD) δ 162.24, 137.44, 127.58, 81.68, 79.21, 22.70.

Cyclic ether (5b). Paraformaldehyde (1.60 g, 53.3 mmol) was dissolved in 9 M HCl (20 mL) at 60 °C, the solution was cooled to RT and compound **4b** (0.690 g, 1.78 mmol) was added and the solution was stirred for 24 h. Water was added to the mixture (11 mL) and stirred for another 12 h. The resulting precipitate was filtered, washed with water and dried *in vacuo* to give ether **5b** as a white powder (0.465 g, 47%). Compound **5b** was obtained as a mixture of two conformers in a 58 : 42 ratio. ^{1}H NMR (500 MHz, DMSO-d_6) major conformer: δ 7.63 (s, 4H), 5.40 (d, J = 11.3 Hz, 4H), 5.32 (d, J = 11.2 Hz. 4H) 5.01 (d, J = 11.2 Hz, 4H), 4.62 (d, J = 11.3 Hz, 4H), 1.18 (s, 6H). Minor conformer: δ 7.62 (s, 4H), 5.39 (d, J = 11.3 Hz, 4H), 5.32 (d, J = 11.2 Hz, 4H), 5.03 (d, J = 11.2 Hz, 4H), 4.57 (d, J = 11.3 Hz, 4H), 1.27 (s, 6H). ^{13}C NMR (126 MHz, DMSO-d_6) major conformer: δ 157.56, 134.84, 128.73, 77.87, 73.96, 71.30, 70.57, 18.77. Minor conformer: δ 157.56, 134.59, 128.73, 77.89, 73.89, 71.30, 70.57, 19.14. HR-MS (APCI−): m/z $[C_{24}H_{26}N_8O_7 + Cl]^-$ observed: 589.1570, m/z $[C_{24}H_{26}N_8O_7 + Cl]^-$ calculated: 589.1568.

Dimeric clip (7b). Compound **5b** (0.460 g, 0.83 mmol) and compound **10** (2.31 g, 5.83 mmol) were dissolved in a mixture of TFA (12 mL) and acetic anhydride (12 mL). The solution was heated to 95 °C for 4 h. The solvents were removed by rotary evaporation and the resulting solid was washed with

methanol (200 mL). The crude product was dissolved in water (15 mL) and precipitated with acetone (120 mL). The precipitate was filtered and dissolved in water (20 mL); the pH of the solution was adjusted to 7 using 1 M NaOH and the water was removed by rotary evaporation. The resulting solid was washed with methanol and diethyl ether and dried *in vacuo* to afford **7b** as a yellowish solid (1.01 g, 59%). ^{1}H NMR (500 MHz, D_2O) major conformer: δ 7.71 (s, 4H), 7.03 (s, 4H), 6.94 (s, 4H), 5.41 (d, J = 16.3 Hz, 4H), 5.23 (d, J = 15.7 Hz, 4H), 4.25 (m, 4H), 4.15 (m, 20H), 3.18 (m, 16H), 2.28 (m, 16H), 1.31 (s, 6H). Minor conformer: δ 7.74, (s, 4H), 7.03 (s, 4H), 6.91(s, 4H), 5.41 (d, J = 16.3 Hz, 4H), 5.29 (d, J = 15.7 Hz, 4H), 4.25 (m, 4H), 4.15 (m, 20H), 3.18 (m, 16H), 2.28 (m, 16H), 1.36 (s, 6H). ^{13}C NMR (126 MHz, D_2O, 1,4-dioxane as internal reference) major conformer: δ 159.30, 150.82, 135.96, 129.49, 128.92, 127.84, 115.92, 115.83, 85.04, 80.64, 69.66, 69.51, 48.64, 37.41, 35.97, 25.10, 18.95. Minor conformer: δ 159.30, 150.72, 135.92, 129.67, 128.92, 127.84, 115.92, 115.63, 85.11, 80.36, 69.66, 69.44, 48.64, 37.38, 35.97, 25.10, 18.69. HR-MS (ESI+): m/z $[C_{72}H_{82}N_8Na_8O_{36}S_8 + 2Na]^{2+}$ observed: 1060.5797, m/z $[C_{72}H_{82}N_8Na_8O_{36}S_8 + 2Na]^{2+}$ calculated: 1060.5796.

Glycoluril derivative (9). Compound **3a** (0.334 g, 1.01 mmol) and compound **8**[29] (0.853 g 4.10 mmol) were dissolved in acetic acid (15 mL) and 96% H_2SO_4 (0.5 mL) was added. The solution was heated to reflux for 4 h, cooled to RT and poured into water (100 mL), which resulted in the formation of a precipitate. The precipitate was collected by filtration, washed with water and acetone and dried *in vacuo* to give **8** as a pale yellow powder (0.411 g, 96%). ^{1}H NMR (500 MHz, 95% DCOOD) δ 7.88 (d, J = 7.0 Hz, 2H,), 7.83 (t, J = 7.5 Hz, 1 H), 7.80 (d, J = 9.0 Hz, 2H), 7.62 (t, J = 7.0 Hz, 2 H), 7.57 (d, J = 9.0 Hz, 2 H), 7.31 (m, 2H), 7.20 (m, 3 H). ^{13}C NMR (126 MHz, 95% DCOOD) δ 195.78, 195.41, 162.80, 143.11, 135.99, 134.85, 132.95, 132.29, 129.96, 129.63, 129.51, 129.32, 128.42, 128.08, 126.91, 83.88, 83.31.

Monomeric clip (12). Diphenyl glycoluril cyclic ether[30] (1.021 g, 27.96 mmol) and compound **10**[21] (3.198 g, 80.28 mmol) were dissolved in a mixture of TFA (15 mL) and acetic anhydride (15 mL). The solution was heated to 95 °C for 4 h. The solvents were removed by rotary evaporation and the resulting solid was washed with methanol (200 mL). The crude product was dissolved in water (15 mL) and precipitated with acetone (120 mL). The precipitate was collected by filtration and dissolved in water (20 mL); the pH of the solution was adjusted to 7 using 1 M NaOH and the water was removed by rotary evaporation. The resulting solid was washed with methanol and diethyl ether and dried *in vacuo* to afford compound **12** as a yellowish solid (0.961 g, 32%). ^{1}H NMR (300 MHz, D_2O) δ 7.29 (m, 10H), 6.90 (s, 4H), 5.38 (d, J = 16.0 Hz), 4.12 (m, 8H), 3.93 (d, J = 16.0 Hz), 3.20 (m, 8H), 2.28 (m, 8H). ^{13}C NMR (126 MHz, D_2O, 1,4-dioxane as internal reference) δ 160.11, 150.71, 133.60, 129.71, 129.39, 128.87, 128.22, 115.72, 86.67, 69.44, 48.70, 37.34, 25.13. HR-MS (ESI−): m/z $[C_{44}H_{46}N_4Na_4O_{18}S_4 - Na]^-$ observed: 1049.1937, m/z $[C_{44}H_{46}N_4Na_4O_{18}S_4 - Na]^-$ calculated: 1049.1930.

Competing financial interest

The authors declare no competing financial interest.

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