A Cucurbituril Derivative That Exhibits Cation-Modulated Self-Assembly
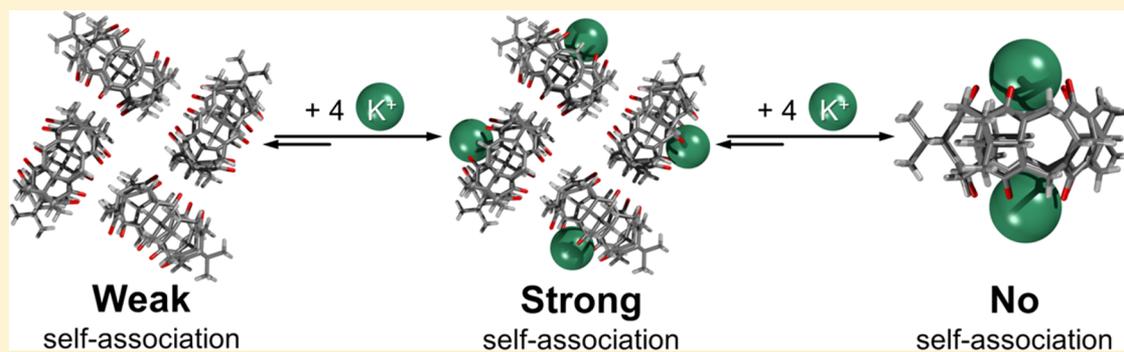
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S *Supporting Information*

ABSTRACT: Cucurbiturils are the most potent artificial receptors known for many organic molecules in water. However, little is known about their supramolecular chemistry in organic solvents. Here we present a new cucurbituril derivative, **1**, and investigate its supramolecular properties in methanol. The macrocycle resembles a five-membered cucurbituril in which four glycoluril units are replaced with propanediurea. Macrocycle **1** can bind to one cation such as potassium or anilinium via each of its opposed portals. The stability of these complexes in methanol at nanomolar concentrations exceeds that of complexes between metal cations and crown ethers. Moreover, macrocycle **1** forms a self-assembled tetrameric aggregate in the solid state and in methanol. The tetramer is stabilized by the addition of up to 1 equiv of a cation but is fully disassembled in the presence of 2 equiv of the cation. Cations can thus be used to tune the aggregation of **1** in solution.

INTRODUCTION

There is a great interest in synthetic supramolecular systems in which one binding event involving a receptor molecule permits or influences subsequent supramolecular interactions, because such systems mimic those found in nature. Several studies have examined systems in which metal cations serve as guests that interact with some host molecule and thereby affect the binding of a second guest. There are various ways in which the presence of a cation can modulate host–guest binding. In cases involving flexible host molecules, cation binding can induce conformational or configurational changes in the host's structure, affecting the binding of the second guest to a remote site.[1−10] This process is known as an allosteric interaction, and cation binding can have either positive or negative effects on the binding of the second guest. In systems where a cucurbituril derivative serves as the host, metal cations can interact with the oxygen atoms of the portals on either side of the rigid macrocycle and thus compete with the guest molecule for the macrocycle's binding sites.[11−15] This causes the apparent binding constant of the complex to decrease as the cation concentration increases. It has also been reported that metal cations induce the folding of the acyclic glycoluril decamer (an acyclic analogue of the cucurbituril structure) into a double-helical assembly.[16] However, the metal cation modulated aggregation of cucurbiturils has not been reported.

Cucurbiturils are popular hosts, particularly for neutral and cationic organic compounds, which they bind with affinities of up to 10^{17} M^{-1}.[17−22] With only two exceptions,[23,24] all studies on the binding and supramolecular chemistry of cucurbiturils have been conducted in water. It was recently reported that inclusion complexes between bipyridinium derivatives and cucurbit[7]uril form more rapidly and are thermodynamically more stable in water than in DMSO solution.[24] This is probably due to hydrophobic interactions, which are the dominant forces governing the binding of cucurbiturils to organic guests in water.[25−27] Both inclusion complexes and external complexes of cucurbiturils have been described in the literature. Stable external complexes are usually formed as a result of strong ion–dipole interactions between a cation and the oxygen atoms lining one of the two opposing portals of the cucurbituril. For example, cucurbit[6]uril binds monovalent inorganic cations in water with an affinity greater than that of 18-crown-6.[28] However, the stability of complexes between cucurbiturils and metal cations in organic solvents has not yet been evaluated. This is mainly because there are few cucurbituril derivatives with good solubility in organic media. Recently, we and others reported the synthesis of pressocucurbit[5]uril (**2**; see Chart 1),

Chart 1. Structures of Macrocycles 1 and 2
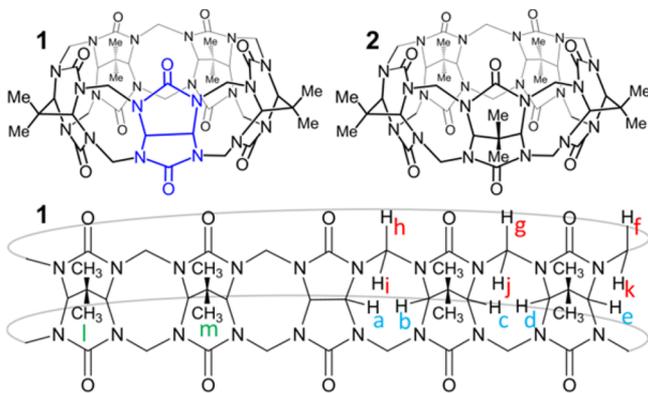
an analogue of cucurbit[5]uril in which all of the glycoluril units are replaced by propanediurea units.[29,30] This molecule exhibited good solubility in methanol, and here we present an investigation into its supramolecular chemistry in this solvent. More importantly, we present a new cucurbit[5]uril derivative consisting of one glycoluril and four propanediurea units (**1**; see Chart 1). We demonstrate that, unlike **2**, macrocycle **1** can form cyclic tetrameric aggregates in methanol because of its lone glycoluril unit. The architecture of these supramolecular aggregates can be tuned by adding cations to the solution.

■ RESULTS AND DISCUSSION

Synthesis of 1. Propanediurea and glycoluril are monomers easily accessible in multigram quantities. This enabled us to investigate several reactions yielding macrocycles containing both units. Mixtures of both urea-based monomers were reacted with paraformaldehyde under aqueous acidic conditions at elevated temperatures. The composition of the resulting product mixture could be tuned by adjusting the relative starting quantities of the two monomers. For example, when the monomers were reacted in an equimolar ratio, complex reaction mixtures containing both five- and six-membered macrocycles with different numbers of the two kinds of building blocks were obtained (Figure S22 in the Supporting Information). After some experimentation, we found that the number of different products could be minimized by reacting glycoluril and propanediurea in a molar ratio of 1:10 and performing the reaction with excess paraformaldehyde in concentrated HCl at 95 °C for 24 h (Scheme 1). Surprisingly,

Scheme 1. Synthesis of 1
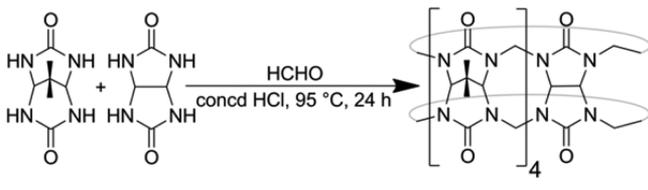
only two different macrocycles were found in the resulting mixture: decamethylpressocucurbit[5]uril (**2**) and the new macrocycle **1**, which is structurally similar to **2** but with one propanediurea unit replaced by a glycoluril unit. The two macrocycles were separated by exploiting their different solubilities: **2** precipitated from the reaction mixture, while **1** remained in solution together with small amounts of impurities.

The major impurity, NH_4Cl resulting from the decomposition of propanediurea, was removed by ion exchange chromatography (Amberlyst A-26 OH), after which a recrystallization from water provided pure **1** in 22% yield. The macrocycle is soluble in D_2O (2.4 mM) and CD_3OD (8.9 mM) at 20 °C. It is also possible to prepare oversaturated solutions of **1** in methanol (up to 12 mM) that remain transparent for several days.

X-ray Crystal Structure of 1. Single crystals of **1** suitable for X-ray analysis were obtained by slow crystallization from water. The crystal structure confirms that the macrocycle contains one glycoluril moiety and four propanediurea units (Figure 1). The unit cell features two symmetrically
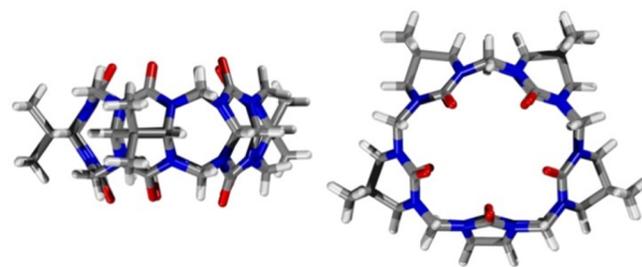

Figure 1. Side and top views of the X-ray crystal structure of **1**. Color code: C, gray; H, white; N, blue; O, red. Solvent molecules and the second symmetrically independent molecule are omitted for clarity.

independent molecules of macrocycle **1** ($Z = 4$) with very similar parameters; because they are so similar, only one is shown in Figure 1. The distances between the ureidyl O atoms of each propanediurea unit in the macrocycle are rather similar, ranging from 5.667(3) to 5.905(4) Å. However, the distance between the oxygen atoms in the glycoluril unit is significantly greater (6.279(3) Å). Consequently, the oxygen atoms of the glycoluril unit stand out from the planes defined by oxygen atoms of the propanediurea units on each side of the macrocycle. Similarly, the distances between the carbon atoms of the opposed methylene bridges connecting adjacent propanediurea units (3.679(5)−3.734(4) Å) are greater than those of the methylene bridges connecting propanediurea and glycoluril units (3.525(4) and 3.574(4) Å). These size differences within the macrocycle occur because the bending of the propanediurea units is more pronounced than that of the glycoluril unit.

Self-Association of 1. The supramolecular properties of cucurbiturils have been almost exclusively investigated in water, because most of these macrocycles are insoluble in organic solvents. However, macrocycle **1** shows good solubility in methanol; therefore, we used ^1H NMR spectroscopy to investigate its supramolecular chemistry in this solvent. The chemical shifts of several protons in the macrocycle were found to depend on its concentration in the methanolic solution (Figure 2). Such behavior is usually indicative of self-association. The concentration dependence was most pronounced for the methine hydrogen atoms of the glycoluril unit (H*a*) and the neighboring propanediurea units (H*b*) as well as the methylene protons projecting outward from the portal of the macrocycle in the positions adjacent to the glycoluril unit (H*i*). These protons may be most strongly affected because the molecule's surface is flatter and more accessible in the region around the glycoluril unit, allowing it to form hydrogen bonds with the five oxygen atoms comprising one portal of a second
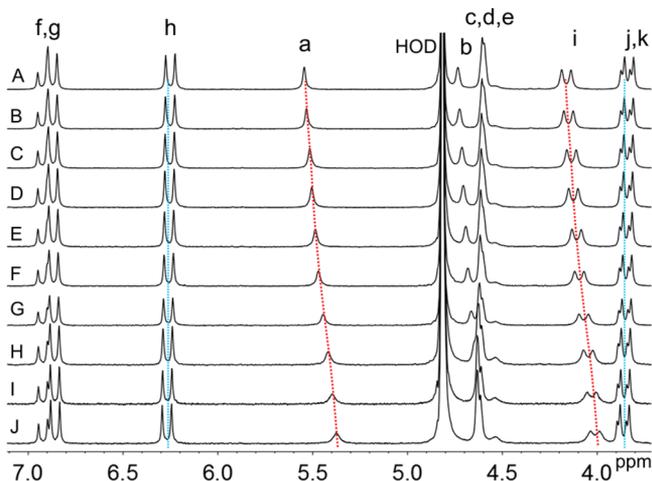
Figure 2. NMR spectra (300 MHz, CD₃OD, 30 °C) of **1** at concentrations (A) 11 mM, (B) 10 mM, (C) 9 mM, (D) 8 mM, (E) 7 mM, (F) 6 mM, (G) 5 mM, (H) 4 mM, (I) 3 mM, and (J) 2 mM.

molecule of **1**. The self-association of this molecule is discussed in more detail later in this article. Importantly, the chemical shifts of the protons of macrocycle **2** in methanol were not concentration dependent. Therefore, the glycoluril unit of **1** appears to be crucial for its self-association. In addition, we did not observe any self-association of **1** in D_2O, probably because water solvates the macrocycle more strongly than does methanol and thus suppresses the self-association process.

Supramolecular Interactions of 1 with Cations. Cucurbiturils are known to form supramolecular complexes with inorganic cations in which the cations are stabilized on the macrocycle's portals via ion–dipole interactions. However, there are no reports in the literature describing cucurbituril–cation interactions in methanol. We therefore used ¹H NMR spectroscopy to investigate the binding of **1** to KCl (Figure 3) in this solvent. Adding up to 2 equiv of KCl to a solution of **1** in CD₃OD caused all of the peaks in the spectrum except those corresponding to Ha, Hb, and Hi to undergo rather small upfield or downfield shifts. Adding more KCl did not cause any further shifts of these signals. This pattern of complexation-
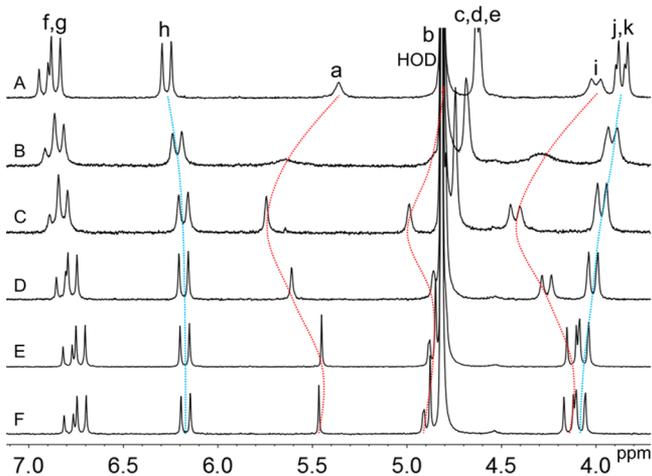

Figure 3. ¹H NMR spectra (300 MHz, CD₃OD, 30 °C) of **1** (1.9 mM) (A) in the absence and in the presence of (B) 0.5 equiv, (C) 1 equiv, (D) 1.5 equiv, (E) 2 equiv, and (F) 5 equiv of KCl.

induced shifts is consistent with a binding mode in which each of the two portals of **1** is occupied by one potassium cation.

This binding mode was further confirmed by isothermal titration calorimetry (ITC), which showed that the two portals represent independent binding sites for potassium cations (Figure S5 in the Supporting Information). Surprisingly, the resonances of protons Ha, Hb, and Hi were much more strongly influenced by the addition of KCl. The addition of 1 equiv of KCl caused all three peaks to undergo a very pronounced downfield shift of 0.38−0.43 ppm. Adding more KCl up to 2 equiv caused these peaks to undergo an upfield shift; no further changes in their chemical shifts were observed upon adding KCl beyond 2 equiv. To interpret this unexpected observation, we first looked at the results of the dilution experiment (Figure 2), which showed that the formation of the self-associated species that dominates at higher concentrations of **1** is accompanied by downfield shifts of the Ha, Hb, and Hi signals. The addition of up to 1 equiv of KCl also causes pronounced downfield shifts of these signals, suggesting that addition of the salt enhances the macrocycle's self-association. In this case, when one portal of **1** is occupied by a potassium cation, the opposing portal is free to interact with a second molecule of the macrocycle. When more than 1 equiv of KCl is added, potassium cations start occupying both portals of individual macrocycle molecules. Moreover, the affinity of the portal for potassium cations is presumably greater than its affinity for other molecules of **1**. Consequently, self-assembly is suppressed and a 1:2 complex of **1** with potassium is formed. When a solution of **1** in methanol containing 1 equiv of potassium was diluted (Figure S12 in the Supporting Information), the signals corresponding to Ha, Hb, and Hi underwent a significant upfield shift, confirming that self-association occurred under these conditions. Conversely, diluting a methanolic solution of **1** containing 2 equiv of KCl had no effect on the peaks' chemical shifts (Figure S13 in the Supporting Information), indicating that self-association did not occur under these conditions.

Additional NMR experiments in which the potassium salt was replaced with an anilinium salt (Figure S14 in the Supporting Information) were performed to support the proposed sequence of binding events and to shed further light on the nature of the self-association of **1**. Unlike potassium, the anilinium ion has protons that can be observed by ¹H NMR spectroscopy, making it possible to study its binding to the macrocycle in more detail. Titrating a methanolic solution of **1** with anilinium yielded spectra similar to those observed during titration with KCl: the signals of the Ha, Hb, and Hi protons were shifted downfield in the presence of 1 equiv of anilinium and then shifted upfield on the addition of a second equivalent of the salt. This suggests that the same sequence of events occurs during titration with both cations. ROESY experiments were then performed on three samples containing **1** and anilinium in different ratios, with the concentration of the macrocycle being 10.3 mM in all cases. We first analyzed a solution of **1** in CD₃OD in the absence of the cation (Figure S16 in the Supporting Information). Cross-peaks were observed between the well-separated singlet of the glycoluril methine proton Ha and the protons surrounding the carbonyl portals (Hf, Hg, Hh). Such H−H interactions are not possible within a single macrocycle molecule. This result thus supports the formation of self-association complexes of macrocycle **1** involving interactions between a carbonyl portal of one molecule and the glycoluril protons of another. The

ROESY spectrum of a 1:1 mixture of **1** with anilinium also features cross-peaks between H*a* and the H*f*, H*g*, and H*h* protons. (Figure 4), together with cross-peaks between the
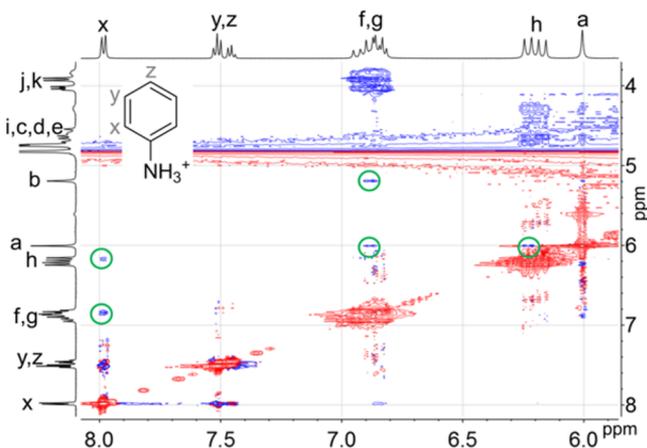

Figure 4. Portion of the $^1H-^1H$ ROESY spectrum (500 MHz, mixing time 200 ms, CD$_3$OD, 30 °C) of a 1:1 mixture of macrocycle **1** and anilinium (10.3 mM).

anilinium proton in the ortho position and the H*f*, H*g*, and H*h* protons on the portal of **1**. This suggests the occurrence of both self-association and the formation of a 1:1 complex between **1** and anilinium. Finally, the only cross-peaks observed in the ROESY spectrum of the 1:2 mixture of **1** with anilinium (Figure S18 in the Supporting Information) are those associated with the binding of the cation to the macrocycle, which is consistent with the absence of self-association in the presence of 2 equiv of the cation.

X-ray Crystal Structure of the Tetrameric Aggregate. After several attempts, we obtained crystals of **1** suitable for X-ray crystallography from an oversaturated equimolar (10.9 mM) methanolic solution of **1** and anilinium chloride (Figure 5). Figure 5A shows two very similar but symmetrically
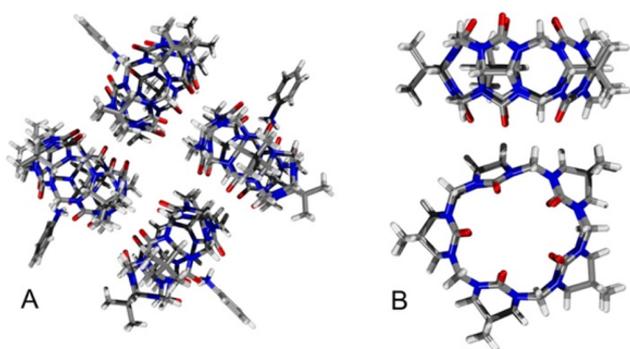

Figure 5. (A) Crystal structure of a tetrameric aggregate of the **1**·anilinium complex. (B) Selected fragments of the aggregate showing the interactions between two macrocycles.

independent 1:1 complexes of **1** with anilinium; four such 1:1 complexes aggregate to form the self-assembled tetrameric structure. The angle between the plane of the anilinium ring and the plane containing the oxygen atoms of the macrocycle is 82.07(7)° in one of the symmetrically independent complexes and 86.91(8)° in the other. The ammonium group is stabilized above the center of the ring defined by the portal's oxygen

atoms, with which it forms multiple N–H···O hydrogen bonds; the O–N distances range from 2.729(3) to 2.866(3) Å. More importantly, the macrocycles are self-assembled into a cyclic tetrameric aggregate that is stabilized by C–H···O hydrogen bonding interactions between hydrogen atoms on the convex face of one molecule of **1** and the oxygen atoms of one portal on another molecule of **1**. The H*a* and H*b* protons, along with two of the H*i* protons (for proton assignments, see Chart 1), are located in closest proximity to the oxygen atoms of the portal. Each of these hydrogen atoms is distant by 2.220 and 2.999 Å from at least two oxygen atoms of the portal.

DOSY Experiments. The results obtained by analyzing the crystal structure are consistent with those observed for methanolic solutions of **1**; in both cases, there is clear evidence of self-assembly. The formation of the self-assembled aggregates is driven by the formation of C–H···O hydrogen bonds between the oxygen atoms of one molecule of the macrocycle and the H*a*, H*b*, and H*i* protons of another. However, it was not clear whether the self-assembled structure in solution resembles the tetrameric aggregates observed in the solid state or whether some other kind of self-association complex is formed. We performed diffusion-ordered spectroscopy (DOSY) experiments to address this issue. Solutions of **1** (4 mM) in methanol were prepared, and the macrocycle's diffusion coefficient was measured in the presence of 0.0, 0.5, 1.0, 1.5, 2.0, 3.0, and 4.0 equiv of KCl. The diffusion coefficients were determined by considering four separate resonances of **1**. Figure 6 shows that the diffusion coefficient of **1** decreased
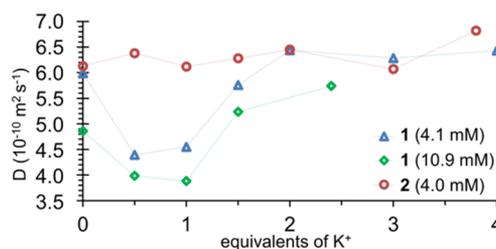

Figure 6. Dependence of the diffusion coefficients of macrocycles **1** and **2** on the concentration of KCl. Diffusion coefficients were determined by considering the macrocycles' proton resonances. The lines are shown to guide the eye.

significantly after the addition of 1 equiv of KCl. This is consistent with earlier NMR experiments, which indicated that the abundance of self-assembled aggregates increases when the **1**:K$^+$ ratio is 1:1. Further addition of the salt up to 2 equiv was accompanied by an increase in the diffusion coefficient; this increase stopped after the addition of excess KCl. Similar results were obtained at a higher concentration (10.9 mM) of **1** (Figure 6).

These results support the proposed formation of a 1:2 complex between **1** and the potassium cation that suppresses the self-association of the macrocycle. Note that the diffusion coefficient measured in the absence of KCl is lower than that in the presence of excess KCl. This indicates that self-association occurs to some degree in the absence of KCl but is cancelled in the presence of 2 equiv of KCl. The difference in the diffusion coefficients of the two states is particularly pronounced at the higher concentration of **1** (10.9 mM) because the amount of tetramer increases with the macrocycle's concentration. We also performed identical DOSY experiments using **2** in place of **1** (Figure 6) and found that the diffusion coefficient of **2** was not

dependent on the KCl concentration. This confirms that, unlike **1**, macrocycle **2** does not self-associate in methanol. Glycoluril units are therefore essential for the self-assembly process.

To estimate the number of molecules of **1** comprising the aggregates formed in methanol, we assumed that the diffusion coefficient obtained in the presence of 2 equiv of K⁺ corresponds to the diffusion of a 1:2 complex of the macrocycle with potassium. This species can be regarded as a monomeric unit that can aggregate further (with the loss of one cation) under the appropriate conditions. We then computed the ratios of the diffusion coefficients of the monomeric unit and the oligomers obtained at different concentrations. The resulting numbers correspond to the oligomerization number of the aggregates if we assume that both the monomer and the oligomers are roughly spherical (for details, see the Supporting Information).[31] The highest monomer:oligomer ratios of 1.45 and 1.37 (at 4.1 mM of **1**) and 1.44 and 1.48 (at 10.9 mM of **1**) were computed for the solutions containing 0.5 and 1.0 equiv of KCl. Theoretically, the monomer:oligomer ratios for dimeric, trimeric, and tetrameric aggregates should be 1.26, 1.44, and 1.59, respectively. Moreover, the self-association process observed in methanol is fast on the NMR time scale; therefore, the proton resonances used to determine the diffusion coefficients are actually averages of the free and self-assembled forms of **1**. Therefore, the experimentally determined monomer:oligomer ratio should be regarded as a lower bound on the true value. As such, the observed ratio of 1.48 suggests that tetrameric or higher oligomers are formed in methanolic solution.

ITC Experiments. To evaluate the strength of the self-association of **1** in methanol, we performed ITC dilution experiments in the absence of salt (Figure S9 in the Supporting Information). To simplify the calculations involved, we assumed that only a tetrameric complex was formed. The experimental data fitted this binding model well, yielding an association constant (K_a) of 2.0×10^6 M^{-3}. We were not able to calculate K_a for the formation of a tetrameric complex in the presence of the potassium cation due to competition of the cation for the macrocycle **1**.

ITC titration experiments were then performed to investigate the binding of macrocycles **1** and **2** with cations (Figure S5–S8 in the Supporting Information). ITC titration against a solution of each of macrocycle yielded a titration curve with two distinct steps corresponding to the formation of 1:1 and 1:2 complexes. The association constants for the **2**·potassium complexes are $(2.00 \pm 0.94) \times 10^9$ M^{-1} for the 1:1 complex and $(2.76 \pm 0.31) \times 10^6$ M^{-1} for the 1:2 complex. Similarly, K_1 and K_2 values of $(5.13 \pm 4.86) \times 10^8$ and $(1.69 \pm 0.85) \times 10^6$ M^{-1} were obtained for the **2**:anilinium complexes. The affinity between macrocycle **1** and cations is probably influenced by the formation of self-association complexes. Thus, data obtained for complexes of macrocycle **1** with potassium ($K_1 = (3.70 \pm 2.54) \times 10^8$ M^{-1}, $K_2 = (2.74 \pm 0.47) \times 10^6$ M^{-1}) and with anilinium ($K_1 = (1.35 \pm 0.50) \times 10^8$ M^{-1}, $K_2 = (5.76 \pm 0.39) \times 10^5$ M^{-1}) are only informative. The association constants determined for complexes of **1** and **2** with cations are even higher than those between potassium and crown ethers.[32] Constants determined for the first and second binding events appeared to be different, indicating major negative cooperativity. The reason for the different affinities of cations to structurally identical binding portals during the first and second binding events can be derived from quantum chemical calculations under vacuum. After binding of the first cation to

one portal, the affinity of the opposite portal decreases, as demonstrated by a decrease in the negative electrostatic potential (Figures S23 and S24 in the Supporting Information). It can be expected that the presence of solvent suppresses this effect due to its screening capabilities. However, our experiments show that the negative cooperativity is strong enough to take place even in solution.

CONCLUSION

The new cucurbituril derivative **1** was prepared, consisting of four propanediurea units and one glycoluril unit connected by two rows of methylene bridges. This macrocycle is soluble in methanol, allowing us to perform the first investigation of the supramolecular chemistry of any cucurbituril in this solvent. Experiments were performed using ¹H NMR spectroscopy, ITC, DOSY, and X-ray crystallography. Macrocycle **1** can self-assemble into cyclic tetrameric aggregates in methanol. Its self-association is attributable to the formation of multiple C−H···O hydrogen-bonding interactions between the oxygen atoms forming one portal of one molecule of **1** and the hydrogen atoms around the glycoluril unit of a second molecule of **1**. The formation of the tetramer is sensitive to the presence of cations such as potassium and anilinium (see Figure 7).
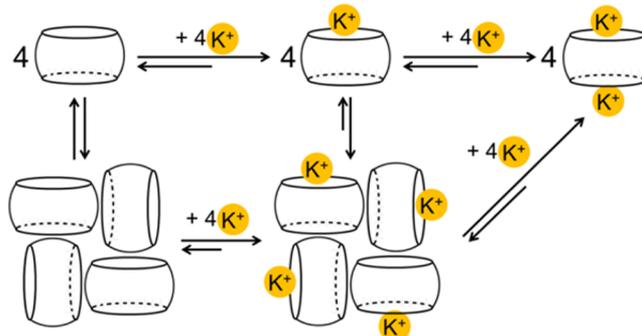

Figure 7. Self-association of macrocycle **1** and its dependence on the potassium cation concentration.

The presence of 1 equiv of cation leads to the formation of 1:1 complexes that are stable at nanomolar concentrations, and the formation of the 1:1 complex reinforces the tetrameric aggregation of the macrocycle. Adding a second equivalent of the cation leads to the formation of a new 2:1 complex in which each portal of **1** is occupied by one cation because the portals' interaction with the cation is substantially stronger than that with the convex face of a second molecule of **1**. This causes the complete disappearance of the macrocyclic aggregates. In other words, small quantities of a cation (up to 1 equiv) promote the formation of tetrameric aggregates of **1**, while excess quantities of the cation promote their disassociation. The glycoluril unit is crucial for the self-association of **1** because the related macrocycle **2** that consists exclusively of propanediurea units does not self-associate. Similar self-assembly can therefore be expected to occur in other cucurbiturils containing at least one glycoluril unit bearing methine protons in organic solvents and also in concentrated aqueous solutions.

EXPERIMENTAL SECTION

Chemicals were commercially available and were used without further purification. 9,9-Dimethylpropanediurea and macrocycle **2** were prepared according to the published procedures.[30] NMR spectra

were recorded on a spectrometer with working frequencies of 300.13 MHz for ^{1}H and 75.48 MHz for ^{13}C or a spectrometer with working frequencies of 500.13 MHz for ^{1}H and 125.77 MHz for [13]C. Both spectrometers were equipped with a BBFO probe. All experiments were recorded at 303.15 K. Mass spectra were recorded on a MALDI-TOF spectrometer. Samples were ionized with the aid of a nitrogen laser (wavelength 337 nm, maximum power 6 MW). α-Cyano-4-hydroxycinnamic acid (HCCA) was used as a matrix. Isothermal titration calorimetry (ITC) experiments were performed using a VP-ITC microcalorimeter. Experiments were carried out in HPLC-grade MeOH at 303.15 ± 0.1 K. X-ray intensity data were measured at 120 K on a rotating anode partial χ geometry diffractometer using Mo Kα (λ = 0.71075 Å) radiation. CCDC 1472328 (**1**) and CCDC 1472330 (**1** + aniline) contains supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Synthesis of 1. 9,9-Dimethylpropanediurea (1.84 g, 10 mmol), glycoluril (0.142 g, 1 mmol), and paraformaldehyde (0.991 g, 33 mmol) were mixed in HCl (37%, 5 mL). The mixture was heated, and all solid material dissolved at 45 °C. The solution was stirred at 50 °C for 30 min and then heated to 95 °C for 24 h. The resulting mixture was cooled and left in the refrigerator (4 °C) overnight. A white precipitate and crystalline material were removed by filtration. The obtained solution was treated with acetone until a white precipitate appeared. The solid was collected by filtration, washed with acetone, and then dissolved in a small amount of water and the solution neutralized by passing it through a column filled with a strongly basic anion exchange resin in OH⁻ form. The solvent was removed under reduced pressure, and the solid was recrystallized in H_2O to provide the pure product (220 mg, 0.22 mmol, 22%) as a white powder.

^{1}H NMR (500 MHz, D_2O, 30 °C): δ 6.77 (d, 2H, CH_2, J = 14.7 Hz); 6.71 (d, 4H, CH_2, J = 14.7 Hz); 6.15 (d, 4H, CH_2, J = 15.0 Hz); 5.44 (s, 2H, CH); 4.80−4.73 (m, 8H, CH); 4.14−4.09 (m, 10H, CH_2); 1.22 (s, 12H, CH_3); 1.18 ppm (s, 12H, CH_3). ^{1}H NMR (500 MHz, CD_3OD, 30 °C): δ = 6.93 (d, 2H, CH_2, J = 14.2 Hz); 6.87 (d, 4H, CH_2, J = 14.3 Hz); 6.25 (d, 4H, CH_2, J = 14.6 Hz); 5.54 (s, 2H, CH); 4.73 (s, 2H, CH); 4.64−4.57 (m, 6H, CH); 4.16 (d, 4H, CH_2, J = 14.6 Hz); 3.85 (d, 2H, CH_2, J = 14.2 Hz); 3.83 (d, 4H, CH_2, J = 14.3 Hz); 1.15 (s, 12H, CH_3); 1.12 ppm (s, 12H, CH_3). ^{13}C NMR (125 MHz, CD_3OD, 30 °C): δ = 155.3, 150.6, 150.1, 77.8, 77.6, 77.6, 77.6, 70.9, 61.5, 61.3, 57.2, 32.1, 31.8, 21.0, 20.7 ppm. MALDI-TOF HRMS (HCCA matrix, positive mode): m/z calculated for [$C_{42}H_{54}N_{20}O_{10}$ + H⁺] 999.440, found 999.441 ± 0.005.

ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01288.

Solubility determination, ^{1}H, ^{13}C, and 2D NMR spectra, MALDI MS, NMR and ITC titrations, and computational study details with absolute energies and tables of atom coordinates (PDF)
Crystallographic data (CIF)
Crystallographic data (CIF)

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Notes
The authors declare no competing financial interest.

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