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Propanediurea-Based Molecular Clips Bind Halide Anions: An Insight into the Mechanism of Cucurbituril Formation

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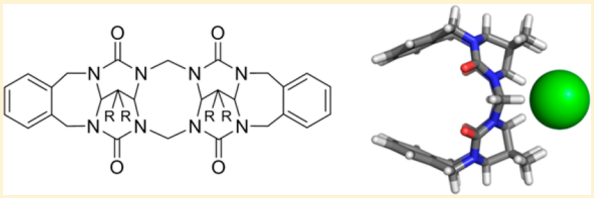
Supporting Information

ABSTRACT: The synthesis and supramolecular properties of the first methylene-bridged propanediurea-based dimers are described. These dimers, bearing an aromatic sidewall, have the shape of molecular clips. Unlike glycoluril-based dimers, these clips neither dimerize nor accept any organic guests, due to their small cavities. Both propanediurea- and glycoluril-based dimers bind halide anions on the convex side of the molecules, even in highly polar organic solvents. This observation brings new insights into the mechanism of cucurbituril formation.



INTRODUCTION

Glycolurils represent important building blocks for molecules that function as hosts in supramolecular chemistry. The most important glycoluril-based host molecules are cucurbiturils.[1−6] They are prepared by the acid-catalyzed condensation of formaldehyde with glycoluril, having four nitrogen atoms available for the reaction. The resulting macrocyclic compounds are composed of *n* glycoluril units connected by 2*n* methylene bridges arranged into two rows. When the nitrogen atoms of glycoluril at positions 2 and 4 are blocked from reacting with formaldehyde, the condensation reaction results in the formation of bambusurils.[7−11] Bambusurils have recently started to be recognized for their extremely strong binding of inorganic anions, not only in organic solvents but also in water. In contrast, cucurbiturils are known as the artificial hosts with the highest binding affinities toward neutral and cationic organic guests in water.[12−16] Acyclic cucurbituril derivatives have been studied by our group and that of Isaacs in order to further explore the mechanism of cucurbituril formation and also to design host molecules with more flexible structures in comparison with cucurbiturils.[17−26] This paper focuses on molecular clips formed by glycoluril dimers and framed by aromatic sidewalls. Recently, it was shown that the glycoluril units in the cucurbituril structure can be replaced by propanediurea.[27−29] This inspired us to investigate whether the substitution of propanediurea for glycoluril was also possible in glycoluril dimers and how the substitution would affect the supramolecular properties of the resulting host molecules. Here, we present our results.

RESULTS AND DISCUSSION

We prepared two molecular clips, **6** and **7**, which differed in the type of propanediurea that was used (Scheme 1). Clip **6** contained propanediureas with unsubstituted methylene bridges, while the propanediureas of clip **7** bore two methyl substituents at the same positions. Both clips were prepared in two steps, following similar synthetic protocols (Scheme 1). The first step was the preparation of an *o*-xylylene-side-protected propanediurea. Adopting a previously described synthetic procedure,[22] we prepared the side-protected propanediurea by the acid-catalyzed intramolecular cyclocondensation of *o*-xylylene bisurea (**1**) with diacetals (**2** and **3**). Diacetal **2** was commercially available, while diacetal **3** was obtained by a two-step reaction starting from triethyl orthoformate and isobutyraldehyde.[30] The reaction between bisurea **1** and the diacetals proceeded in water acidified with HCl. The resulting *o*-xylylene-protected propanediureas (**4** and **5**) precipitated out of the reaction mixture and were collected by filtration, with no need for additional purification. In the second step, the prepared propanediureas (**4** and **5**) were connected via methylene bridges by reaction with paraformaldehyde to obtain molecular clips **6** and **7**. The reaction proceeded in concentrated HCl, which was necessary to dissolve the *o*-xylylene propanediureas. The products precipitated out from the reaction mixture, and the starting materials were washed out with water. Electrospray ionization mass spectrometry (ESI-MS) in negative mode revealed that both molecular clips were isolated as complexes with chloride. Thus, solutions of **6** or **7** in methanol were passed through a column filled with Amberlyst A26 ion-exchange resin, and chloride-free clips were obtained in quantitative yields after evaporation of the solvent.

The crystal structures of both **6** and **7** (Figure 1) revealed that they were C-shaped diastereomers and possessed C_{2v} symmetry. The present structures are best compared to the analogous glycoluril dimers, which have been reported in our previous study.[22] The xylylene sidewalls showed dihedral angles of 54.2° (**6**) and 60.6° (**7**) and virtually enclosed the cavity, while in the glycoluril dimer the xylylene sidewalls were nearly parallel, showing dihedral angles of 13.0 and 16.7° for the two

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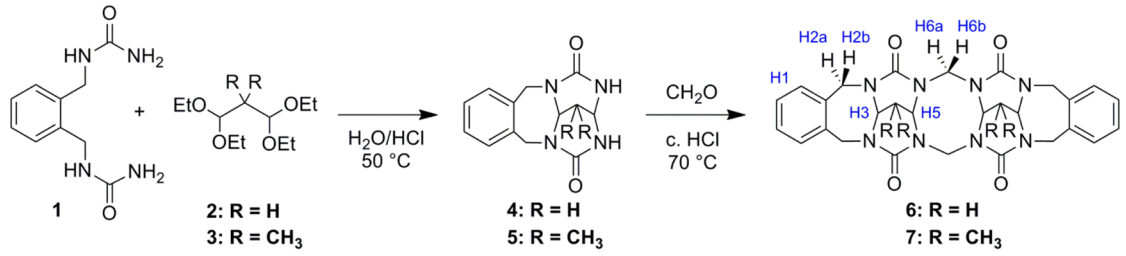
Scheme 1. Synthesis of Molecular Clips 6 and 7



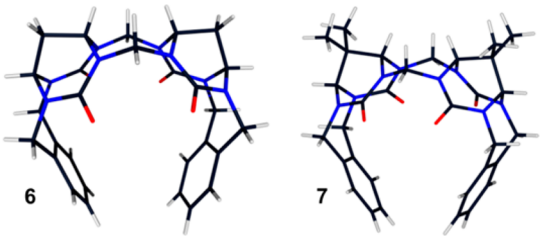


Figure 1. X-ray structures of propanediurea dimer clips **6** and **7**.

crystallographically independent molecules. Such a change in the clip conformation was clearly caused by the presence of an extra $CH_2/C(CH_3)_2$ moiety in the propanediurea-based building units, which were less planar than glycoluril-based units; the distance between the methine carbons defining the ridge of the propanediurea-based unit in **6** was 2.37 Å, while in the glycoluril-based unit it was only 1.54 Å. The carbonyl oxygen atoms acted as acceptors in hydrogen bonds with molecules of formic acid and water in the crystal structures of **6** and **7**, respectively. In addition, solvating molecules of HCOOH formed C−H···O contacts with hydrogen atoms at the convex face of clip **6**, thus indirectly confirming an area of positive electrostatic potential in the clip, which is discussed later in detail. Molecules of water formed similar C−H···O contacts in **7**; inside the clip, a molecule of water with one-fourth occupancy was found, suggesting only a slight affinity of water toward the clip interior.

Molecular clips derived from glycoluril dimers are known to form dimeric self-assemblies.[22,31−33] Therefore, we performed dilution experiments using ^{1}H NMR (Figure S11 in the Supporting Information) to verify that the positions of the proton signals of clips **6** and **7** were not dependent on their concentration in CD_2Cl_2. This clearly showed that the clips did not aggregate in the solution. This is not surprising, because the propanediurea-based clips, with the entrance closed by the xylylene sidewalls, were sterically hindered from self-association. For the same reason, these clips did not bind aromatic guests such as resorcinol. We decided to test the affinity of the clips toward water and bromide, because the formation of the corresponding complexes was indicated by X-ray analysis and ESI-MS, respectively. When solutions of clips **6** and **7** in CD_2Cl_2 were titrated with water, we did not observe any change in the positions of the clip signals, indicating the absence of a supramolecular complex. However, titration of the clips with tetrabutylammonium bromide (TBABr) resulted in pronounced changes in the NMR spectra of the clips. For example, the addition of an excess (35 equiv) of bromide into a solution of clip **7** induced a downfield shift of H5 (0.925 ppm) and H6b (0.322 ppm), while proton H6a (0.148 ppm) shifted upfield (Figure 2). In contrast, the complexation-induced chemical shifts of the remaining protons, H1, H2a, and H2b, were

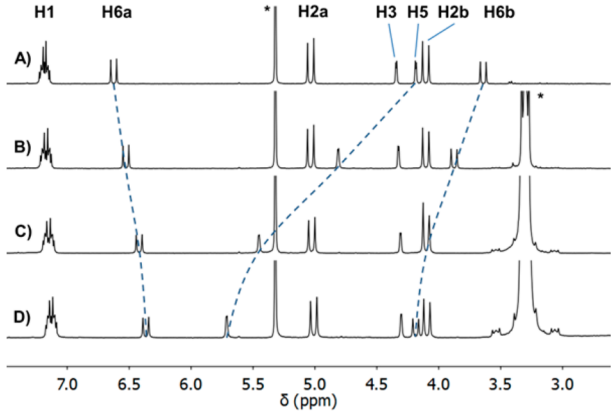


Figure 2. ^{1}H NMR spectra (300 MHz, CD_2Cl_2) of **7** in the absence (A) and in the presence of 4.3 equiv (B), 17.4 equiv (C), and 34.6 equiv (D) of TBABr. The asterisks denote signals of CH_2Cl_2 and TBA^+.

very minor. The significant downfield shift of H5 and H6b was consistent with a binding mode in which the bromide anion was located on the convex side of the clips, where it was stabilized by a weak hydrogen interaction C−H···X^- with the corresponding protons.

We constructed a Job plot (Figure S10 in the Supporting Information) to confirm the 1:1 stoichiometry of the complex. Fitting the chemical shift of the clip protons as a function of the concentration of bromide (Figure S9 in the Supporting Information) afforded a relative association constant (K_{rel}) of 25.8 M^{-1} for the 1:1 complex (Table 1). Please note that all

Table 1. Relative Association Constants K_{rel} for 1:1 Complexes of the Propanediurea Clips 6 and 7 with Halide Anions, Determined by ^{1}H NMR Spectroscopy at 30 °C

guest	**6**·CD_2Cl_2	**7**·CD_2Cl_2	**7**·CD_3CN
F^- (TBA^+)	12.8	9.6	9.3
Cl^- (TBA^+)	23.1	22.4	15.5
Br^- (TBA^+)	30.0	25.8	18.0
I^- (TBA^+)	18.9	32.0	19.7

association constants shown here are relative, as the clips competed for halide with the TBA cation. NMR titrations and Job plots, as obtained for the interaction between clip **7** and bromide, were also recorded using clip **6** instead of **7** and different halide anions. The K_{rel} values for specific clip−anion systems are given in Table 1. Several conclusions can be drawn from Table 1. (1) The presence of methyl substituents on the propanediurea unit of **7** did not influence halide binding, as both clips **6** and **7** showed similar affinity to the corresponding anions. (2) The stability of the complexes depended only marginally on the size of the anions. The lower affinity of the clips to smaller anions probably reflected the higher energy of

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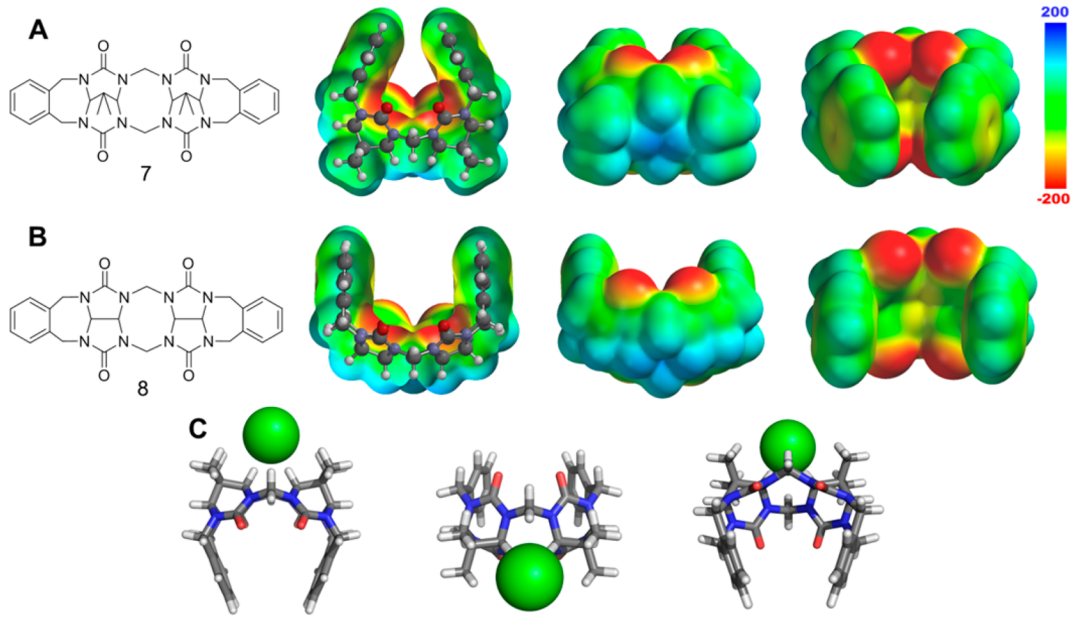

Figure 3. Geometries and properties of the clips and their complexes obtained at the B3LYP/6-311G* level of theory. Structure and electrostatic potential map of (A) clip **7** and (B) the glycoluril dimer clip **8** (IsoVal = 0.002 au, 200 to −200 kJ/mol). (C) Geometry of the complex between **7** and Cl^-: (left) top view; (middle) back view; (right) front view.

solvation of smaller anions. The clips had to compete with solvent molecules in the solvation shell, which resulted in a decrease in their binding energies. (3) The stabilities of the complexes were lower in acetonitrile in comparison with dichloromethane, which is in agreement with the different polarities of the two solvents.

A map of the electrostatic potential of clip **7** was calculated to verify the proposed binding mode of the anions (Figure 3A). The area of lowest potential on the clip, i.e., the area most suitable for halide binding, was on the convex face of the molecule, defined by the methine and methylene hydrogen atoms, which is in agreement with the binding site derived from the NMR experiments. The binding of the anions to the convex face of the clips was further supported by DFT calculations (Figure 3C). When the chloride anion was placed in different locations around clip **7**, the geometry optimization always drove the anion to one of three different positions, among which the proposed binding site was significantly favored (Figure S16 in the Supporting Information).

The formation of supramolecular complexes between clips **6** and **7** and halide anions may contribute to a better understanding of the mechanism of cucurbituril formation. Unlike our clips, prepared from propanediurea, cucurbiturils are usually formed by methylene-bridged glycolurils. However, the glycoluril and propanediurea dimer motifs are very similar (Figure 3A,B). Particularly important is the fact that the convex faces of both propanediurea dimers and glycoluril dimers (the structural motifs of CB) are decorated by methine together with methylene hydrogen atoms. We calculated an electrostatic potential map for a molecular clip similar to **7** but containing two glycoluril instead of propanediurea units (Figure 3B). Our calculation identified a region defined by the methine and methylene atoms on the convex face as that with the lowest electron density in the molecule.

Thus, both dimers have similar binding sites for anions. Indeed, binding motifs similar to those proposed here for the propanediurea clip−anion complexes were previously observed between cucurbit[6]uril and chloride in the solid state.[34] In that complex, six binding sites on the convex face of cucurbit[6]uril were occupied by six chloride anions. How do our findings contribute to an understanding of the mechanism of cucurbituril formation? Day and co-workers previously demonstrated that the distribution of cucurbituril homologues in reaction mixtures depended on the type and concentration of acid used in the cucurbituril syntheses. They suggested that the differences in cucurbituril distribution may be caused by the different natures of the anions formed from different acids.[35,36] They speculated that the interiors of acyclic oligomers (the precursors of cucurbiturils), with positive electrostatic potentials, promoted the binding of anions during the macrocyclization reaction, influencing the distribution of cucurbituril homologues. However, our experiments with propanediurea clips support a mechanism in which the anion influences the formation of cucurbiturils through its binding at the convex rather than the concave face of the cucurbituril precursors. Our group and that of Isaacs proposed that the first step in cucurbituril formation was the formation of the kinetic product, namely, an S-shaped glycoluril dimer, which was subsequently transformed into the C-shaped dimer.[25,37−40] We also previously demonstrated that the rate of this conversion accelerated with increasing concentration of HCl.[25] Unlike the C-shaped dimer, the S-shaped dimer does not offer binding sites for anions. Therefore, we suggest that the interaction with anions contributed to the stabilization of the C-shaped dimer and the subsequent longer oligomers and thus influenced the equilibria during cucurbituril formation.

Although our investigations were carried out in organic solvents, cucurbiturils are synthesized in concentrated mineral acid solutions. Therefore, we decided to investigate the binding between anions and clip **7** in a more competitive solvent. Investigation in aqueous acidic solutions was not possible because of the low-quality ^{1}H NMR spectra of **7**. Thus, we carried out the titration of **7** with bromide anions in highly polar d_6-DMSO. The addition of bromide was accompanied by

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downfield (H5 and H6b protons) and upfield (H6a proton) shifts similar to those observed during the titration experiments performed in CD_2Cl_2. The calculated K_{rel} of 2.7 M^{-1} for the **7**·Br^- complex was significantly lower than that obtained in CD_2Cl_2. Finally, we tested the effects of the structural differences between propanediurea-based clip **7** and glycoluril-based clip **8**[22] (Figure 3A,B) on their interaction with the anions. The addition of Br^- to a solution of **8** in d_6-DMSO induced a shift of the protons located on the convex face of the clip (Figures S14 and S15 in the Supporting Information), allowing the calculation of K_{rel} as 0.6 M^{-1}. Thus, **7** is better suited for bromide binding than **8**. Despite the low stability of the **8**·Br^- complex, the anion could still function as a template when its concentration was sufficiently high. Considering the typical conditions for the synthesis of cucurbiturils (concentrated HCl with a Cl^- concentration of 11 M, and a glycoluril concentration of 1 M) and the calculated K_{rel} = 0.6 M^{-1} (despite the fact that the binding in an aqueous environment will probably be lower than that in DMSO), we estimate that about 86% of the binding sites (formed by the connection of two glycoluril units by two methylene bridges) in the resulting oligomeric chains (Figure 4) would be occupied by the anions.

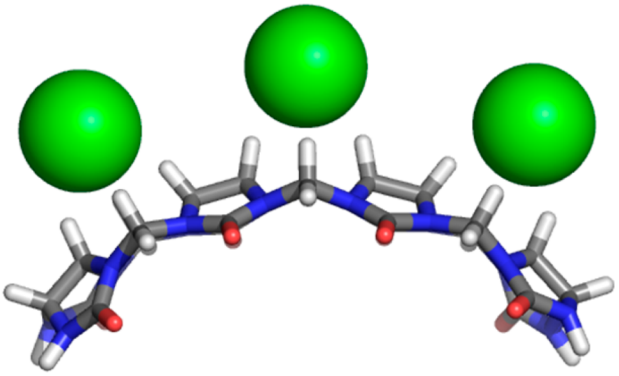

Figure 4. Pictorial view of proposed complex formed during synthesis of cucurbiturils.

CONCLUSION

In conclusion, we prepared two propanediurea dimers, **6** and **7**, decorated with aromatic sidewalls. Combining ^{1}H NMR spectroscopy with DFT calculations, we showed that the clips bound halides on their convex faces in a 1:1 stoichiometry. The complexes were stabilized by four weak hydrogen bonding interactions between the methine and methylene hydrogen atoms of the clip and the anion. Moreover, we showed that not only clip **7** but also its glycoluril-based analogue **8** were able to form this type of complex in DMSO. Although the relative stabilities of these complexes in DMSO were rather low (2.5 and 0.6 M^{-1} for the **7**·Br^- and **8**·Br^- complexes, respectively), we propose that a similar type of complex can form during cucurbituril synthesis when concentrated acids are used. Therefore, the type of anion can influence the distribution of cucurbituril products in the resulting mixture.

EXPERIMENTAL SECTION

General Methods. Chemicals were commercially available and were used without further purification. NMR spectra were recorded on a spectrometer with working frequencies of 500.13 MHz (^{1}H) and 125.77 MHz (^{13}C) and a spectrometer with working frequencies of 300.13 MHz (^{1}H) and 75.48 MHz (^{13}C). Both spectrometers were equipped with a BBFO probe. All experiments were recorded at 303.15 K. High-resolution mass spectra were recorded by an accurate-mass TOF LC/mass spectrometer using multimode ESI/APCI as an ion source and a manual pump for sampling. Diffraction data were collected at 120 K on a diffractometer with graphite-monochromated Mo Kα radiation. The structures were solved by direct methods and refined by full-matrix least-squares methods. CCDC 1480172 (**6**) and CCDC 1480704 (**7**) contain 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.

Synthetic Procedures and Characterization. *o-Xylylenepropanediurea (**4**).* *o*-Xylylenebisurea (6.0 g, 27.0 mmol), 1,1,3,3-tetraethoxypropane (6.5 mL, 6.0 g, 27.1 mmol), and concentrated HCl (8.8 mL) were dissolved in water (600 mL). The reaction mixture was heated at 50 °C for 3 days and then cooled to 5 °C. The resulting precipitate was collected by filtration and washed with water (20 mL) and acetone (20 mL) to give **4** (4.9 g, 69.5%). ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.33−7.10 (m, 6H), 5.29 (s, 1H), 4.80 (d, J = 15.0 Hz, 2H), 4.44 (s, 1H), 4.33 (d, J = 15.0 Hz, 2H), 2.28 (s, 2H). ^{13}C NMR (126 MHz, DMSO-d_6): δ 154.6, 139.3, 130.4, 127.1, 70.4, 56.8, 51.9, 28.9 HR-MS (ESI+): m/z $[C_{13}H_{14}N_4O_2 + H]^+$ observed 259.1190, m/z $[C_{13}H_{14}N_4O_2 + H]^+$ calculated 259.1189.

*o-Xylylenepropanediurea Dimer (**6**).* *o*-Xylylenepropanediurea (**4**; 0.50 g, 2.0 mmol) and paraformaldehyde (0.18 g, 6.9 mmol) were dissolved in concentrated HCl (10 mL). The reaction mixture was heated at 70 °C for 2 h and then cooled to room temperature and stirred overnight. The resulting precipitate was collected by filtration and washed with water (2 × 20 mL) and acetone (10 mL) to give **6**·HCl (0.39 g, 72.2%). The crude product was dissolved in methanol and passed through a column packed with Amberlyst A26 ion-exchange resin. After solvent evaporation, product **6** was obtained in quantitative yield. Single crystals for X-ray analysis were grown from a solution of **6** in 60% formic acid by water vapor diffusion. ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.11 (s, 8H), 6.24 (d, J = 13.8 Hz, 2H), 5.34 (s, 2H), 5.12 (s, 2H), 4.83 (d, J = 15.0 Hz, 4H), 4.29 (d, J = 15.0 Hz, 4H), 3.98 (d, J = 13.8 Hz, 2H), 2.30 (t, J = 3.0 Hz, 4H). ^{13}C NMR (126 MHz, DMSO-d_6): δ 151.1, 137.9, 129.6, 127.1, 68.1, 66.9, 57.5, 51.9, 27.8 HR-MS (ESI+): m/z $[C_{28}H_{28}N_8O_4 + H]^+$ observed 541.2309, m/z $[C_{28}H_{28}N_8O_4 + H]^+$ calculated 541.2306.

*o-Xylylene-9,9-dimethylpropanediurea (**5**).* A mixture of *o*-xylylenebisurea (0.51 g, 2.0 mmol), 1,1,3,3-tetraethoxy-2,2-dimethylpropane (0.49 g, 2.0 mmol), and concentrated HCl (0.75 mL) was dissolved in water (50 mL). The reaction mixture was heated at 50 °C for 3 days and then cooled to 5 °C. The resulting precipitate was collected by filtration and washed with water (20 mL) and acetone (20 mL) to give **5** (0.24 g, 41.9%). ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.27−7.14 (m, 4H), 7.11 (d, J = 4.5 Hz, 2H), 4.81 (d, J = 15.0 Hz, 2H), 4.77 (s, 1H), 4.24 (d, J = 14.9 Hz, 2H), 3.87 (s, 1H), 1.22 (s, 6H). ^{13}C NMR (126 MHz, DMSO-d_6): δ 153.5, 138.9, 129.8, 126.5, 78.5, 64.7, 51.6, 31.6, 22.3 HR-MS (APCI+): m/z $[C_{15}H_{18}O_2N_4 + H]^+$ observed 287.1502, m/z $[C_{15}H_{18}O_2N_4 + H]^+$ calculated 287.1503.

*o-Xylylene-9,9-dimethylpropanediurea Dimer (**7**).* *o*-Xylylene-9,9-dimethylpropanediurea (**6**; 0.14 g, 0.5 mmol) and paraformaldehyde (0.47 g, 1.5 mmol) were dissolved in concentrated HCl (3.0 mL). The reaction mixture was heated at 70 °C for 3 h and then cooled to room temperature and stirred overnight. The resulting precipitate was collected by filtration and washed with water (5 mL) and acetone (5 mL) to give **7**·HCl (0.13 g, 43.6%). The crude product was dissolved in methanol and passed through a column packed with Amberlyst A26 ion-exchange resin. After solvent evaporation, product **7** was obtained in quantitative yield. Single crystals for X-ray analysis were grown by slow evaporation of a chloroform solution of **7**. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.19−7.06 (m, 8H), 6.37 (d, J = 13.7 Hz, 2H), 5.04 (d, J = 2.5 Hz, 2H), 4.87 (d, J = 15.1 Hz, 4H), 4.67 (d, J = 2.3 Hz, 2H), 4.23 (d, J = 15.1 Hz, 4H), 3.86 (d, J = 13.7 Hz, 2H), 1.13 (s, 12H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 150.8, 138.1, 129.7, 127.1, 76.4, 74.5, 58.5, 52.1, 31.0, 21.5 HR-MS (ESI+): m/z $[C_{32}H_{36}N_8O_4 + H]^+$ observed 597.2933, m/z $[C_{32}H_{36}N_8O_4 + H]^+$ calculated 597.2932.

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■ ASSOCIATED CONTENT

Supporting Information

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^{1}H NMR spectra for all compounds, NMR titration data, and X-ray and DFT calculation details (PDF)

X-ray crystallographic data for compound **6** (CIF)

X-ray crystallographic data for compound **7** (CIF)

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Notes

The authors declare no competing financial interest.

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