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Synthesis and Stacked Conformations of Symmetrical and Unsymmetrical Oligo-ureas of Metaphenylenediamine

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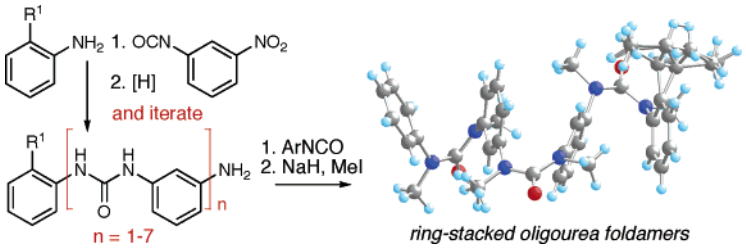

The addition of substituted anilines to nitro-substituted isocyanates followed by reduction generates new aniline-substituted ureas, which can be further extended in a one- or two-directional iterative manner to form oligomeric ureas based on a *m*-phenylenediamine monomer. Oligo-ureas with up to eight urea linkages are reported. Fully N-substituted oligo-ureas are crystalline, and the X-ray crystal structures display ring-stacked conformations. ^{1}H NMR studies indicate that the stacked conformation persists in solution.

Introduction

Oligomers or polymers that adopt a defined secondary structure have been termed foldamers,[1] and considerable progress has been made toward using synthetic foldamers to mimic the conformations of biological oligomers.[2] *N*,*N*′-Dimethyl-*N*,*N*′-diaryl ureas generally adopt a conformation about the two N−CO bonds that allows the aryl rings to lie cis to one another, presumably because of favorable π-stacking.[3] On the basis of NMR and X-ray crystallographic evidence, it also appears that oligo-ureas of *N*,*N*-dimethylmetaphenylenediamine also exhibit this ring stacking, extended over a longer range, generating a helical conformation in both solid state and solution.[4,5] As part of a program of research[6] into methods for rational control of conformation, and potential applications for such control, we were interested in developing versatile routes to a series of foldamers based upon oligo-ureas, and in this paper, we describe our synthetic approach.

Results and Discussion

Synthesis of Unsymmetrical Oligo-ureas. Symmetrical oligo-ureas (i.e., at least two urea linkages) have been synthesized[7] by multiple condensation reactions,[4] but for our studies, a more flexible route to unsymmetrical oligo-ureas of various chain lengths was required. We chose to use an iterative method beginning with a terminal aniline **1**. Condensation with the

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(7) Full experimental data remain unreported.

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SCHEME 1. Synthesis of Oligo-ureas

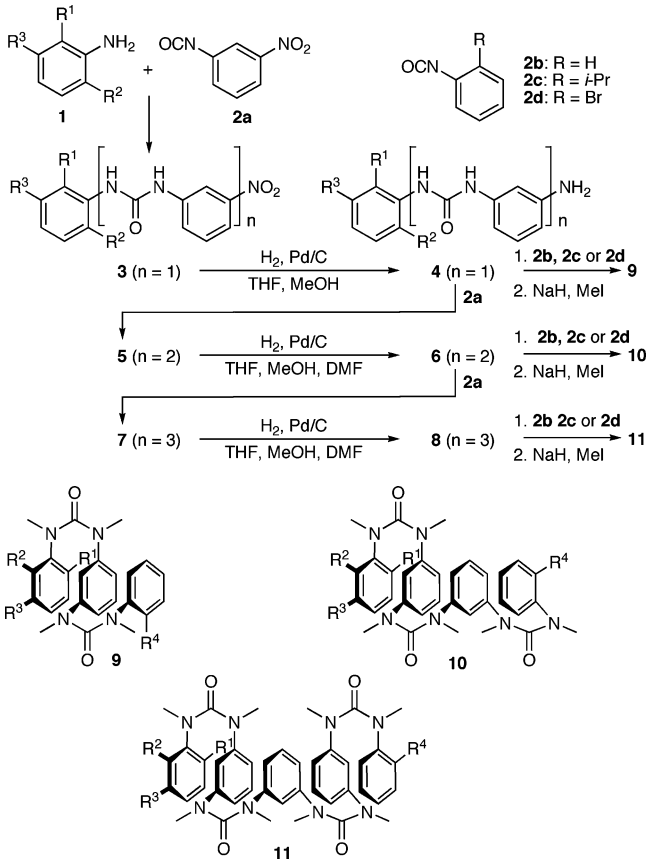


TABLE 1. Synthesis of Unsymmetrical Oligo-ureas

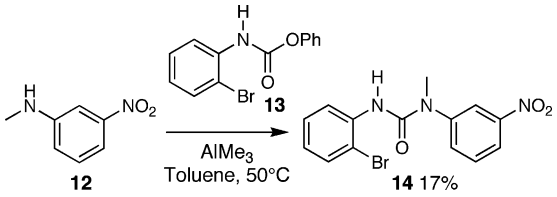
entry	compound	R^1	R^2	R^3	R^4	steps[a]	yield[b] (%)
1	**9a**	*s*-Bu	H	H	H	4	57
2	**9b**	Et	Et	H	Br	4	53
3	**9c**	H	H	Et	Br	4	43
4	**9d**	H	H	*i*-Pr	Br	4	67
7	**10a**	*s*-Bu	H	H	H	6	47
8	**10b**	Et	Et	H	Br	6	42
9	**10c**	H	H	*i*-Pr	Br	6	41
11	**11a**	*s*-Bu	H	H	H	8	48
12	**11b**	*s*-Bu	H	H	*i*-Pr	8	35
13	**11c**	Et	Et	H	Br	8	17
14	**11d**	*i*-Pr	H	H	Br	8	17
15	**11e**	H	H	*i*-Pr	Br	8	30

[a] Number of synthetic steps from **1** to product. [b] Overall yield of *N*-methylated oligo-urea. Intermediates were not isolated.

available *meta*-nitrophenyl isocyanate **2a** generated the rather intractable ureas **3**, which turned out to be only sparingly soluble, precluding reduction of the nitro group using tin chloride. However, hydrogenation over palladium in a solvent mixture of THF and methanol returned the anilines **4** in good yield, ready for further iterative cycles of condensation and reduction. Up to three cycles were achieved, forming the amino-di-urea **6** via nitrourea **5** and amino-tri-urea **8** via nitrodiurea **7** (Scheme 1).

The aminourea oligomers **4**, **6**, and **8** were generally capped by condensation with an available isocyanate **2.** The N-unprotected oligo-ureas formed by these methods were all more or less completely insoluble in chlorinated solvents, but global methylation with an excess of methyl iodide and sodium hydride in THF gave tractable, and in some cases beautifully crystalline, permethylated oligo-ureas **9**, **10**, and **11** (Table 1).

SCHEME 2. Direct Formation of a Methylated Urea



SCHEME 3. Symmetrical Di-ureas

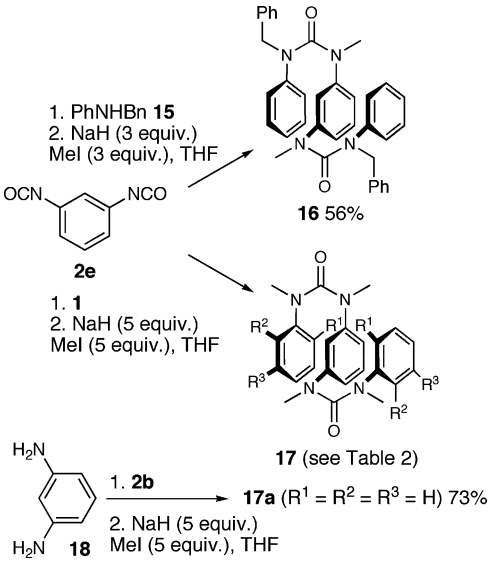


TABLE 2. Synthesis of Symmetrical Di-ureas

entry	compound	R^1	R^2	R^3	yield (%)
1	**17a**	H	H	H	73[a]
2	**17b**	*i*-Pr	H	H	85[b]
3	**17c**	Et	H	H	83[b]
4	**17d**	Br	H	H	46[b,c]
5	**17e**	Et	Et	H	75[b]
6	**17f**	H	H	*i*-Pr	77[b]
7	**17g**	H	H	Et	76

[a] From **18**. [b] From **2e**. [c] NaOH instead of NaH was used in the methylation; NaH gave mainly decomposition products.

In view of the difficulty of handling the intermediate NH oligo-ureas, we attempted N-methylation of the nitroaryl ureas **3** and **5** formed as the chain grows. However, these reactions gave mainly decomposition products. We also tried to form methylated ureas directly from *N*-methyl-*O*-phenylcarbamates,[8] but these failed to react with *N*-methyl anilines. The reaction of the *N*-methyl aniline **12** with an NH carbamate **13** proceeded only in the presence of trimethylaluminum[9] to give low yields of the mono-N-methylated urea **14** (Scheme 2).

Synthesis of Symmetrical Oligo-ureas. Symmetrical di-ureas **16** and **17** were made by condensation of an appropriate aniline (either secondary anilines such as **15** or primary anilines **1**) with the available *meta*-phenylene diisocyanate **2e** (Scheme 3 and Table 2). Alternatively, *meta*-phenylenediamine **18** was condensed with an isocyanate **2**.

The synthesis of longer symmetrical oligo-ureas (triurea **23**, tetraurea **24**, heptaurea **25**, and octaurea **26**) was carried out by linking together anilines **4** or **8** using carbonyl diimidazole

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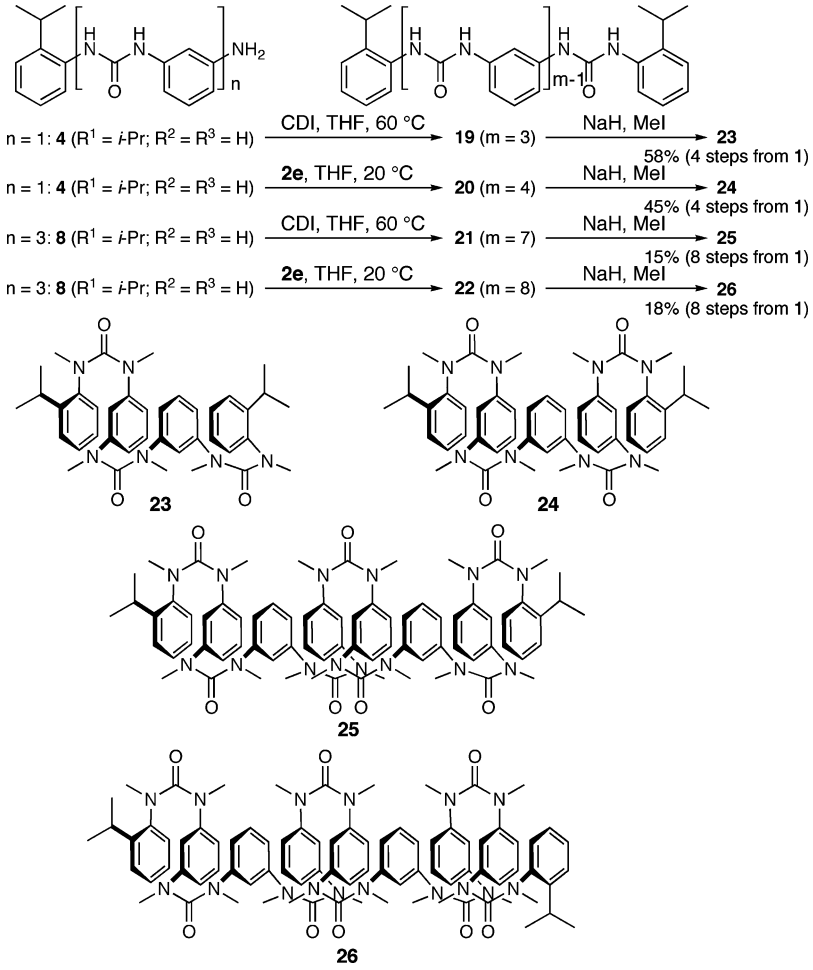
SCHEME 4. Symmetrical Oligo-ureas



(for oligomers containing odd numbers of urea linkages) or *meta*-phenylene diisocyanate **2e** (for oligomers containing even numbers of urea linkages) (Scheme 4). The products **23**−**26** were isolated after methylation of the NH oligo-ureas **19**−**22**.

Conformation. Stacked structures were exhibited in the solid state by the crystalline di-ureas **17a**,**b**,**e**−**g**, whose X-ray crystal structures are shown in Figure 1. All of the oligo-ureas furthermore exhibit in their ^{1}H NMR spectra in $CDCl_3$ an upfield shift of the 2 proton of the phenylenediamine rings to around 6.0 ppm due to the shielding effect characteristic of rings participating in a π-stacked structure.[4] Viewing the ring stack end-on (as shown in the second of each pair of structures in Figure 1) clearly shows how the H-2′ proton (shaded) is sandwiched between the two aromatic rings. The upfield shift is even more pronounced at low temperature (the other aromatic signals remain largely unshifted) possibly indicating annealing of the stacked conformation as the temperature drops.

Rotation about the Ar−N bonds of **17b**,**c** generates in principle three diastereoisomeric conformers −(syn,syn, syn,-anti, and anti,anti) by the terminology of Figure 2.[10] Similar sets of conformers are in principle possible for **17f**,**g** as well. In the crystalline state, *ortho*-substituted **17b** adopts the syn,-syn conformation, while the *meta*-substituted ureas **17f**,**g** adopt an anti,anti conformation. However, for **17f**,**g**, the Ar−N bonds bear no *ortho* substituents, and the three conformers interconvert too fast to be distinguishable by NMR even at low temperature. In **17b**,**c**, the two Ar−N bonds at the middle ring rotate too fast on the NMR time scale for conformers to be evident,[11] leaving only the two relative orientations of the terminal rings (Et or *i*-Pr groups syn or anti) as detectable conformers. At low temperature (below −30 °C in $CDCl_3$), the ^{1}H NMR spectra of **17b**,**c** do indeed exhibit two sets of peaks in a ratio of 55:45 for **17b** and 50:50 for **17c**. Raising the temperature of the NMR probe resulted in coalescence, from which we deduce barriers of 59.6 ± 2.5 (**17b**) and 61.3 ± 1.8 (**17c**) kJ mol^{-1}, respectively, for interconversion of the conformers.

Diurea **9a** is chiral by virtue of its terminal *sec*-butyl group. The Ar−N bond adjacent to the *sec*-butyl group can therefore adopt two diastereoisomeric conformations relative to the *sec*-butyl stereogenic center. In the ^{1}H NMR spectrum of this compound, the two conformers were evident in a 50:50 ratio. In the X-ray crystal structure of **9a** (Figure 3a), each unit cell contains one molecule of the di-urea in each of the two conformations. The di-urea is a rudimentary helix, and this result may have important implications for future applications of the chirality of helical oligo-ureas.

Of the more extended oligo-ureas, only **10a** was crystalline. Figure 3b shows its solid-state conformation, containing four stacked aryl rings. Like **9a**, its NMR spectrum showed a 1:1

(10) More detailed studies of the conformational preferences and stereodynamics of simple ureas will be reported shortly: Clayden, J.; Pickworth, M.; Jones, L., manuscript in preparation.

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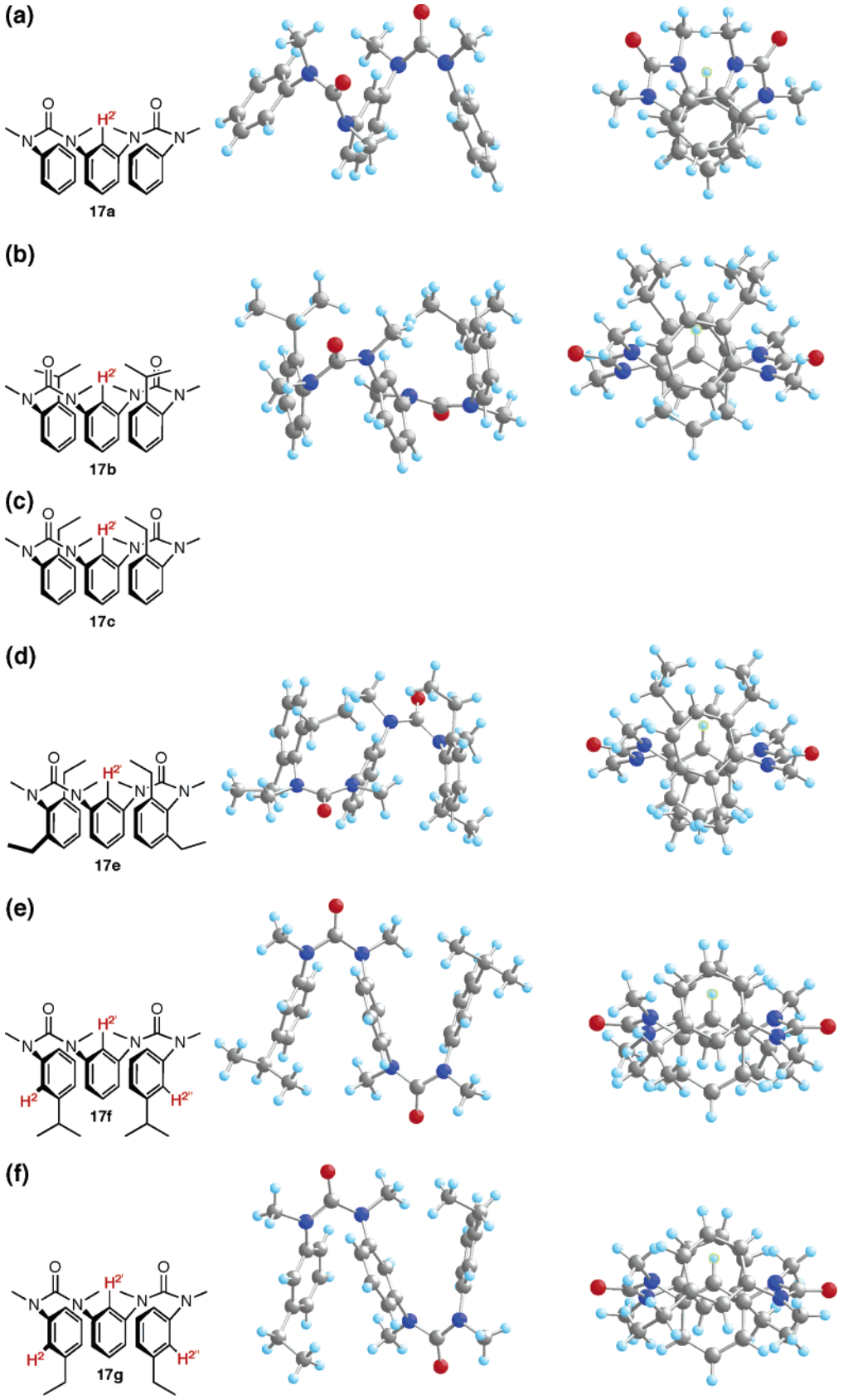

FIGURE 1. (a) Stacked conformation of **17a**. NMR [$\delta(H^{2'}) = 6.08$ (23 °C)] and X-ray crystal structure. (b) Stacked conformation of **17b**. NMR [$\delta(H^{2'}) = 5.88$ (23 °C)] and X-ray crystal structure. (c) Stacked conformation of **17c**. NMR [$\delta(H^{2'}) = 5.81$ (23 °C)] (d) Stacked conformation of **17e**. NMR [$\delta(H^{2'}) = 5.65$ (23 °C)] and X-ray crystal structure. (e) Stacked conformation of **17f**. NMR [$\delta(H^{2'}) = 5.99$ (23 °C) and 5.80 (−50 °C); $\delta(H^{2,2''}) = 6.52$ (23 °C) and 6.36 (−50 °C)] and X-ray crystal structure. (f) Stacked conformation of **17g**. NMR [$\delta(H^{2'}) = 6.01$ (23 °C) and 5.81 (−60 °C); $\delta(H^{2,2''}) = 6.49$ (23 °C) and 6.35 (−60 °C)] and X-ray crystal structure.

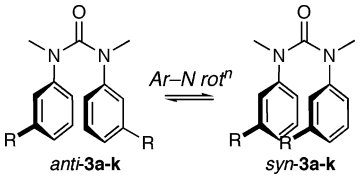

FIGURE 2. Conformers about a urea linkage.

mixture of two conformers due to the stereogenic center within the *sec*-butyl group. The tetra- and octa-ureas **11b**,**d**, **24**, and **26** showed upfield shifts in their aromatic signals (Figure 4) characteristic of stacked conformations. As the stack of π-systems lengthens, in principle a helix forms, and our ongoing work seeks to determine the stability of, and to find ways to control, such helical conformations.

Experimental Section

***N,N′,N″,N‴*-Tetramethyl-1-(2-*sec*-butylphenylureyl)-3-phenylureylbenzene 9a.** Under a nitrogen atmosphere, 3-nitrophenylisocyanate (500 mg, 3.05 mmol, 1 equiv) was dissolved in dry THF (10 mL), and 2-*sec*-butylaniline (550 μL, 3.66 mmol, 1.2 equiv) was added. The reaction mixture was stirred at room temperature (r.t.) for 3 h and evaporated under reduced pressure. CH_2Cl_2/petroleum ether was added, and the was solid collected by filtration. The white powder was dried under vacuum and dissolved in MeOH (20 mL). Pd/C 10% (50 mg) was added, and the reaction mixture was stirred overnight, at r.t., under a hydrogen atmosphere. After removal of the Pd/C by filtration through celite, the solvent was evaporated under reduced pressure, and the product was precipitated in CH_2Cl_2/petroleum ether and collected by filtration. The white powder was dried under vacuum and dissolved in dry THF (20 mL), and phenyl isocyanate (663 μL, 6.10 mmol, 2 equiv) was added. The reaction mixture was stirred at r.t. for 3 h and evaporated under reduced pressure. CH_2Cl_2 was added, and the solid was collected by filtration. The white powder was dried under vacuum and partially dissolved in THF (20 mL). NaH 60% in mineral oil (610 mg, 15.2 mmol, 5 equiv) and methyl iodide (950 μL, 15.2 mmol, 5 equiv) were added successively, and the reaction mixture was stirred overnight before adding H_2O (2 mL). The aqueous phase was extracted with CH_2Cl_2, and the combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography on silica gel (AcOEt/petroleum ether: 50:50) afforded 802 mg (57%) of urea **9a** as a white powder. mp: 113 °C. IR ν_{max} cm^{-1}: 3057, 2963, 1659, 1650, 1597, 1431,

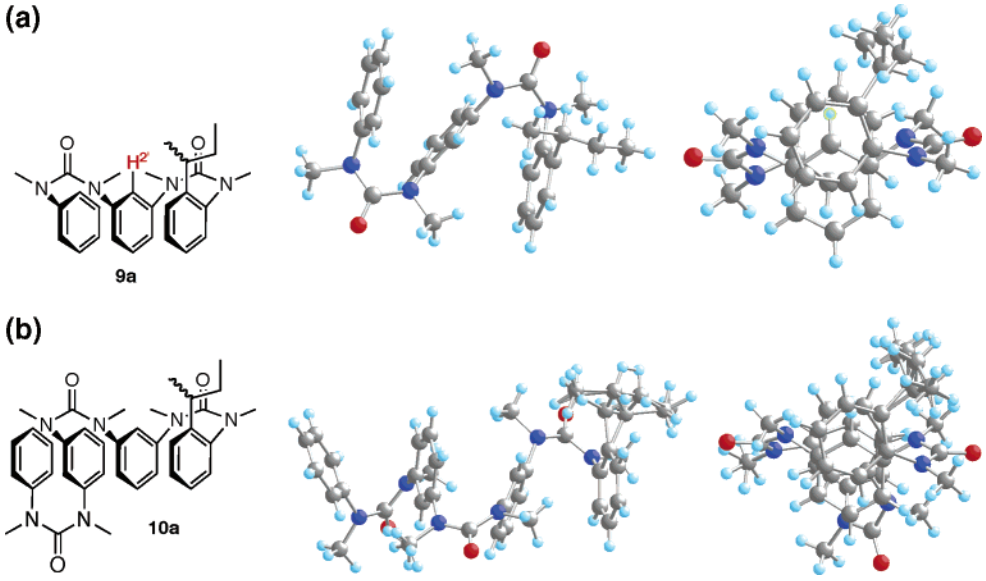

FIGURE 3. (a) Stacked conformation of **9a**. NMR [δ(H$^{2'}$) = 5.96 (23 °C)] and X-ray crystal structure (b) Stacked conformation of **10a**. X-ray crystal structure.

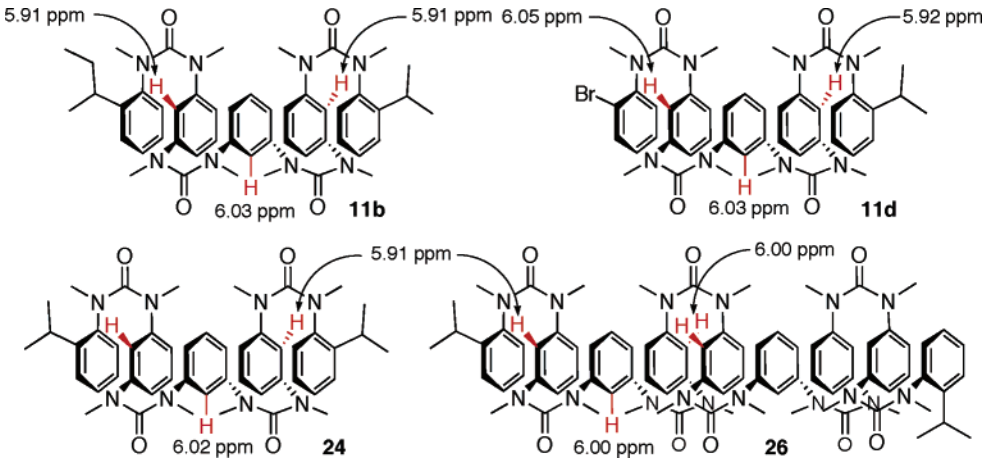

FIGURE 4. Stacked conformations in tetra- and octa-ureas. ^{1}H NMR shifts at 23 °C.

878. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 0.73 (3H, bs), 1.13 (3H, bs), 1.48 (2H, m), 2.52 (1H, sept, $J = 7.0$ Hz), 2.84 (3H, s), 2.97 (3H, s), 3.07 (3H, s), 3.13 (3H, s), 5.96 (1H, t, $J = 2.0$ Hz), 6.23 (1H, d, $J = 7.8$ Hz), 6.36 (1H, d, $J = 7.7$ Hz), 6.51 (1H, d, $J = 8.0$ Hz), 6.62 (1H, t, $J = 7.7$ Hz), 6.70 (2H, d, $J = 7.2$ Hz), 6.77 (1H, t, $J = 8.0$ Hz), 6.84−7.06 (5H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 12.5, 21.0 (bs), 31.9 (bs), 34.4, 39.1, 39.3, 39.7, 40.0, 122.4, 122.6, 123.2, 124.9, 125.6, 125.7, 126.3, 126.7, 128.5, 128.6 (2C), 142.4 (bs), 144.8 (bs), 145.3, 146.0, 146.5, 160.7, 161.7. MS (APCI$^+$): 459.5 (MH^+). HRMS for $C_{28}H_{35}N_4O_2$ (MH^+): calcd: 459.2755; found: 459.2753. Elem. Anal. for $C_{28}H_{34}N_4O_2$: calcd: C, 73.33%; H, 7.47%; N, 12.22%; found: C, 73.45%; H, 7.65%; N, 12.18%.

***N,N′,N″,N‴,N⁗,N⁗′*-Hexamethyl-1-[3-(2-*sec*-butylphenylureyl)phenyl]-3-[(3-phenylureyl)phenyl]urea 10a.** Under a nitrogen atmosphere, 3-nitrophenylisocyanate (300 mg, 1.83 mmol, 1 equiv) was dissolved in dry THF (7 mL), and 2-*sec*-butylaniline (340 μL, 2.19 mmol, 1.2 equiv) was added. The reaction mixture was stirred at r.t. for 3 h and evaporated under reduced pressure. CH_2Cl_2/petroleum ether was added, and the solid was collected by filtration. The white powder was dried under vacuum and dissolved in THF/MeOH: 70:30 (50 mL). Pd/C 10% (30 mg) was added, and the reaction mixture was stirred overnight, at r.t., under hydrogen atmosphere. After removal of the Pd/C by filtration through celite, the solvent was evaporated under reduced pressure, and the product was precipitated in CH_2Cl_2/petroleum ether and collected by filtration. The sequence of events starting from the addition of 3-nitrophenylisocyanate (1.5 equiv in THF, 30 mL) to hydrogenation (in MeOH/DMF: 80:20, 30 mL) was repeated. After precipitation in CH_2Cl_2, the white powder (516 mg) was dried under vacuum and dissolved in dry THF (40 mL). Phenylisocyanate (270 μL, 2.48 mmol, 2.0 equiv) was added. The reaction mixture was stirred at r.t. for 3 h and evaporated under reduced pressure. CH_2Cl_2 was added, and the solid was collected by filtration. The white powder was dried under vacuum and partially dissolved in THF (20 mL). 60% NaH in mineral oil (397 mg, 9.92 mmol, 8 equiv) and methyl iodide (620 μL, 9.92 mmol, 8 equiv) were added successively. The reaction mixture was stirred overnight, and H_2O (2 mL) was added. The aqueous phase was extracted with CH_2Cl_2, and the combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography on silica gel (CH_2Cl_2/MeOH: 90:10) afforded 536 mg (47%) of urea **10a** as a white powder. mp: 106 °C. IR ν_{max} cm^{-1}: 3002, 2963, 2930, 1659, 1650, 1597, 1430, 1357. ^{1}H NMR (500 MHz, $CDCl_3$) δ(ppm): 0.68−1.48 (8H, bm), 2.51 (1H, sext, $J = 7.0$ Hz), 2.82 (3H, s), 2.91 (3H, s), 2.92 (3H, s), 2.94 (3H, s), 3.07 (3H, s), 3.12 (3H, s), 5.93 (1H, t, $J = 1.8$ Hz), 6.05 (1H, t, $J = 1.9$ Hz), 6.21 (1H, d, $J = 7.4$ Hz), 6.33 (1H, d, $J = 8.0$ Hz), 6.36 (1H, m), 6.42 (2H, m), 6.61 (1H, t, $J = 6.9$ Hz), 6.70 (3H, m), 6.76 (1H, t, $J = 7.8$ Hz), 6.88 (1H, t, $J = 7.4$ Hz), 6.93 (1H, t, $J = 7.4$ Hz), 6.99 (2H, t, $J = 7.5$ Hz), 7.04 (1H, dd, $J = 1.3$, 7.8 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ(ppm): 12.6 (bs), 21.0 (bs), 31.9 (bs), 34.4, 39.1, 39.1, 39.2, 39.3, 39.7, 40.0, 122.1, 122.2, 122.5, 122.6, 123.1, 123.2, 125.0, 125.6 (2C), 125.7, 126.3, 126.7, 128.4, 128.5 (3C), 128.6, 142.5, 145.3, 145.6, 145.8, 145.9 (2C), 146.6, 160.4, 160.7, 161.7. MS (APCI$^+$): 622 (MH^+). HRMS for $C_{37}H_{45}N_6O_3$ (MH^+): calcd: 622.3548; found: 622.3552. Elem. Anal. for $C_{37}H_{44}N_6O_3$: calcd: C, 71.59%; H, 7.14%; N, 13.54%; found: C, 71.75%; H, 7.12%; N, 13.36%.

***N,N′,N″,N‴,N⁗,N⁗′,N⁗″,N⁗‴*-Octamethyl-1-[3-(2-*sec*-butylphenylureyl)phenylureyl]-3-[3-(phenylureyl)phenylureyl]benzene 11a.** Under a nitrogen atmosphere, 3-nitrophenylisocyanate (600 mg, 3.66 mmol, 1 equiv) was dissolved in dry THF (20 mL) and 2-*sec*-butylaniline (680 μL, 4.38 mmol, 1.2 equiv) was added. The reaction mixture was stirred at r.t. for 3 h and evaporated under reduced pressure. CH_2Cl_2/petroleum ether was added, and the solid was collected by filtration. The white powder was dried under vacuum and dissolved in THF/MeOH: 70:30 (100 mL). Pd/C 10% (50 mg) was added, and the reaction mixture was stirred overnight, at r.t., under a hydrogen atmosphere. After removal of the Pd/C by filtration through celite, the solvent was evaporated under reduced pressure, and the product was precipitated in CH_2Cl_2/petroleum ether and collected by filtration. The sequence of events from addition of 3-nitrophenylisocyanate (2 equiv in THF, 50 mL) to hydrogenation (in MeOH/DMF: 80:20, 50 mL) was repeated twice in a similar manner. After precipitation in CH_2Cl_2, the white powder (1.3 g) was dried under vacuum and dissolved in dry THF/DMF: 40:5 (45 mL). Phenylisocyanate (522 μL, 4.80 mmol, 2.0 equiv) was added. The reaction mixture was stirred at r.t. for 3 h and evaporated under reduced pressure. CH_2Cl_2 was added, and the solid was collected by filtration. The white powder was dried under vacuum and partially dissolved in THF (50 mL). 60% NaH in mineral oil (960 mg, 24.0 mmol, 10 equiv) and methyl iodide (1.50 mL, 24.0 mmol, 10 equiv) were added successively, and the reaction mixture was stirred overnight. H_2O (5 mL) was added, and the aqueous phase was extracted with CH_2Cl_2. The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. Purified by recrystallization from Et_2O/petroleum ether gave the urea **11a** (1.33 mg, 48%) as a white powder. mp: 86 °C. IR ν_{max} cm^{-1}: 3004, 2965, 1659, 1597, 1428. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 0.71−1.72 (8H, m), 2.50 (1H, m), 2.80 (3H, s), 2.88 (3H, s), 2.90 (3H, s), 2.91 (6H, s), 2.93 (3H, s), 3.07 (3H, s), 3.12 (3H, s), 5.92 (1H, t, $J = 1.7$ Hz), 6.04 (2H, t, $J = 1.8$ Hz), 6.21 (1H, d, $J = 8.0$ Hz), 6.35 (6H, m), 6.61 (1H, t, $J = 7.3$ Hz), 6.70 (5H, m), 6.96 (5H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 12.5, 29.6, 34.4, 39.05, 39.09 (2C), 39.13, 39.2, 39.3, 39.8, 40.0, 122.0 (2C), 122.1, 122.2, 122.5, 122.6, 123.0 (2C), 123.2, 125.0, 125.6 (2C), 125.7, 126.4, 126.7, 128.3, 128.4, 128.57 (2C), 128.62, 145.3, 145.6, 145.7 (3C), 145.8 (3C), 146.7, 160.3 (2C), 160.7, 161.6. MS (APCI$^+$): 783 (MH^+). HRMS for $C_{46}H_{55}N_8O_4$ (MH^+): calcd: 783.4341; found: 783.4332. Elem. Anal. for $C_{46}H_{54}N_8O_4$: calcd: C, 70.56%; H, 6.95%; N, 14.31%; found: C, 70.12%; H, 6.82%; N, 14.00%.

***N,N′,N″,N‴*-Tetramethyl-1,3-diphenyldiureylbenzene 17a.** Under nitrogen atmosphere, 1,3-phenylenediamine (100 mg, 0.925 mmol, 1 equiv) was dissolved in dry THF (7 mL) and phenylisocyanate (440 μL, 1.85 mmol, 2.2 equiv) was added. The mixture was stirred at r.t. for 3 h and evaporated under reduced pressure. CH_2Cl_2 was added, and the solid was collected by filtration. The white powder was dried under vacuum and suspended in THF (15 mL). 60% NaH in mineral oil (185 mg, 4.63 mmol, 5 equiv) and methyl iodide (290 μL, 4.63 mmol, 5 equiv) were added successively, and the reaction mixture was stirred overnight before adding H_2O (2 mL). The aqueous phase was extracted with CH_2Cl_2 and the combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography on silica gel (AcOEt/PE: 30:70) afforded 270 mg (73%) of urea **17a** as a white powder. mp: 168 °C. IR ν_{max} cm^{-1}: 3061, 1659, 1593, 1494, 1425, 1357. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 2.96 (6H, s), 3.12 (6H, s), 6.06 (1H, t, $J = 2.1$ Hz), 6.43 (2H, dd, $J = 2.1$, 8.0 Hz), 6.70 (5H, m), 6.88 (2H, m), 6.99 (4H, dt, $J = 1.2$,8.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 39.1, 39.3, 122.2, 123.2, 124.9, 125.7, 128.4, 128.5, 145.3, 145.7, 160.8. MS (CI/NH_3): 403 (MH^+, 100). MS (EI, 70 ev): 402 (M^+, 3), 134 (100), 106 (85). HRMS for $C_{24}H_{27}N_4O_2$ (MH^+): calcd: 403.2129; found: 403.2128. Elem. Anal. for $C_{24}H_{26}N_4O_2$: calcd: C, 71.62%; H, 6.51%; N, 13.92%; found: C, 71.85%; H, 6.61%; N, 13.99%.

***N,N′,N″,N‴,N⁗,N⁗′*-Hexamethyl-1,3-bis[3-(2-isopropylphenylureyl)phenyl]urea 23.** Under nitrogen atmosphere, 3-nitrophenylisocyanate (700 mg, 4.27 mmol, 1 equiv) was dissolved in dry THF (10 mL), and 2-isopropylaniline (725 μL, 5.12 mmol, 1.2 equiv) was added. The reaction mixture was stirred at r.t. for 3 h and evaporated under reduced pressure. CH_2Cl_2/petroleum ether was added, and the solid was collected by filtration. The white powder was dried under vacuum and dissolved in MeOH (30 mL). Pd/C 10% (100 mg) was added, and the reaction mixture was stirred overnight, at r.t., under a hydrogen atmosphere. After removal of the Pd/C by filtration through celite, the solvent was evaporated

under reduced pressure, and precipitation from CH_2Cl_2/petroleum ether and filtration gave a white powder (1.09 g). The white powder was dried under vacuum and dissolved in dry THF (30 mL). Carbonyl diimidazole (CDI) (330 mg, 2.02 mmol, 0.5 equiv) was added. The reaction mixture was stirred at 70 °C for 18 h and evaporated under reduced pressure. CH_2Cl_2 was added, and the solid was collected by filtration. The white powder was dried under vacuum and suspended in THF (30 mL). 60% NaH in mineral oil (646 mg, 16.2 mmol, 8 equiv) and methyl iodide (1.01 mL, 16.2 mmol, 8 equiv) were added successively, and the mixture was stirred overnight before adding H_2O (2 mL). The aqueous phase was extracted with CH_2Cl_2, and the combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography on silica gel (CH_2Cl_2/MeOH: 95:5) afforded 766 mg (55%) of urea **23** as a white powder. mp: 164 °C. IR ν_{max} cm^{-1}: 2995, 2965, 1659, 1651, 1597, 1428, 1355, 872. ^1H NMR (300 MHz, $CDCl_3$) δ(ppm): 1.10 (12H, d, J = 6.8 Hz), 2.77 (2H, m), 2.82 (6H, s), 2.92 (6H, s), 3.07 (6H, s), 5.94 (2H, t, J = 1.9 Hz), 6.27 (2H, dd, J = 1.3, 7.9 Hz), 6.35 (2H, dd, J = 1.0, 7.9 Hz), 6.42 (2H, dd, J = 1.1, 8.0 Hz), 6.65 (2H, dt, J = 1.5, 7.5 Hz), 6.75 (2H, t, J = 8.0 Hz), 6.95 (2H, t, J = 7.3 Hz), 7.08 (2H, dd, J = 1.5, 7.8 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 22.7, 25.2, 27.2, 39.1, 39.7, 40.0, 122.6, 122.7, 123.3, 125.8, 126.3, 126.8, 128.5, 128.6, 141.9, 145.8, 145.9, 146.5, 160.4, 161.7. MS ($APCI^+$): 649 (MH^+). HRMS for $C_{39}H_{49}N_6O_3$ (MH^+): calcd: 649.3861; found: 649.3871. Elem. Anal. for $C_{39}H_{48}N_6O_3$: calcd: C, 72.19%; H, 7.46%; N, 12.95%; found: C, 71.96%; H, 7.40%; N, 12.78%.

***N,N′,N″,N‴,N⁗,N⁗′,N⁗″,N⁗‴*-Octamethyl-1,3-bis[3-(2-isopropylphenylureyl)phenylureyl]benzene 24.** Under nitrogen atmosphere, 3-nitrophenylisocyanate (700 mg, 4.27 mmol, 1 equiv) was dissolved in dry THF (10 mL), and 2-isopropylaniline (725 μL, 5.12 mmol, 1.2 equiv) was added. The mixture was stirred at r.t. for 3 h and evaporated under reduced pressure. CH_2Cl_2/petroleum was added, and the solid was collected by filtration. The white powder was dried under vacuum and dissolved in MeOH (30 mL). Pd/C 10% (100 mg) was added, and the reaction mixture was stirred overnight, at r.t., under hydrogen atmosphere. After removal of the Pd/C by filtration on celite, the solvent was evaporated under reduced pressure, and the product was precipitated in CH_2Cl_2/petroleum ether and collected by filtration (1.09 g). The white powder was dried under vacuum and dissolved in dry THF (30 mL). 1,3-Phenylene diisocyanate (326 mg, 2.02 mmol, 0.5 equiv) was added. The mixture was stirred at r.t. for 3.5 h and evaporated under reduced pressure. CH_2Cl_2 was added, and the solid was collected by filtration. The white powder was dried under vacuum and suspended in THF (20 mL). 60% NaH in mineral oil (808 mg, 20.2 mmol, 10 equiv) and methyl iodide (1.26 mL, 20.2 mmol, 10 equiv) were added successively, and the reaction mixture was stirred overnight before adding H_2O (2 mL). The aqueous phase was extracted with CH_2Cl_2, and the combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography on silica gel (CH_2Cl_2/MeOH: 95:5) afforded 785 mg (45%) of urea **24** as a white powder. mp: 152 °C. IR ν_{max} cm^{-1}: 3005, 2968, 1659, 1650, 1597, 1431, 1357. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.08 (12H, d, J = 6.8 Hz), 2.78 (2H, m), 2.80 (6H, s), 2.88 (6H, s), 3.05 (6H, s), 5.91 (2H, t, J = 2.0 Hz), 6.02 (1H, t, J = 2.0 Hz), 6.26 (2H, dd, J = 1.2, 7.9 Hz), 6.30 (2H, dd, J = 2.1, 8.0 Hz), 6.33 (2H, d, J = 7.9 Hz), 6.38 (2H, d, J = 8.0 Hz), 6.63 (3H, m), 6.68 (1H, d, J = 8.0 Hz), 6.74 (1H, d, J = 8.0 Hz), 6.93 (2H, dt, J = 1.2, 7.5 Hz), 7.07 (2H, dd, J = 1.4, 7.9 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 22.7, 25.2, 27.2, 39.0, 39.1, 39.7, 40.0, 122.0, 122.4, 122.5, 122.9, 123.2, 125.8, 126.3, 126.8, 128.3, 128.4, 128.6, 141.8, 145.6, 145.7, 145.8, 146.5, 160.2, 161.6. MS ($APCI^+$): 811 (MH^+). HRMS for $C_{48}H_{59}N_8O_4$ (MH^+): calcd: 811.4667; found: 811.4654. Elem. Anal. for $C_{48}H_{58}N_8O_4$: calcd: C, 71.08%; H, 7.21%; N, 13.82%; found: C, 71.02%; H, 7.14%; N, 13.79%.

***N,N′,N″,N‴,N⁗,N⁗′,N⁗″,N⁗‴,N⁗⁗,N⁗⁗′,N⁗⁗″,N⁗⁗‴,N⁗⁗⁗,N⁗⁗⁗′*-Tetradecamethyl-1,3-bis[3-(3-(3-(2-isopropylphenylureyl)phenylureyl)phenylureyl)phenyl]urea 25.** By the method used for compound **10a**, 3-nitrophenylisocyanate (1.05 g, 6.41 mmol, 1 equiv) and 2-isopropylaniline (1.09 mL, 7.69 mmol, 1.2 equiv) gave an intermediate aniline. Carbonyldiimidazole (151 mg, 0.930 mmol, 0.5 equiv) was used instead of phenylisocyanate, heating the mixture for 5 h in THF at 70 °C. Methylation in THF (30 mL) with NaH 60% in mineral oil (744 g, 18.6 mmol, 20 equiv) and methyl iodide (1.16 mL, 18.6 mmol, 10 equiv) gave crude material that was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH: 90:10) to yield urea **25** (640 mg, 15%) as a white powder. mp: 192 °C. IR ν_{max} cm^{-1}: 3003, 2968, 1659, 1650, 1597, 1431, 1356, 874. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.08 (12H, d, J = 6.9 Hz), 2.77 (2H, m), 2.78 (6H, s), 2.84 (6H, s), 2.85 (6H, s), 2.86 (12H, s), 2.89 (6H, s), 3.04 (6H, s), 5.90 (2H, t, J = 1.8 Hz), 6.00 (4H, m), 6.25−6.38 (14H, m), 6.65 (6H, m), 6.71 (2H, t, J = 8.0 Hz), 6.93 (2H, t, J = 7.5 Hz), 7.06 (2H, d, J = 7.8 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 22.7, 25.2, 27.2, 39.1 (10C), 39.7, 39.9, 122.0, 122.5, 122.8, 123.1, 125.8, 126.3, 126.7, 128.3, 128.4, 128.6, 141.8, 145.4, 145.5, 145.60, 145.61, 145.7, 145.8, 146.5, 160.1, 160.2, 161.6. MS ($APCI^+$): 1298 (MH^+). Elem. Anal. for $C_{75}H_{88}N_{14}O_7$: calcd: C, 69.42%; H, 6.84%; N, 15.11%; found: C, 69.30%; H, 6.82%; N, 15.13%.

***N,N′,N″,N‴,N⁗,N⁗′,N⁗″,N⁗‴,N⁗⁗,N⁗⁗′,N⁗⁗″,N⁗⁗‴,N⁗⁗⁗,N⁗⁗⁗′,N⁗⁗⁗″,N⁗⁗⁗‴*-Hexadecamethyl-1,3-bis[3-(3-(3-(2-isopropylphenylureyl)phenylureyl)phenylureyl)phenylureyl]-benzene 26.** By the method used for compound **10a**, 3-nitrophenylisocyanate (525 mg, 3.20 mmol, 1 equiv) and 2-isopropylaniline (545 μL, 3.85 mmol, 1.2 equiv) gave an intermediate aniline. 1,3-Phenyldiisocyanate (74.5 mg, 0.465 mmol, 0.5 equiv) was used instead of phenyl isocyanate. After methylation in THF (20 mL) with NaH 60% in mineral oil (372 g, 9.3 mmol, 20 equiv) and methyl iodide (580 μL, 9.3 mmol, 10 equiv), a crude product was obtained that was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH: 90:10) to yield octa-urea **26** (415 mg, 18%) was isolated by as a white powder. mp: 196 °C. IR ν_{max} cm^{-1}: 3005, 2968, 2932, 1659, 1650, 1597, 1431, 1356, 875. ^1H NMR (500 MHz, $CDCl_3$) δ (ppm): 1.08 (12H, d, J = 6.5 Hz), 2.77 (2H, m), 2.79 (6H, s), 2.85 (18H, s), 2.86 (12H, s), 2.89 (6H, s), 3.05 (6H, s), 5.91 (2H, t, J = 2.0 Hz), 6.00 (5H, m), 6.25−6.31 (12H, m), 6.33 (2H, d, J = 8.0 Hz), 6.37 (2H, d, J = 6.0 Hz), 6.61−6.67 (7H, m), 6.72 (2H, t, J = 8.0 Hz), 6.93 (2H, t, J = 7.5 Hz), 7.07 (2H, dd, J = 1.2, 7.8 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 22.7, 25.3, 27.2, 39.1 (12C), 39.7, 40.0, 122.0, 122.5, 122.8, 122.9, 123.2, 125.8, 126.3, 126.8, 128.4, 128.5, 128.6, 141.8, 145.50 (4C), 145.55, 145.58, 145.63, 145.7, 145.8, 146.5, 160.0, 160.1, 160.2, 161.6. MS ($APCI^+$): 1461 (MH^+). Elem. Anal. for $C_{84}H_{98}N_{16}O_8$: calcd: C, 69.11%; H, 6.77%; N, 15.35%; found: C, 68.84%; H, 6.81%; N, 15.11%.

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Supporting Information Available: Experimental procedures and data for **9b−d, 10b**,**c, 11b**,**e, 16**, and **17b−g**. X-ray crystallographic data (CIF) for **9a**, **10a**, **17a**, **17b**, **17e**, **17f**, and **17g**. This material is available free of charge via the Internet at http://pubs.acs.org.

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