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Hydrogen Bonding vs Steric Gearing in a Hexasubstituted Benzene

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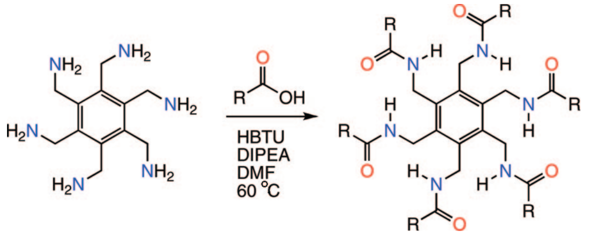
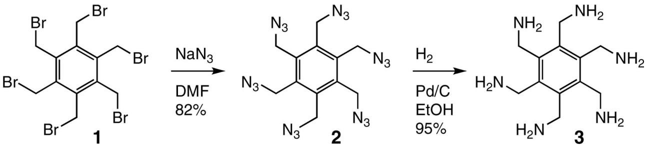


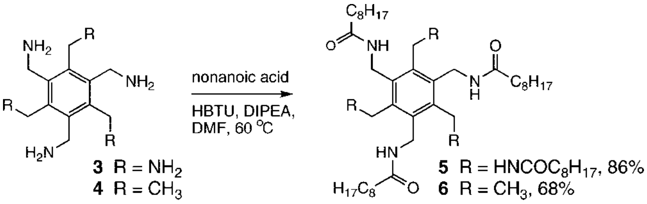
Treatment of hexakis(bromomethyl)benzene with excess NaN_3, followed by hydrogenation of the resultant polyazide, affords hexamine **3** in high yield. Coupling to six equivalents of nonanoic acid provides hexamide **5** without chromatographic purification. The N*H* resonance of **5** appears far downfield (~9.7 ppm) in $CDCl_3$ and is unaffected by changes in concentration or by addition of chloride or trifluoromethanesulfonate ions. DFT calculations predict that **5** exists as a bowl, with all six substituents intramolecularly H-bonded together on one side of the plane defined by the anchoring arene.

In favored conformations of 1,3,5-substituted 2,4,6-triethylbenzenes, the functional arms typically reside on the same face of the central ring, directed away from the three ethyl groups.[1] Host molecules derived from such systems therefore feature a degree of built-in preorganization. The scaffold that bears aminomethyl groups at the 1,3,5-positions has been particularly popular; recognition units including boronic acids,[2] cholic acids,[3] catecholates,[4] guanidiniums,[5] ureas,[6] and thioureas[7] have been appended to it, allowing for binding of a variety of analytes.

SCHEME 1



SCHEME 2



This paper describes the synthesis of a benzene with six aminomethyl groups around its periphery and the structure of a polyamide derived from it. We expected the latter compound to display the familiar pattern of arms alternating up and down, thus forming two equivalent clefts for anion recognition.[8]

The starting material for the present synthesis is the known compound hexakis(bromomethyl)benzene (**1**), which is prepared from mesitylene in two steps.[9] Published procedures for the exhaustive bromomethylation of mesitylene call for treatment of the hydrocarbon with paraformaldehyde and a source of HBr, using glacial acetic acid as solvent. We found that the presence of Zn, as described for the bromomethylation of homologous 1,3,5-triethylbenzene,[10] is effective here as well. Room-temperature stirring of **1** with an excess of sodium azide in DMF solvent (Scheme 1), followed by precipitation with water, afforded the polyazide[11] **2** as an analytically pure solid. Proton NMR spectra of **2** in $CDCl_3$ or DMSO-d_6 show a single resonance at 4.64 and 4.80 ppm, respectively, in accord with its high degree of symmetry. Hydrogenation of **2** over 10% Pd/C in absolute ethanol was followed visually, with complete disappearance of the solid azide requiring >24 h. Samples of **3** prepared in this manner were sufficiently pure to be used in subsequent reactions. If necessary, traces of Pd(II) species can be removed from water-soluble **3** by reversed-phase HPLC.

All six NH_2 groups of **3** were converted into secondary amides using standard coupling conditions (Scheme 2). Product **5** readily dissolves in chloroform, and in ethanol or toluene with heating, although attempts to grow diffraction-quality crystals from these solvents were unsuccessful. Results from a series of ^1H NMR experiments in $CDCl_3$ are consistent with a strongly hydrogen-bonded monomer. Solutions of **5** at concentrations of 0.00016 and 0.0053 M have the same N*H* chemical shift, which remained unchanged by addition of 20-fold excesses of

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(10) Wallace, K. J.; Hanes, R.; Anslyn, E.; Morey, J.; Kilway, K. V.; Siegel, J. *Synthesis* **2005**, 2080–2083.

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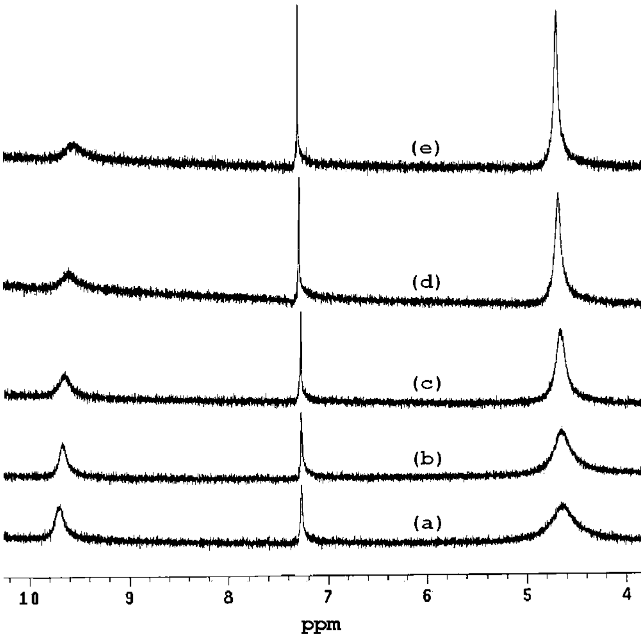

FIGURE 1. Variable-temperature ^1H NMR spectra of **5**, showing N*H* and benzylic C*H*$_2$ signals: (a) 23, (b) 30, (c) 40, (d) 50, and (e) 60 °C. Residual protons in the $CDCl_3$ solvent appear at 7.26 ppm.

Cl^- or $CF_3SO_3^-$ ions (as tetraethylammonium salts). Furthermore, neither heating nor the presence of a protic solvent caused pronounced shifts in the amide proton. When a 0.0049 M solution of **5** was warmed from room temperature to 60 °C in a flame-sealed tube, the N*H* resonance at 9.69 ppm moved upfield by less than 0.2 ppm (Figure 1). This peak appears at 9.40 ppm in 9:1 (v:v) $CDCl_3-CD_3OD$, indicating that H-bonds between **5** and methanol are weaker than those within **5** alone.

In contrast, the N*H* signal of triamide control compound **6**, found at 5.22 ppm in chloroform-*d* solution, moved downfield by >0.5 ppm during titrations with Et_4N^+ Cl^- or Et_4N^+ $CF_3SO_3^-$. Association constants of 12 and 41 M^{-1}, respectively, were derived from these experiments.[12]

DFT calculations[13,14] were performed to shed light on the anomalous solution behavior of **5**. In the most stable conformation to be identified,[15] all six nonanamide substituents lie on one side of the benzene plane, forming a bowl (Figure 2a). Averaging the distances between the *C*═O atoms of *para*-disposed arms gives a calculated diameter of 9.1 Å. An uninterrupted seam of hydrogen-bonds (average N*H*···*O*═C separation = 1.88 Å) circles the molecule. In the gas phase, the bowl is favored by 15.2 kcal/mol over an alternating up/down conformation that benefits from steric gearing[16] (Figure 2b). This value narrows to 3.1 kcal/mol when a solvent dieletric corresponding to chloroform is applied using COSMO.[17]

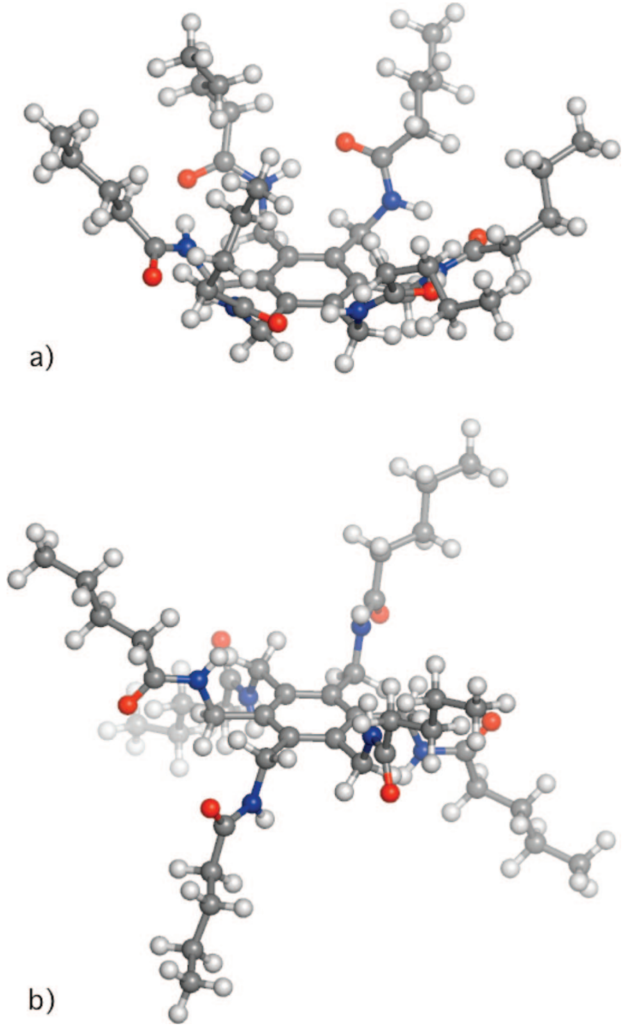

FIGURE 2. DFT-optimized views of truncated **5**[13] in the (a) bowl and (b) up/down conformations.

In summary, the spatial predilection toward alternating α and *β* substituents in hexafunctionalized benzenes can be overcome by intramolecular H-bonding. Although **5** fails as an anion receptor because its N*H* donor atoms are occupied,[18] the hexamide *cavity* warrants further examination as a potential site for supramolecular chemistry.

Experimental Section

Hexakis(azidomethyl)benzene (2). A round-bottomed flask was charged with 50 mL of DMF and 10.19 g (16.04 mmol) of **1**. With

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[12] For ^1H NMR binding studies, **6** was dissolved in $CDCl_3$ to concentrations of 0.004–0.005 M. Aliquots of tetraethylammonium salt solution were added while the chemical shift of the N*H* protons of **6** was followed until [anion] was at least six times greater than [**6**]. To account for dilution effects, the titrant solution also contained **6** at the initial concentration. The data were analyzed using the nonlinear fitting program WinEQNMR: Hynes, M. J. *J. Chem. Soc., Dalton Trans.* **1993**, 311–312.

[13] Calculations employed the Becke−Tsuneda−Hirao gradient-corrected functional with double-numerical plus polarization basis sets, a 20 bohr cutoff, and a fine integration grid and ran to the default convergence criteria of 10^{-6} hartrees for the SCF and 10^{-3} hartrees/bohr for the gradient in geometry optimizations. Octyl groups in **5** were truncated to butyl to conserve computational resources.

[14] (a) Becke, A. D. *J. Chem. Phys.* **1988**, *88*, 1053–1062. (b) Tsuneda, T.; Hirao, K. *Chem. Phys. Lett.* **1997**, *268*, 510–520. (c) Delley, B. *J. Chem. Phys.* **1990**, *92*, 508–517. (d) Delley, B. *J. Chem. Phys.* **2000**, *113*, 7756–7764.

[15] A 40000-step Monte Carlo conformational search with the Merck force field was performed within the MacroModel program (Schrodinger, Inc.), where the initial conformation had alternating up/down arms. The lowest energy result of the search coincided with the bowl conformation. For discussions of conformational mobility in 1,3,5–2,4,6-facially segregated benzenes, see: (a) Turner, D. R.; Paterson, M. J.; Steed, J. W. *J. Org. Chem.* **2006**, *71*, 1598–1608. (b) Wallace, K. J.; Belcher, W. J.; Turner, D. R.; Syed, K. F.; Steed, J. W. *J. Am. Chem. Soc.* **2003**, *125*, 9699–9715.

[16] For discussions of gearing effects in systems without triethyl substitution, see: Lampkins, A. J.; Abdul-Rahim, O.; Castellano, R. K. *J. Org. Chem.* **2006**, *71*, 5815–5818.

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stirring, sodium azide (12.77 g, 196.0 mmol) was added in portions over several minutes. After 24 h at room temperature, the contents of the flask were poured into 500 mL of water. The precipitated product was collected by filtration, washed with water, and dried under vacuum to afford 5.35 g (82%) of light tan-colored **2**: mp = 165–168 °C; ^{1}H NMR ($CDCl_3$) δ 4.64 (s, 12H); ^{1}H NMR (DMSO-d_6) δ 4.80 (s, 12H); ^{13}C NMR (DMSO-d_6) δ 47.2, 136.4; IR (film) ν_{max} 2075, 1250 cm^{-1}. Anal. Calcd for $C_{12}H_{12}N_{18}\cdot 0.5(H_2O)$: C, 34.53; H, 3.14; N, 60.41. Found: C, 34.47; H, 2.90; N, 60.46. *CAUTION! Organic azides are prone to violent decomposition, and appropriate precautions should be taken when handling and storing them.*

Benzene-1,2,3,4,5,6-hexaylhexamethanamine (3). Palladium on carbon (10 wt %, 0.240 g) was added to a dry hydrogenation flask, immediately followed by 125 mL of absolute ethanol. Hexazide **2** (2.51 g, 6.15 mmol) was added, and the mixture was agitated under 50 psi of H_2 until solid **2** was no longer visible in the flask (approximately 96 h). Filtration through two thicknesses of filter paper and evaporation of the filtrate yielded 1.48 g (95%) of **3** as a white solid. Further purification could be effected via RP-HPLC (C_{18} column, H_2O/0.01% TFA eluting at 1.0 mL/min, 254 nm): mp dec at 130 °C; ^{1}H NMR ($CDCl_3$) δ 1.67 (s, 12H), 4.07 (s, 12H); ^{13}C NMR ($CDCl_3$) δ 40.5, 139.8; IR (solid) ν_{max} 3315, 3244, 2981, 1589 cm^{-1}; HRMS (ESI) calcd for $C_{12}H_{25}N_6$ $(M + H)^+$ 253.2135, found 253.2125.

***N,N′,N″,N‴,N⁗,N′′′′′*-(Benzene-1,2,3,4,5,6-hexaylhexakis(methylene))hexanonanamide (5).** Hexamine **3** (0.10 g, 0.40 mmol), nonanoic acid (0.41 g, 2.6 mmol), *O*-(benzotriazol-1-yl)-*N,N,N′,N′*-tetramethyluronium hexafluorophosphate (HBTU, 1.13 g, 3.0 mmol), and *N,N*-diisopropylethylamine (DIPEA, 0.37 g, 2.9 mmol) were combined in 10 mL of DMF. The reaction mixture was heated to 60 °C for 18 h with stirring under N_2. Upon cooling, the light orange mixture was poured into 100 mL of H_2O. The precipitated solid was collected by filtration, washed with water, and dried under vacuum. Trituration with hot ethyl acetate afforded 0.38 g (86%) of off-white **5**: mp dec at 222 °C; ^{1}H NMR ($CDCl_3$) δ 0.87 (t, 18H), 1.27 (m, 60H), 1.61 (m, 12H), 2.25 (t, 12H), 4.63 (s, 12H), 9.74 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 14.1, 22.6, 25.8, 29.2, 29.4, 29.5, 31.9, 36.3, 38.1, 137.4, 175.3; IR (solid) ν_{max} 3340, 3288, 2922, 1678, 1618, 1541 cm^{-1}. Anal. Calcd for $C_{66}H_{120}N_6O_6$: C, 72.48; H, 11.06; N, 7.68. Found: C, 72.23; H, 11.09; N, 7.63.

***N,N′,N″*-(2,4,6-Triethylbenzene-1,3,5-triyl)tris(methylene)trinonanamide (6).** Triamine **4**[10] (0.203 g, 0.814 mmol), nonanoic acid (0.406 g, 2.57 mmol), HBTU (1.08 g, 2.86 mmol), and DIPEA (0.427 g, 3.30 mmol) were combined in 10 mL of DMF. The reaction mixture was heated to 60 °C for 18 h with stirring under N_2, during which time it became red-brown in color. Upon cooling, the precipitated product was collected by filtration and washed with water. Drying under vacuum gave 0.373 g (68%) of **6** as a faintly pink solid: mp = 213–215 °C; ^{1}H NMR ($CDCl_3$) δ 0.87 (t, 9H), 1.20 (t, 9H), 1.27 (br s, 30H), 1.63 (m, 6H), 2.16 (t, 3H), 2.69 (q, 6H), 4.48 (d, 6H), 5.22 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 14.1, 16.5, 22.6, 23.0, 25.7, 29.1, 29.3, 29.4, 31.8, 36.7, 38.1, 132.4, 144.2, 172.8; IR (solid) ν_{max} 3299, 2926, 1627, 1534 cm^{-1}. Anal. Calcd for $C_{42}H_{75}N_3O_3\cdot 0.5(H_2O)$: C, 74.29; H, 11.28; N, 6.19. Found: C, 74.38; H, 11.21; N, 6.36.

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Supporting Information Available: Detailed variable-temperature ^{1}H NMR data for **5**, molecular modeling coordinates for **5**, representative ^{1}H NMR binding curves for **6** + Cl^- and **6** + $CF_3SO_3^-$, and ^{1}H/^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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