Preorganized Metallomacrocycles: Improved Binding and Selectivity of NH_3 over Primary Amines

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Three new metallohosts (**2**−**4**) were synthesized by the uranyl-templated macrocyclization of the appropriate dialdehydes **13a**−**c** and 1,2-phenylenediamine in methanol. Cyclization of the dialdehyde **13b** led to two isomers (**3a**, major, and **3b**, minor), which only differed in the orientation of the isopropyl substituents on the outer phenolic rings of the terphenyl moiety. The binding constants in $CDCl_3$ of ammonia and benzylamine were determined by ^1H NMR spectroscopy. The binding of ammonia by these hosts follows **1** ≈ **2** ≈ **4** < **3b** < **3a**. The binding of benzylamine follows **1** ≈ **2** ≈ **4** ≈ **3b** ≪ **3a**. Monte Carlo free-energy perturbation calculations reproduced the binding of ammonia and *n*-propylamine quite well. The much larger binding of benzylamine by host **3a** was rationalized by a much deeper positioning of the guest in the cavity of the host compared to **3b**.

Introduction

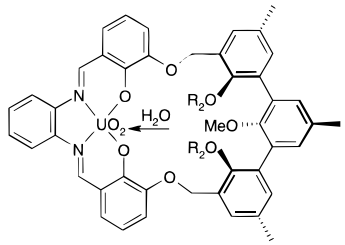
In a previous article[1] we have shown that the preorganized metallomacrocycle **1** (Chart 1) binds ammonia in chloroform with a higher association constant than *n*-propylamine and benzylamine. The maximum selectivity (K_{NH_3}/K_{RNH_2}) obtained was 33. The binding of ammonia or a primary amine is actually a substitution reaction of a water that is bound in the cavity. The presented molecular mechanics calculations suggested that host **1** did not use all available binding sites of the ammonia. Beside the binding of the lone pair of ammonia to the uranyl cation, only two of the hydrogens were used. This observation has stimulated us to improve the binding and selectivity of ammonia over primary amines by two ways. The first was the introduction of bulkier substituents on the outer phenol moieties of the terphenyl unit. The inner anisole moiety was not changed because the above-mentioned calculations showed that this acceptor site was not used. The second approach was the introduction of an extra binding site by bridging the outer phenol groups with a diethylene glycol chain.

In this article the syntheses of three new hosts and the experimental and calculated Gibbs free-energy change of binding of NH_3, $PrNH_2$, and $PhCH_2NH_2$ are described. These calculations were complemented with some additional simulations and gave a good rationale of the observed binding and selectivity.

Results and Discussion

Synthesis. The synthesis of the hosts **2**−**4** starts from the well-known terphenyl **5**,[2] which was methylated on the inner phenol moiety according to a literature procedure (Scheme 1).[3]

Chart 1



1 R_2 = Me
2 R_2 = Et
3 a,b R_2 = *i*-Pr
4 R_2,R_2 = -$CH_2CH_2OCH_2CH_2$-

Formylation of **6** was performed with hexamethylenetetraamine in CF_3COOH at 90 °C.[1] The remaining outer phenol moieties were alkylated with EtI, *i*-PrI, and diethylene glycol ditosylate, respectively, with K_2CO_3 as a base in CH_3CN. The formyl groups were subsequently reduced with $NaBH_4$, followed by conversion of the hydroxymethyl groups into bromomethyl groups with PBr_3 leading to **10**. The dialdehydes **13a,b**, required for the formation of the hosts **2**−**4**, were obtained by reaction of **10** with the allyl-protected 2,3-dihydroxybenzaldehyde **11**,[4] followed by palladium-catalyzed deallylation. The macrocyclization of **13** with 1,2-phenylenediamine was carried out in the presence of $UO_2(OAc)_2$, giving the desired hosts in 7−35% yield.[5] The hosts **2**−**4** gave a characteristic absorption for the imine bond in the IR spectrum ($\nu_{N=C}$ 1603−1604 cm^{-1}), and the imine proton

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(5) Similar to the synthesis of **1**,[1] the Ba^{2+}-templated macrocyclization of **13c** with 1,2-phenylenediamine is possible. However, this reaction failed for **13b**.

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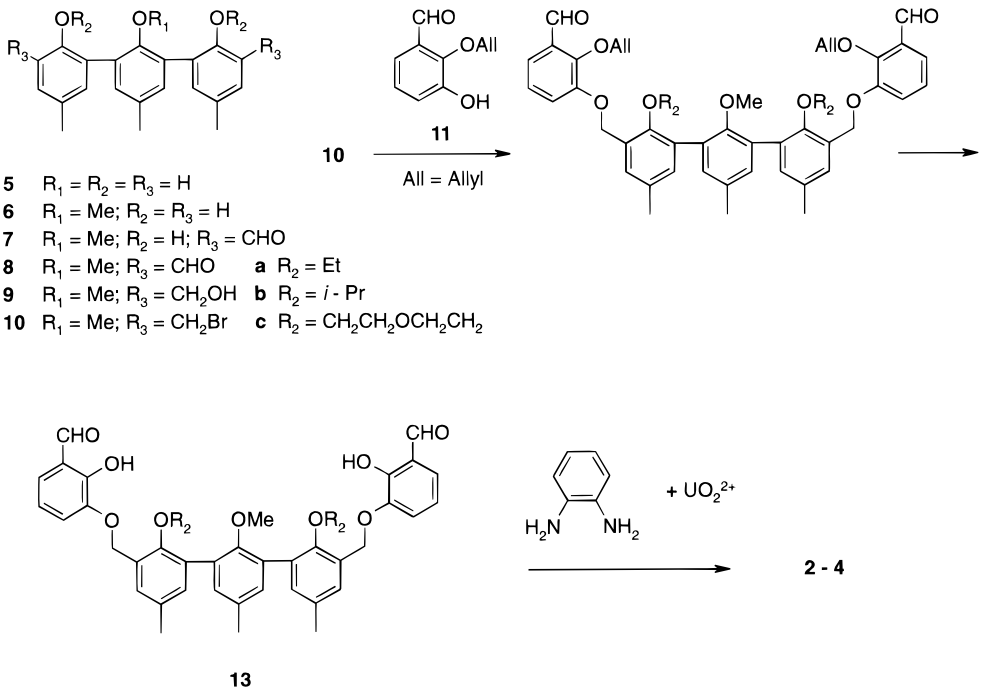
Scheme 1



shows the expected absorption in the ^{1}H NMR spectrum at 9.27−9.43 ppm.[1,4] The ^{1}H NMR spectra further show an AB system for the benzylic protons, confirming the cyclic nature of the hosts. The positive and negative FAB mass spectra exhibit distinct peaks for M^+ and M^- (**2**); $(M + H)^+$, $(M + Na)^+$, and M^- (**3a**,**b**); and $(M + Na)^+$ and M^- (**4**). The cyclization of **13b** with **11** gave two cyclic products which could be separated by column chromatography. Both gave ^{1}H NMR spectra that show a set of signals in agreement with a plane of symmetry through the inner phenol ring of the terphenyl moiety, indicating that the two isopropyl groups are mirror-related. Both isomers gave two doublets for the two methyl groups of the isopropyl substituents, as expected because there is no symmetry relation. Standard 2D ROESY and NOESY NMR spectroscopy on the major isomer **3a** showed that the CH groups of the isopropyl substituents point outward, whereas the minor isomer **3b** has the CH groups pointing inward. Host **3a** has a clear NOE contact between the CH group of the isopropyl substituent with the axial hydrogen of the benzylic group. The methyl group of the isopropyl substituent closest to the uranyl cation also has a NOE contact with the axial hydrogen of the benzylic group, whereas the methyl group of the isopropyl substituent closest to the terphenyl unit has a NOE contact with hydrogen of the inner phenyl ring. The minor isomer **3b** showed a NOE contact of the CH and one of the methyl groups of the isopropyl substituents with the hydrogen of the inner phenyl ring of the terphenyl unit, whereas the other methyl group has a NOE contact with the axial benzylic hydrogen. These two isomers are most likely conformational isomers. The fact that they could be separated implies that the activation barrier must be in the order of 20−25 kcal/mol.

Binding of NH_3 and $PhCH_2NH_2$. The binding of ammonia or a primary amine in host **1**−**4** is a substitution reaction of a bound water (eq 1).[1,4]

$$L{\cdot}H_2O + RNH_2 \overset{K}{=} L{\cdot}RNH_2 + H_2O \qquad (1)$$

The $\Delta G°$ values of binding ($CDCl_3$, 293 K) of ammonia and benzylamine were determined as previously described[1] and are given in Table 1.

The binding of ammonia and benzylamine by host **2** is essentially the same as by host **1**. This is also the case for host **4** with respect to ammonia, but the binding of benzylamine by host **4** is reduced compared to host **1**. The result is a small increase in the selectivity of ammonia over benzylamine ($K_{ammonia}/K_{benzylamine}$) from 17 for host **1** to 52 for host **4**. It is apparent that the introduction of an extra acceptor atom in host **4** is hardly beneficial for the selective binding of ammonia compared to host **1**. The hosts **3a,3b**, however, show interesting behavior. Host **3a** shows a large increase of binding affinity of ammonia compared to host **1**, but it also strongly binds benzylamine. The resulting selectivity $K_{ammonia}/K_{benzylamine}$ is only 2. The binding affinity of ammonia by host **3b** is smaller than by host **3a**, but larger than by host **1**. The binding affinity of benzylamine by host **3b** is small, leading to a selectivity $K_{ammonia}/K_{benzylamine}$ of 2000. These results imply that the arrangement of the isopropyl group has a determining effect on the binding and selectivity, which will be addressed on the basis of (Gibbs free-energy) calculations in the next section.

Gibbs Free-Energy Calculations. The Gibbs free-energy calculations[6] are accessible by Monte Carlo free-energy perturbation (MC-FEP) simulations,[7] which rely on a thermodynamic cycle. It basically comes down to

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Table 1. Experimental[a] and Calculated[b] Binding Free Energies (kcal/mol) of 1−4 with NH_3 and RNH_2 (Chloroform, 293 K)

	NH_3		$PhCH_2NH_2$	$MeNH_2$	$EtNH_2$	*n*-$PrNH_2$	
host	$\Delta G°_{exp}$	$\Delta G°_{calcd}$	$\Delta G°_{exp}$	$\Delta G°_{calcd}$	$\Delta G°_{calcd}$	$\Delta G°_{exp}$	$\Delta G°_{calcd}$
1	−3.47	−4.82	−1.78	−2.47	−2.74	−2.60	−2.38
2	−3.54		−1.47				
3a	−5.91	−7.14	−5.47	−0.19			
3b	−4.51	−6.13	−1.36	−0.84			
4	−3.58	−4.84	−1.23				

[a] Errors are in the order of $<\pm 0.10$ kcal/mol, as determined from duplicate experiments. [b] Errors are in the order of $\pm 0.10-0.26$ kcal/mol (see Experimental Section).

the calculation of the Gibbs free-energy change of perturbing guest 1 into guest 2, both bound to a particular host and in neat solvent. Proper subtraction of the two ΔG's gives, via $\Delta G° = -RT \ln K$, the association constant K in eq 1. The required perturbations are for the conversion of the water molecule to the amine. All MC−FEP calculations have been performed with the BOSS program.[7] However, before setting out the CPU intensive calculations, the 'balance' between the water, modeled as TIP3P,[8] and ammonia was addressed. Ammonia was modeled with point charges $q_N = -1.05$, $q_H = 0.35$ and the Lennard−Jones parameters $\sigma = 2.940$ Å and $\epsilon = 0.150$ kcal/mol for N and $\sigma = 1.425$ Å and $\epsilon = 0.0498$ kcal/mol for H, respectively.[9] The interaction energy with Na^+ is experimentally known (−24.0 and −29.1 kcal/mol for one water and one ammonia, respectively)[10] and has been calculated with the Åqvist model[11] of Na^+ (−22.16 and −26.84 kcal/mol for water and ammonia, respectively). This gives a difference of 4.68 kcal/mol, which is close to the experimental value of 5.10 kcal/mol. Hence, the balance between the two models seems adequate for our purpose. The calculated $\Delta G°$'s are summarized in Table 1. The calculated binding affinity of ammonia follows the experimental data, i.e., **1** ≈ **2** ≈ **4** < **3b** < **3a**, but is in absolute sense too negative. However, the difference between the experimental and calculated numbers is rather constant, suggesting that a systematic error is made in the calculations. A likely source is the simple description of the electrostatic interactions by point charges, neglecting, e.g., polarization effects, etc. The similar binding constants for **1** and **4** were studied in some more detail with a Monte Carlo run in chloroform. The average interaction energy between host and ammonia was -33.90 ± 0.09 for host **1** and -37.00 ± 0.15 kcal/mol for **4**, respectively. This small favoring of **4** is apparently offset by unfavorable changes in intramolecular free-energy components. Snapshots of the ammonia complexes of **1** and **4** are shown in Figure 1. Visual checking a number of saved configurations showed no *four-point* binding of ammonia in host **4**, suggesting that the extra oxygen atom is not positioned correctly for the formation of a third hydrogen bond. Occasionally, hydrogen bonding of ammonia to this oxygen atoms occurs, but at the expense of another hydrogen bond.

The $\Delta G°$ of binding of *n*-propylamine by host **1** is experimentally -2.60 ± 0.10 kcal/mol. The ΔG of binding was also calculated through a series of individual MC−FEP calculations, i.e., $H_2O \leftrightarrow NH_3$, $NH_3 \leftrightarrow MeNH_2$, $MeNH_2 \rightarrow EtNH_2$, and $EtNH_2 \rightarrow$ *n*-$PrNH_2$. The calculated $\Delta G°$ of binding of *n*-propylamine by host **1** is −2.38 kcal/mol, in good agreement with the experimental value. These calculations also show that the binding of $MeNH_2$, $EtNH_2$, and *n*-$PrNH_2$ does not differ significantly, suggesting that the steric demands imposed by the host are similar for all three primary amines. This is probably also true for benzylamine, and therefore no calculations have been performed. A second reason to refrain from such calculations is the formidable perturbations needed. It would require probably 20 or more windows and long equilibrations to get reliable results.

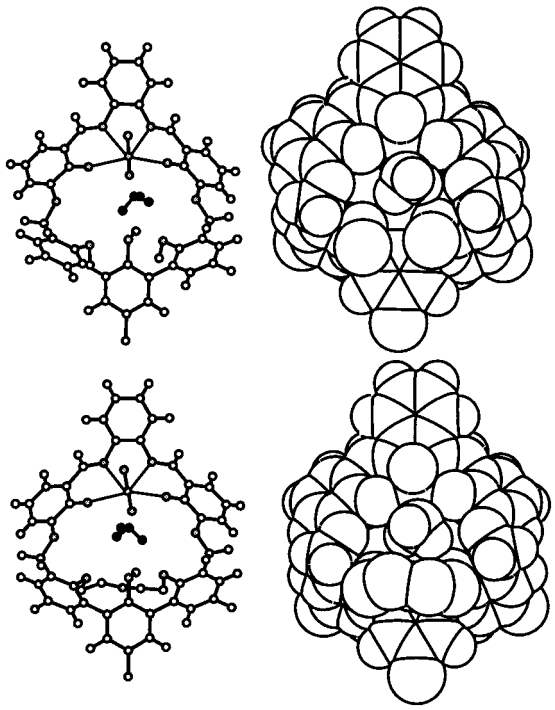

Figure 1. Snapshots of **1**·NH_3 (top) and **4**·NH_3 (bottom).

As a model for the binding of benzylamine, the $\Delta G°$ of binding of methylamine by the hosts **3a,3b** was calculated. The $\Delta G°$ of binding of methylamine by the minor isomer **3b** was calculated as −0.84 kcal/mol, which is the same order of magnitude as the experimental binding of benzylamine ($\Delta G° = -1.36$ kcal/mol). The conclusion that host **3b** does not impose special steric constraints on the binding of primary amines is probably also valid here. The minimized structure[12] of **3b**·$PhCH_2NH_2$ is shown in Figure 2 and shows that the guest is not deeply bound by the host. In fact, the phenyl moiety is out of the cavity. This picture also suggests that here methylamine is a good model for benzylamine.

The interaction energy between host and guest is −15.85 kcal/mol (van der Waals and electrostatic part are −10.19 and −5.66 kcal/mol, respectively; the U···N distance is 2.710 Å). However, the calculated binding affinity of methylamine by host **3a** is only −0.19 kcal/mol, which is much too small compared to the experimental value ($\Delta G° = -5.47$ kcal/mol). Here, obviously methylamine does not suffice as a model for benzylamine. The minimized structure[12] of **3a**·$PhCH_2NH_2$ is shown in Figure 2 and shows that the guest is bound more deeply

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(12) The minimization was carried out as described in ref 1, but with a constant dielectric constant.

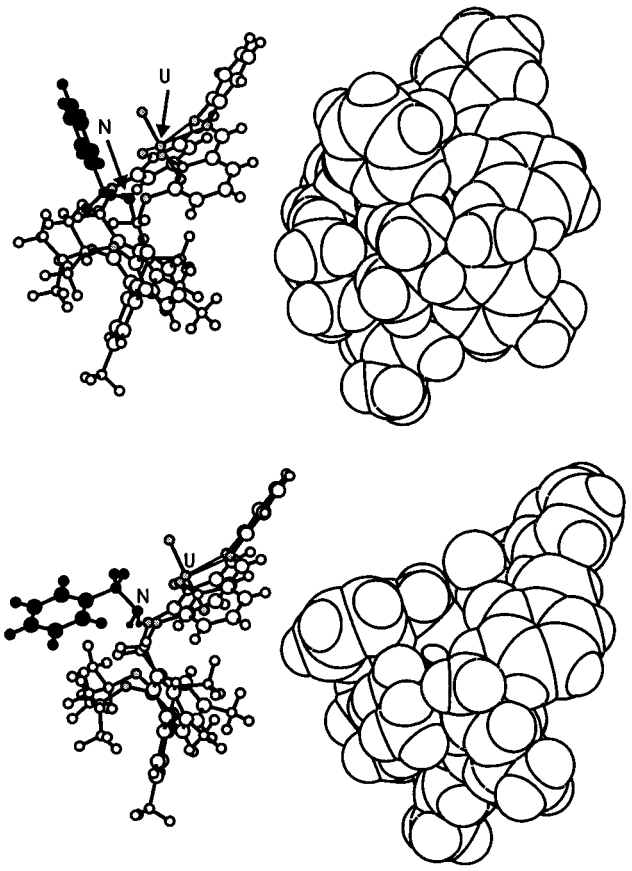

Figure 2. Minimized structures of **3a**·$PhCH_2NH_2$ (top) and **3b**·$PhCH_2NH_2$ (bottom).

in the cavity of the host, compared to **3b**·$PhCH_2NH_2$. The interaction energy between host and guest is −28.28 kcal/mol (van der Waals and electrostatic part are −13.03 and −15.24 kcal/mol, respectively; the U···N distance is 2.848 Å), reflecting this deeper binding. The much larger interaction between host **3a** and $PhCH_2NH_2$ compared to host **3b** might be the origin of the higher binding free energy.

Conclusions

The binding affinity of ammonia and the selectivity of ammonia over primary amines can be improved by changing the methyl substituents in host **1**, leading to hosts **2**−**4**. The calculated free energies of binding are in good (quantitative) agreement with experiment. The analysis of the experimental observations was complemented by addition calculations, suggesting that predictions based on such simulations should be possible.

Experimental Section

Synthesis. 3,3″-(2,2″-Dihydroxy-2′-methoxy-5,5′,5″-trimethyl[1,1′:3′,1″]terphenyl)dialdehyde (7). A solution of compound **6** (5.0 g, 15 mmol) and HMTA (6.3 g, 45 mmol) in 90 mL of CF_3COOH was heated at 60 °C for 3.5 days, followed by the addition of 180 mL of water. After stirring for 3 h at 60 °C the mixture was poured into 600 mL of ethyl acetate and neutralized with a saturated solution of $NaHCO_3$. The aqueous layer was extracted once with ethyl acetate. The combined organic layers were washed with water and dried with $MgSO_4$, followed by evaporation of the solvent. The desired compound was purified by column chromatography (SiO_2, CH_2Cl_2) to give **7** in 93% yield as a slightly yellow solid: ^{1}H NMR ($CDCl_3$) δ 11.12 (s, 2 H), 9.53 (s, 2 H), 7.45 (d, 2 H, J = 2.1 Hz), 7.37 (d, 2 H, J = 2.1 Hz), 7.15 (s, 2 H), 3.23 (s, 3 H), 2.37 (s, 9 H); MS (FAB, NBA) m/z 388.9 (M^+, calcd for $C_{24}H_{22}O_5$ 390.4).

General Procedure for the Synthesis of 8a,b. A mixture of the appropriate starting material (7−10 mmol), 4−5 equiv of iodoethane or 2-iodopropane, and 4−5 equiv of K_2CO_3 in 80 mL of CH_3CN was refluxed for 5 h, after which it was cooled to room temperature. After removal of the salts, the crude product was purified by column chromatography.

3,3″-(2,2″-Diethoxy-2′-methoxy-5,5′,5″-trimethyl[1,1′:3′,1″]terphenyl)dialdehyde (8a): (SiO_2, CH_2Cl_2−ethyl acetate = 99:1) colorless foam, yield 71%; ^{1}H NMR ($CDCl_3$) δ 10.47 (s, 2 H), 7.86−7.25 (m, 6 H), 3.78 (q, 4 H, J = 7.0 Hz), 3.22 (s, 3 H), 2.42 (s, 3 H), 2.40 (s, 6 H), 1.18 (t, 6 H, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$) δ 190.7, 138.6, 131.7, 127.6 (d), 71.3 (t), 60.7, 20.7, 20.7, 15.3 (q); IR (KBr) 1688 (C═O) cm^{-1}.

3,3″-(2,2″-Diisopropoxy-2′-methoxy-5,5′,5″-trimethyl-[1,1′:3′,1″]terphenyl)dialdehyde (8b): (SiO_2, CH_2Cl_2) yield 55%; ^{1}H NMR ($CDCl_3$) δ 10.49 (s, 2 H), 7.67 (d, 2 H, J = 2.2 Hz), 7.50 (d, 2 H, J = 2.2 Hz), 7.27 (s, 2 H), 3.93 (heptet, 2 H, J = 6.2 Hz), 3.24 (s, 3 H), 2.40 (s, 3 H), 2.38 (s, 6 H), 1.09 (d, 12 H, J = 6.2 Hz); ^{13}C NMR ($CDCl_3$) δ 191.2, 138.8, 131.7, 127.3, 76.3 (d), 60.7, 21.9, 20.7 (q); IR (KBr) 1685 cm^{-1}; MS (FAB, NBA) m/z 475.5 [$(M + H)^+$, calcd for $C_{30}H_{35}O_5$ 475.2], 497.8 $(M + Na)^+$.

3,3″-(2,2″-Bis((2,1-ethanediyloxy)oxy)-2′-methoxy-5,5′,5″-trimethyl[1,1′:3′,1″]terphenyl)dialdehyde (8c). A solution of **7** (4.85 g, 12.5 mmol) and diethylene glycol ditosylate (5.15 g, 12.5 mmol) in 80 mL of CH_3CN was added to a refluxing mixture of K_2CO_3 (3.80 g, 27.5 mmol) in 420 mL of CH_3CN over a period of 10 h, after which the mixture was cooled to room temperature. The salts were filtered off, and the crude product was purified by column chromatography (SiO_2, CH_2Cl_2−Et_2O = 94:6) to give **8c** in 46% yield: mp 218−220 °C; ^{1}H NMR ($CDCl_3$) δ 10.37 (s, 2 H), 7.60 (d, 2 H, J = 2.2 Hz), 7.31 (d, 2 H, J = 2.2 Hz), 7.07 (s, 2 H), 3.80−3.69 (m, 6 H), 3.39−3.36 (m, 2 H), 2.91 (s, 3 H), 2.37 (s, 3 H), 2.33 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 190.7, 138.4, 131.4, 127.5 (d), 75.7, 69.0 (t), 61.1, 20.9, 20.7 (q); IR (KBr) 1684 (C═O) cm^{-1}; MS (FAB, NBA) m/z 460.4 (M^+, calcd for $C_{28}H_{28}O_6$ 460.2).

General Procedure for the Synthesis of 9a−c. The appropriate dialdehyde (6 mmol) was dissolved in a mixture of MeOH and THF (1:1), and 2 mol equiv of $NaBH_4$ was added. After stirring for 3 h at room temperature, 120 mL of water and 240 mL of CH_2Cl_2 were added. The layers were separated, and the aqueous layer was extracted twice with 240 mL of CH_2Cl_2. The combined organic layers were washed twice with a saturated solution of NH_4Cl and subsequently dried with $MgSO_4$. After evaporation of the solvent, the product was obtained in >90% yield and used without purification.

3,3″-(2,2″-Diethoxy-2′-methoxy-5,5′,5″-trimethyl[1,1′:3′,1″]terphenyl)dimethanol (9a): colorless foam; ^{1}H NMR ($CDCl_3$) δ 7.18−7.14 (m, 6 H), 4.74 (s, 4 H), 3.65 (q, 4 H, J = 7.0 Hz), 3.23 (s, 3 H), 2.36 (s, 3 H), 2.33 (s, 6 H), 1.12 (t, 6 H, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$) δ 131.7, 131.5, 128.8 (d), 69.1, 61.9 (t), 60.4, 20.8, 20.7, 15.7 (q).

3,3″-(2,2″-Diisopropoxy-2′-methoxy-5,5′,5″-trimethyl-[1,1′:3′,1″]terphenyl)dimethanol (9b): colorless foam; ^{1}H NMR ($CDCl_3$) δ 7.21 (s, 2 H), 7.15 (d, 2c H, J = 2.0 Hz), 7.14 (d, 2 H, J = 2.0 Hz), 4.74 (s, 4 H), 3.91 (heptet, 2 H, J = 6.2 Hz), 3.25 (s, 3 H), 2.35 (s, 3 H), 2.33 (s, 6 H), 1.05 (d, 12 H, J = 6.2 Hz); ^{13}C NMR ($CDCl_3$) δ 132.0, 131.3, 128.6, 59.9 (d), 74.4, 22.2, 20.8, 20.6 (q), 62.5 (t).

3,3″-(2,2″-Bis((2,1-ethanediyloxy)oxy)-2′-methoxy-5,5′,5″-trimethyl[1,1′:3′,1″]terphenyl)dimethanol (9c): mp 207−210 °C; ^{1}H NMR ($CDCl_3$) δ 7.21 (d, 2 H, J = 2.0 Hz), 7.07 (s, 2 H), 7.03 (d, 2 H, J = 2.0 Hz), 4.83 and 4.64 (AB-q, 4 H, J = 12.3 Hz), 3.89−3.85 (m, 2 H), 3.66−3.62 (m, 4 H), 3.34−3.30 (m, 2 H), 2.96 (s, 3 H), 2.39 (s, 3 H), 2.35 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 131.5, 131.3, 129.1 (d), 73.0, 69.1, 61.1 (t), 60.9, 20.9, 20.8 (q).

General Procedure for the Synthesis of 10a−c. Conversion of the hydroxymethyl groups into bromomethyl groups was carried out by reacting the corresponding compound **9** (5.5

mmol) with 1.5 equiv of PBr_3 in 150 mL of dry toluene. During the addition of PBr_3 to the solution of **9** in toluene, the temperature was kept at 0 °C with an ice bath. After the addition the reaction mixture was stirred for 4−5 h, after which the mixture was washed with brine (2 × 150 mL) and a saturated solution of $NaHCO_3$ (150 mL). After the organic layer was dried with $MgSO_4$, the solvent was evaporated under reduced pressure (yield > 80%).

3,3″-Diethoxy-2′-methoxy-5,5′,5″-trimethyl[1,1′:3′,1″]-terphenyl (10a): colorless foam; ^{1}H NMR ($CDCl_3$) δ 7.19−7.14 (m, 6 H), 4.63 (s, 4 H), 3.71 (q, 4 H, J = 7.0 Hz), 3.22 (s, 3 H), 2.36 (s, 3 H), 2.33 (s, 6 H), 1.16 (t, 6 H, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$) δ 133.1, 131.5, 130.9 (d), 69.0, 29.2 (t), 60.5, 20.7, 15.7 (q); MS (FAB, NBA) m/z 576.6 (M^+, calcd for $C_{28}H_{32}Br_2O_3$ 576.1).

3,3″-(bromomethyl)-2,2″-diisopropoxy-2′-methoxy-5,5′,5″-trimethyl[1,1′:3′,1″]terphenyl (10b): a sample was recrystallized from petroleum ether for a complete characterization, mp 138−140 °C; ^{1}H NMR ($CDCl_3$) δ 7.16 (d, 2 H, J = 2.0 Hz), 7.12 (s, 2 H), 7.07 (d, 2 H, J = 2.0 Hz), 4.57 (s, 4 H), 3.85 (heptet, 2 H, J = 6.1 Hz), 3.17 (s, 3 H), 2.27 (s, 3 H), 2.23 (s, 6 H), 0.98 (d, 12 H, J = 6.2 Hz); ^{13}C NMR ($CDCl_3$) δ 133.2, 131.4, 131.1, 60.0 (d), 74.5, 22.4, 20.7, 20.6 (q), 29.6 (t); MS (EI) m/z 604.102 (M^+, calcd for $C_{30}H_{36}Br_2O_3$ 604.101).

3,3″-Bis(bromomethyl)-2,2″-bis((2,1-ethanediyloxy)oxy)-2′-methoxy-5,5′,5″-trimethyl[1,1′:3′,1″]terphenyl) (10c): a solid was obtained by addition of petroleum ether to a solution of **10b** in CH_2Cl_2; ^{1}H NMR ($CDCl_3$) δ 7.21 (d, 2 H, J = 2.0 Hz), 7.10 (s, 2 H), 7.04 (d, 2 H, J = 2.0 Hz), 4.96 and 4.38 (AB-q, 4 H, J = 9.8 Hz), 4.20−4.08 (m, 2 H), 3.78−3.62 (m, 4 H), 3.36−3.28 (m, 2 H), 2.92 (s, 3 H), 2.41 (s, 3 H), 2.33 (s, 6 H). ^{13}C NMR ($CDCl_3$) δ 132.9, 131.2, 131.1 (d), 72.7, 69.9, 29.0 (t), 60.9, 21.0, 20.7 (q). MS (FAB, NBA) m/z 613.3 [$(M + Na)^+$, calcd for $C_{28}H_{30}Br_2O_4$·Na 613.0].

General Procedure for the Synthesis of 12a−c. A solution of **10** in some CH_3CN and CH_2Cl_2 (1:1) was added to a mixture of 2 equiv of **11** and 4 equiv of K_2CO_3 in CH_3CN (140 mL) that was refluxed prior to this addition for 15−30 min. The resulting mixture was refluxed for 2−2.5 h, after which it was cooled to room temperature. The salts were filtered off and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography (SiO_2, CH_2Cl_2).

((2,2″-Diethoxy-2′-methoxy-5,5′,5″-trimethyl[1,1′:3′,1″]-terphenyl-3,3″-diyl)bis(methyleneoxy))bis(2-(2-propenyloxy)benzaldehyde) (12a): yield 37%, colorless foam; ^{1}H NMR ($CDCl_3$) δ 10.47 (s, 2 H), 7.47−7.39 (m, 2 H), 7.24−7.08 (m, 10 H), 6.18−5.96 (m, 2 H), 5.24 (s, 4 H), 5.48−5.20 (m, 4 H), 4.73 (d, 4 H, J = 6.0 Hz), 3.67 (q, 4 H, J = 7.0 Hz), 3.26 (s, 3 H), 2.38 (s, 3 H), 2.36 (s, 6 H), 1.10 (t, 6 H, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$) δ 190.5, 133.3, 132.2, 131.5, 129.0, 124.2, 119.8, 119.4 (d), 118.9, 75.2, 69.3, 66.7 (t), 60.5, 20.9, 20.7, 15.7 (q); IR (KBr) 1688 (C═O) cm^{-1}.

((2,2″-Diisopropoxy-2′-methoxy-5,5′,5″-trimethyl[1,1′:3′,1″]terphenyl-3,3″-diyl)bis(methyleneoxy))bis(2-(2-propenyloxy)benzaldehyde) (12b). yield 70%, colorless foam; ^{1}H NMR ($CDCl_3$) δ 10.47 (s, 2 H), 7.47−7.39 (m, 2 H), 7.24−7.08 (m, 10 H), 6.20−5.98 (m, 2 H), 5.30 (s, 4 H), 5.45−5.20 (m, 4 H), 4.75 (d, 4 H, J = 6.0 Hz), 3.90 (heptet, 2 H, J = 6.1 Hz), 3.28 (s, 3 H), 2.37 (s, 3 H), 2.35 (s, 6 H), 1.04 (d, 12 H, J = 6.1 Hz); ^{13}C NMR ($CDCl_3$) δ 190.6, 133.3, 132.4, 131.4, 128.6, 124.2, 119.7, 119.3, 74.6 (d), 118.9, 75.2, 66.6 (t), 22.2, 20.9, 20.7 (q); IR (KBr) 1689 (C═O) cm^{-1}.

((2,2″-Bis((2,1-ethanediyloxy)oxy)-2′-methoxy-5,5′,5″-trimethyl[1,1′:3′,1″]terphenyl-3,3″-diyl)bis(methyleneoxy))-bis(2-(2-propenyloxy)benzaldehyde (12c): yield 47%, colorless foam; ^{1}H NMR ($CDCl_3$) δ 10.45 (s, 2 H), 7.47−7.39 (m, 2 H), 7.24−7.08 (m, 10 H), 6.14−5.98 (m, 2 H), 5.45−5.10 (m, 4 H), 4.80−4.62 (m, 4 H), 3.93−3.85 (m, 2 H), 3.71−3.58 (m, 4 H), 3.33−3.21 (m, 2 H), 3.02 (s, 3 H), 2.42 (s, 3 H), 2.37 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 190.5, 133.2, 132.1, 131.4, 129.1, 124.3, 119.9, 118.4 (d), 118.9, 75.2, 73.1, 69.0, 66.8 (t), 61.0, 20.9 (q); IR (KBr) 1685 (C═O) cm^{-1}.

General Procedure for the Synthesis of 13a,b. Deallylation of compound **12** (2 mmol) was performed by the Pd-(PPh_3)$_4$-catalyzed (5−8 mol %) reaction with Et_3N·HCOOH (3 equiv) in a mixture of DMF (50 mL) and water (8 mL). After stirring for 1 h the mixture was poured into 60 mL of ethyl acetate and washed three times with a saturated solution of NH_4Cl (100 mL). The organic layer was dried with $MgSO_4$ and concentrated to dryness.

((2,2″-Diethoxy-2′-methoxy-5,5′,5″-trimethyl[1,1′:3′,1″]-terphenyl-3,3″-diyl)bis(methyleneoxy))dihydroxybenzaldehyde (13a): crude product was purified by column chromatography (SiO_2, CH_2Cl_2−MeOH = 99:1) to give a yellow foam, yield 63%; ^{1}H NMR ($CDCl_3$) δ 11.06 (s, 2 H), 9.93 (s, 2 H), 7.31 (d, 2 H, J = 2.0 Hz), 7.26−7.19 (m, 8 H), 6.94 (dd, 2 H, J = 7.9 Hz, J = 7.9 Hz), 5.26 (s, 4 H), 3.68 (q, 4 H, J = 7.0 Hz), 3.25 (s, 3 H), 2.37 (s, 3H), 2.33 (6 H), 1.08 (t, 6 H, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$) δ 196.5, 132.4, 131.5, 129.3, 125.0, 121.0, 120.4, 119.6 (d), 69.5, 66.9 (t), 60.5, 20.9, 20.7, 15.6, 15.5 (q); IR (KBr) 1657 (C═O) cm^{-1}.

((2,2″-Diisopropoxy-2′-methoxy-5,5′,5″-trimethyl[1,1′:3′,1″]terphenyl-3,3″-diyl)bis(methyleneoxy))dihydroxybenzaldehyde (13b): crude product was purified by column chromatography (SiO_2, CH_2Cl_2−MeOH = 99:1), yield 57%; ^{1}H NMR ($CDCl_3$) δ 11.04 (s, 2 H), 9.94 (s, 2 H), 7.34 (d, 2 H, J = 2.0 Hz), 7.26−7.19 (m, 8 H), 6.93 (dd, 2 H, J = 7.9 Hz, J = 7.9 Hz), 5.28 (s, 4 H), 3.68 (heptet, 4 H, J = 6.1 Hz), 3.27 (s, 3 H), 2.37 (s, 3H), 2.32 (6 H), 1.08 (d, 12 H, J = 6.1 Hz); ^{13}C NMR ($CDCl_3$) δ 196.5, 132.4, 131.4, 128.8, 124.8, 120.4, 119.6, 74.8 (d), 66.8 (t), 60.5, 22.2, 20.9, 20.7 (q); IR (KBr) 1658 (C═O) cm^{-1}.

((2,2″-Bis((2,1-ethanediyloxy)oxy)-2′-methoxy-5,5′,5″-trimethyl[1,1′:3′,1″]terphenyl-3,3″-diyl)bis(methyleneoxy))-dihydroxybenzaldehyde (13c): crude product was purified by column chromatography (SiO_2, CH_2Cl_2), yield 47%; ^{1}H NMR ($CDCl_3$) δ 11.05 (bs, 2 H), 9.92 (s, 2 H), 7.31 (d, 2 H, J = 2.0 Hz), 7.26−7.09 (m, 8 H), 6.95 (dd, 2 H, J = 7.9 Hz, J = 7.9 Hz), 5.38 and 5.07 (AB-q, 4 H, J = 11.2 Hz), 3.95−3.90 (m, 2 H), 3.72−3.53 (m, 4 H), 3.26−3.21 (m, 2 H) 3.02 (s, 3 H), 2.41 (s, 3H), 2.35 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 196.7, 132.3, 131.4, 129.8, 125.0, 120.3, 119.6 (d), 73.2, 68.9, 67.2 (t), 60.5, 20.8 (q); IR (KBr) 1658 (C═O) cm^{-1}.

General Procedure for the Synthesis of 2−4. A solution of 1,2-phenylenediamine (0.7 mmol) in 50 mL of MeOH and a solution of **13** (0.7 mmol) in 50 mL of CH_2Cl_2 were simultaneously added to a refluxing solution (450 mL) of $UO_2(OAc)_2$·$2H_2O$ (0.7 mmol) over a period of 3 h, after which the solution was cooled to room temperature and concentrated under reduced pressure.

(39,41-Diethoxy-40-methoxy-12,17,22-trimethyl-25*H*-3,7:10,14:15,19:20,24:27,31-pentametheno-9*H*-8,26,1,33-benzodioxadiazacyclopentatriacontine-38,42-diolato-(2−)-*N*^{1},*N*^{33},*O*^{38},*O*^{42})dioxouranium (2): crude product was purified by column chromatography (SiO_2, CH_2Cl_2−acetone = 98:2), yield 35%, mp 270 °C dec; ^{1}H NMR ($CDCl_3$) δ 9.35 (s, 2 H), 7.55−7.48 (m, 2 H), 7.46−7.39 (m, 8 H), 7.32−7.29 (m, 2 H), 7.23−7.18 (m, 4 H), 6.65 (dd, 2 H, J = 7.8 Hz, J = 7.8 Hz), 5.75 and 5.02 (AB-q, 4 H, J = 8.8 Hz), 3.92 (ABX_3, 4 H), 3.06 (s, 3 H), 2.45 (s, 3 H), 2.43 (s, 6 H), 0.99 (t, 6 H, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$) δ 165.6, 132.8, 132.2, 130.6, 129.9, 128.7, 125.1, 119.9, 116.7 (d), 71.1, 70.5 (t), 60.9, 21.0, 20.9, 15.2 (q); IR (KBr) 1603 (N═C) cm^{-1}; MS (FAB, NBA) m/z 1030.9 (M^+, calcd for $C_{48}H_{44}N_2O_9U$ 1030.4), 1032.0 [$(M + H)^+$], 1053.8 [$(M + Na)^+$], 1030.6 (M^-). No satisfactory elemental analysis was obtained for the bishydrate.

(39,41-Diisopropoxy-40-methoxy-12,17,22-trimethyl-25*H*-3,7:10,14:15,19:20,24:27,31-pentametheno-9*H*-8,26,1,33-benzodioxadiazacyclopentatriacontine-38,42-diolato-(2−)-*N*^{1},*N*^{33},O^{38,42})dioxouranium (3a,b): crude product was purified by column chromatography (SiO_2, CH_2Cl_2−acetone = 99:1), major isomer **3a** yield 14%, mp 280 °C dec, ^{1}H NMR ($CDCl_3$) δ 9.27 (s, 2 H), 7.49−7.33 (m, 10 H), 7.24−7.14 (m, 4 H), 6.66 (dd, 2 H, J = 7.8 Hz, J = 7.8 Hz), 5.53 and 4.93 (AB-q, 4 H, J = 10.1 Hz), 3.71 (heptet, 2 H, J = 6.0 Hz), 3.00 (s, 3 H), 2.43 (s, 3 H), 2.39 (s, 6 H), 1.04 (d, 6 H, J = 6.0 Hz), 0.93 (d, 6 H, J = 6.0 Hz); ^{13}C NMR ($CDCl_3$) δ 165.3, 132.7, 131.6, 130.8, 129.9, 128.7, 126.0, 119.7, 116.4, 115.1, 76.1 (d), 65.1 (t), 62.5, 22.6, 21.9, 20.8 (q); IR (KBr) 1604 (N═C) cm^{-1}; MS

(FAB, NBA) *m/z* 1059.3 [(M + H)$^+$], 1081.1 [(M + Na)$^+$], 1058.0 (M$^-$). Anal. Calcd for $C_{50}H_{48}N_2O_9U\cdot 2H_2O$: C, 54.84; H, 4.79; N, 2.56. Found: C, 54.42; H, 4.65; N, 2.51.

Minor isomer 3b: yield 7%, mp 280 °C dec; ^{1}H NMR ($CDCl_3$) δ 9.38 (s, 2 H), 7.58−7.30 (m, 12 H), 7.24−7.14 (m, 2 H), 6.66 (dd, 2 H, J = 7.8 Hz, J = 7.8 Hz), 5.93 and 4.87 (AB-q, 4 H, J = 9.0 Hz), 4.10 (heptet, 2 H, J = 6.2 Hz), 2.92 (s, 3 H), 2.47 (s, 3 H), 2.41 (s, 6 H), 1.27 (d, 6 H, J = 6.2 Hz), 0.99 (d, 6 H, J = 6.2 Hz); ^{13}C NMR ($CDCl_3$) δ 165.5, 132.4, 132.1, 130.4, 129.6, 128.7, 124.5, 119.8, 116.6, 78.4 (d), 70.2 (t), 60.3, 22.9, 22.6, 21.1, 20.8 (q); IR (KBr) 1603 (N=C) cm^{-1}; MS (FAB, NBA) *m/z* 1060.0 [(M + H)$^+$], 1081.9 [(M + Na)$^+$], 1058.6 (M$^-$).

(39,41-Bis((2,1-ethanediyloxy)oxy)-40-methoxy-12,17, 22-trimethyl-25*H*-3,7:10,14:15,19:20,24:27,31-pentametheno-9*H*-8,26,1,33-benzodioxadiazacyclopentatriacontine-38,42-diolato(2−)-*N*^{1},*N*^{33},*O*^{38},*O*^{42})dioxouranium (4): crude product was purified by column chromatography (SiO_2, CH_2Cl_2−ethyl acetate = 95:5), yield 35%, mp 280 °C dec; ^{1}H NMR ($CDCl_3$) δ 9.43 (s, 2 H), 7.60−7.30 (m, 10 H), 7.24−7.20 (m, 4 H), 6.68 (dd, 2 H, J = 7.7 Hz, J = 7.7 Hz), 5.74 and 5.04 (AB-q, 4 H, J = 8.7 Hz), 4.02−3.97 (m, 2 H), 3.71−3.65 (m, 4 H), 3.20−3.15 (m, 2 H), 3.03 (s, 3 H), 2.47 (s, 3 H), 2.45 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 165.7, 132.9, 132.0, 130.7, 130.5, 128.8, 126.8, 119.9, 116.9 (d), 75.4, 70.5, 68.7 (t), 60.7, 21.2, 20.9 (q); IR (KBr) 1603 (N=C) cm^{-1}; MS (FAB, NBA) *m/z* 1068.4 [(M + Na)$^+$], 1045.1 (M$^-$). Anal. Calcd for $C_{48}H_{42}N_2O_{10}U\cdot 2H_2O$: C, 53.34; H, 4.29; N, 2.59. Found: C, 53.36; H, 4.25; N, 2.53.

Binding of NH_3, $PrNH_2$, and $PhCH_2NH_2$. These were performed as described before[1] except that the concentration of NH_3 in $CHCl_3$ was determined titrimetrically. A sample was taken from the solution and put into 20 mL of ethanol, followed by tritration with trifluoromethanesulfonic acid, dissolved in 2-propanol.

Gibbs Free-Energy Calculations. Minimized structures were obtained as previously described for **1**,[1] and charges were assigned with the charge equilibration method[13] as implemented in the Cerius[2] package[14] (version 1.5). Symmetry-related charges were averaged. The charge on the uranium was set to +2.0.[15] Except for the substituents on the phenol moieties and the *p*-methyl groups, all hydrogens were treated explicitly. See the Supporting Information for a set of typical charges.[16] The Lennard−Jones parameters for uranium were σ = 2.6727 Å and ϵ = 1.0 kcal/mol.[15] All other Lennard−Jones parameters were taken from the BOSS parameter file.[7] The methylene and/or methyl groups of the guests were treated as united atoms. The (coordinated) water was simulated with the TIP3P model[8] and the (coordinated) ammonia with q_N = −1.05, q_H = 0.35, σ = 2.940 Å, and ϵ = 0.150 kcal/mol for N and σ = 1.425 Å and ϵ = 0.0498 kcal/mol for H, respectively.[9] See Results and Discussion for an evaluation of the balance of these models. The (coordinated) $MeNH_2$ was simulated with q_N = −0.90, q_H = 0.35, and q_{Me} = 0.20,[7] with the Lennard−Jones parameters for N and H as for NH_3 and the united methyl group as in the BOSS parameter file.[7] The methyl group in $EtNH_2$ and the methyl and 'second' methylene group of $PrNH_2$ were not charged. The other charges were as in $MeNH_2$.

Monte Carlo free-energy perturbation (MC-FEP), or importance sampling, simulations were performed with the BOSS program,[7] using the OPLS chloroform model.[17] Details are as follows. The appropriate **z**-matrices for **1**·H_2O/NH_3, **3a**·H_2O/NH_3, **3b**·H_2O/NH_3, **4**·H_2O/NH_3, **1**·NH_3/$MeNH_2$, **1**·$MeNH_2$/$EtNH_2$, **1**·$EtNH_2$/$PrNH_2$, **3a**·NH_3/$MeNH_2$, and **3b**·NH_3/$MeNH_2$ were constructed from the minimized structures. The complexes were placed in a box of 33.0 × 33.0 × 49.5 Å dimension, initially filled with 400 $CHCl_3$s. On the basis of the worst interaction energies, 17 molecules of $CHCl_3$ were removed at the start of the simulations. A cutoff of 11 Å was used for the nonbonded interactions, which were quadratically smoothed to zero between the cutoff and the cutoff − 0.5 Å. The ligand and coordinated guest were sampled independently. Translational and rotational sampling was applied to the ligand (0.02 Å and 2.00°, respectively), in addition to sampling of the phenolic substituents through their dihedrals (sampling range was 5°). The sampling of the bridge in host **4** also included angles and bonds (treated automatically). This gave an acceptance ratio of approximately 35%. The translational and rotational sampling ranges of H_2O/NH_3 were set to 0.15 Å and 15.0°, respectively, giving an acceptance ratio of roughly 40%. The dihedral sampling of RNH_2 was 5.0°, and the translational and rotational sampling ranges were somewhat smaller than with H_2O/NH_3 such that an acceptance ratio of roughly 40% was obatined. A solute move was attempted every 25 solvent moves. Preferential sampling was used.[18] The perturbations were carried out in five equally spaced, double-wide windows. The calculations on $H_2O \leftrightarrow NH_3$ were equilibrated for 1 million configurations, followed by averaging over 2 million configurations. The calculations on R_1NH_2/R_2NH_2 in the absense of a host were equilibrated for 1 million configurations and averaged over 4 million configurations. The perturbations of NH_3 into $MeNH_2$ and the reverse were equilibrated for 3 million configurations and averaged over 4 million configurations. The perturbation of $MeNH_2$ into $EtNH_2$ in host **1** was equilibrated for 4 million configurations and averaged over 3 million configurations. The NPT ensemble at 1 atm and 298 K was used. Full periodic boundary conditions were imposed. This was done by making 26 images in the ±x, ±y, and ±z directions. The standard deviations were between 0.03 and 0.50 kcal/mol for all runs, except for the perturbation of NH_3 into $MeNH_2$ and the reverse which gave standard deviations of 0.69 and 0.78 kcal/mol. As a lower bound estimation of the error, the average of the forward and backward runs was taken, if applicable. Calculations were run on Silicon Graphics workstations and on a Pentium 133 personal computer.[19]

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Supporting Information Available: ^{13}C NMR spectra of compounds **2**−**4** and **7**−**13**; also a set of typical point charges (21 pages). This material is contained in libraries on microfiche, immediately followes this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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