A Generalized and Efficient Preparation of a Novel Class of Macrocyclic Bis(guanidines) from Cyclic Bis(carbodiimides)

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Reaction of readily available macrocyclic bis(carbodiimides) with nitrogen reagents such as ammonia, primary or secondary alkylamines, and α,ω-diamino compounds provided a novel class of macrocyclic bis(guanidines), which were isolated as crystalline solids in high yields (74−98%). The crystal and molecular structure of the bis(guanidine) derived from bicyclo[8.8.2]docosane **10a** has been determined.

Design and synthesis of macropolycyclic receptor molecules for efficient and selective recognition of inorganic oxoanions and negatively charged functional groups (carboxylate, phosphate, etc) on organic and biological substrates is the most basic requirement of supramolecular and biological chemistry. A particular favorable interaction mode showed by abundant biological examples[1] is the complexation of oxoanionic functions by guanidinium groups,[2] which has been exploited by acyclic[3] and cyclic[4] artificial receptors. Incorporation of a guanidinium group into a bicyclic framework paves the way toward polytopic hosts capable of positively dedicated enantioselective recognition.[5] In this context, enzyme mimics formed by the incorporation of two guanidinium-like groups, in the guise of 2-aminoimidazole rings, enhance the rate of phosphodiester P−O bond cleavage under a variety of conditions.[6]

Among the methods described for the preparation of guanidines, only two methods have been successfully applied for the synthesis of macrocyclic guanidines. The first one is based in the S-alkylation of macrocyclic thioureas followed by treatment of the resulting S-thiouronium salts with ammonia[6f,7] to give macrocycles type **1**−**4.**

The second method which allowed the formation of **5** is based on the conversion of a macrocyclic bis(thiourea) into the corresponding bis(carbodiimide) and further treatment with amines[8] (see structures).

In this context, we report herein an efficient and simple method for the tailor-made preparation of new host molecules of different shapes, sizes, and topology bearing two guanidine moieties. The method, based on the reaction of macrocyclic bis(carbodiimides) with amines, allows the tuning of the size and shape of the central hole as well as the complexity by suitable variation of the nature either of the spacers linked to the aromatic ring in the starting *C*,*C*-bis(iminophosphorane) or of the amino compound used as reagent.

Results and Discussion

The starting bis(carbodiimide) **6** was prepared by a two-step sequence: (a) aza-Wittig reaction of 1,2-bis(triphenylphosphoranylideneamino)ethane with carbon disulfide to give the corresponding bis(isothiocyanate) in 93% yield and (b) aza-Wittig reaction of the bis(isothiocyanate) with the above-mentioned bis(iminophosphorane) to give **6** in 97% yield.[9] The bis(carbodiimide) **7** was prepared in 71% yield directly from bis[2,2′-(triphenylphosphoranylideneamino)benzyl] ether by reaction with the system Boc_2O/DMAP.[9]

Bis(carbodiimide) **6** reacted with ammonia and primary and secondary alkylamines at room temperature to give the macrocyclic bis(guanidines) **8**, which were isolated as crystalline solids in yields ranging from 80 to 98%. The presence of an oxygen atom into the tether connecting the two aromatic rings did not affect the behavior observed in the bis(carbodiimide) **6**. Thus, bis(carbodiimide) **7** reacted with ammonia and primary alkylamines to give **9a**−**c** in excellent yields (Scheme 1).

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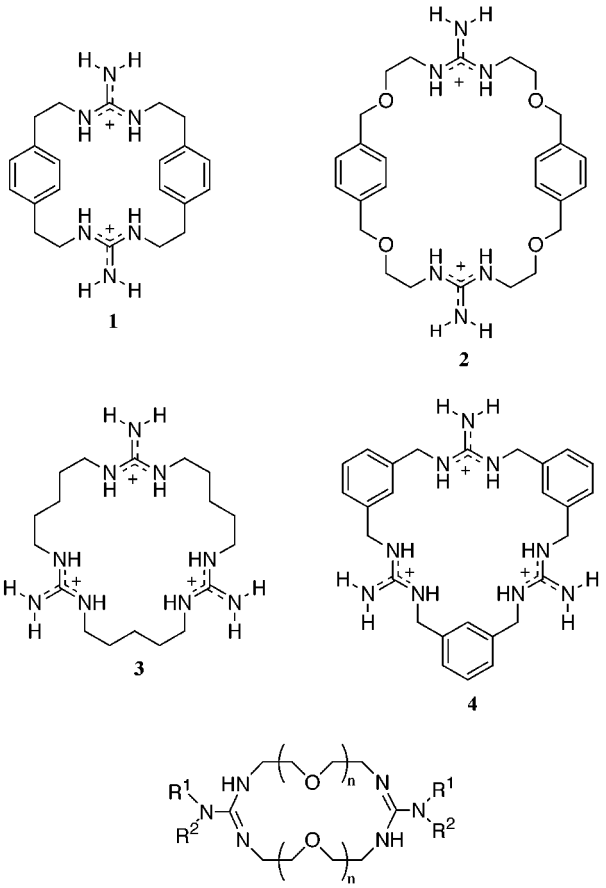
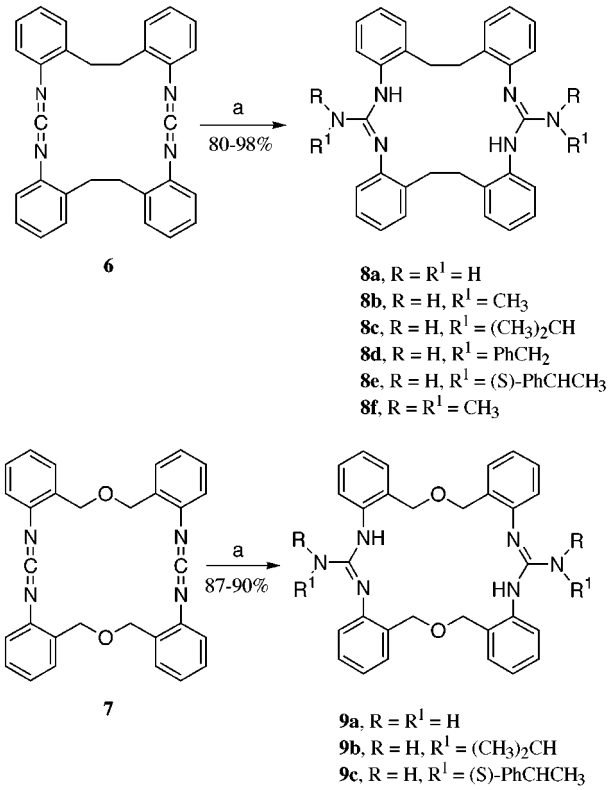


In general, ^{1}H and ^{13}C NMR spectra of compounds **8** and **9** showed broad signals which may be probably due to the existence of conformational and/or tautomeric equilibria associated with the molecule at room temperature. This type of behavior has been recently described in related macrocyclic systems.[10]

In the room-temperature ^{1}H NMR spectrum of **9b** in DMSO-d_6, the twelve methyl protons appeared as a broad singlet at δ 1.22 ppm, whereas the two methine protons and the eight methylene protons revealed as two broad signals centered at δ 3.95 and 4.31 ppm, respectively. The ^{13}C NMR spectrum exhibits the requisite number of signals in broad appearance. When the ^{1}H NMR spectrum was recorded at 363 K, the broad signal at 1.22 ppm appeared clearly as a doublet at δ 1.19 ppm (J = 6.3 Hz) and the signal assigned to the methine protons appeared as a multiplet in the region δ 3.95−3.99 ppm, whereas the signal assigned to the methylene protons remained unchanged.

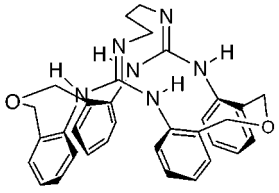
Bis(carbodiimides) **6** and **7** also reacted with α,ω-diamino compounds to give the macrobicycles **10** and **11,** respectively, in yields ranging from 74 to 88% as crystalline solids. High dilution conditions are common for ring closures of this type where multifunctional groups react. Formation of **10** and **11** was accomplished by dropwise addition of a solution of the α,ω-diamino compound in dichloromethane to a solution of the bis(carbodiimide) in the same solvent at room temperature (Scheme 2).

Scheme 1[a]



[a] (a) RR^1NH, CH_2Cl_2, rt.

Positive FAB mass spectrometry was used to show that all the products had the expected molecular formulas. In the ^{1}H NMR spectrum of **11b** the methylene protons of the propylene bridge appeared as three multiplets at δ 1.45−1.49 (2H), 3.08−3.12 (2H), and 3.34−3.62 (2H) ppm, respectively, whereas the $ArCH_2O$ protons are diastereotopic and appeared as a set of four doublets at δ 3.96 (J = 8.1 Hz), 4.44 (J = 12.7 Hz), 4.70 (J = 8.1 Hz), and 5.23 (J = 12.7 Hz), respectively. The ^{13}C NMR spectrum showed two signals for the propylene bridge carbon atoms. These findings suggest that the structure of compound **11b** in solution could be such as the one represented below.



11b

To identify unambiguously the proposed structures, X-ray structure determination of compound **10a** was performed. The final X-ray model of **10a** is shown in Figure 1, drawn with ORTEP.[11] Another molecular perspective showing the ring puckering is given in Figure 2. The bond lengths distribution around C7 and C8 indicates a slight electron delocalization but is mainly

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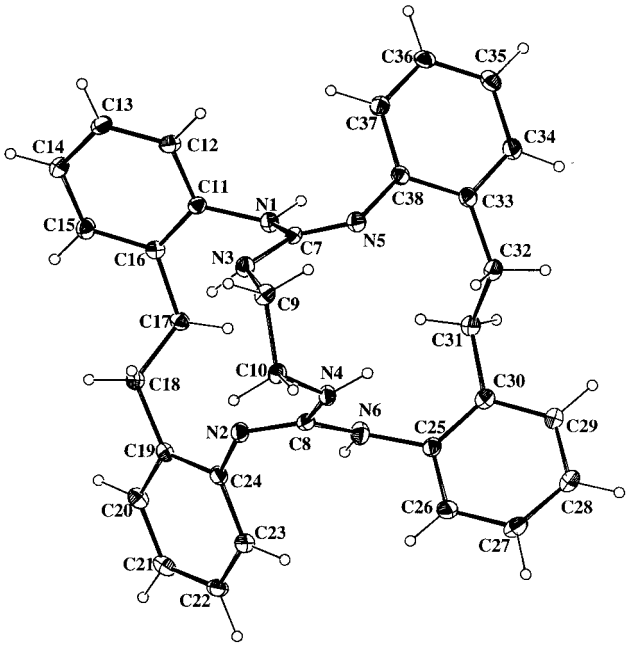
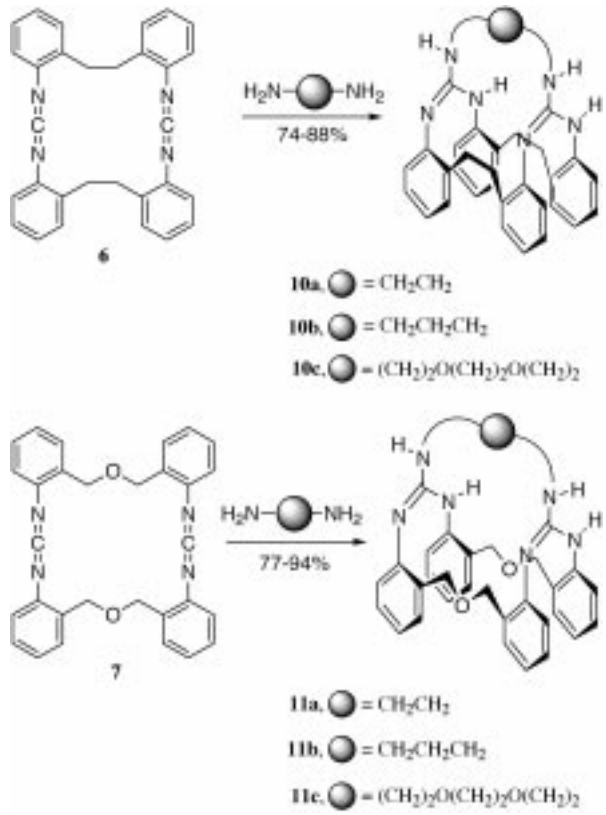


Figure 1. Final X-ray model of **10a** showing the atomic numbering used.

Scheme 2



consistent with the double bonds C7═N5 and C8═N2. No voids were found in this crystal structure, the total packing coefficient[12] being 0.69.

Eventually, macrocyclic bis(guanidines) **8**, **10,** and **11** were converted in high yields (78−92%) into the corresponding bis(guanidinium) salts **12** and **13** by the action of hydrochloric acid. In general, the ^{1}H and ^{13}C NMR

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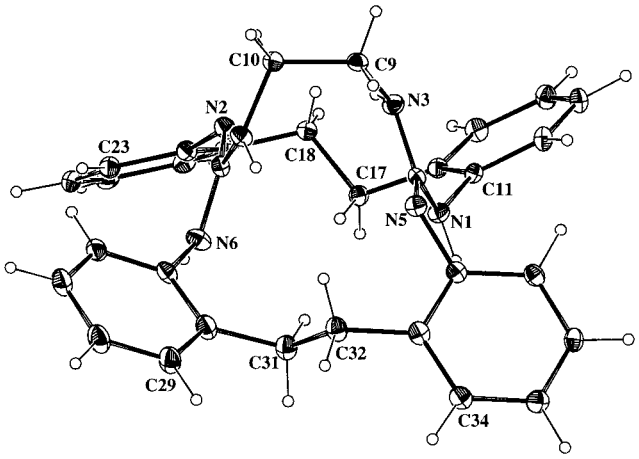
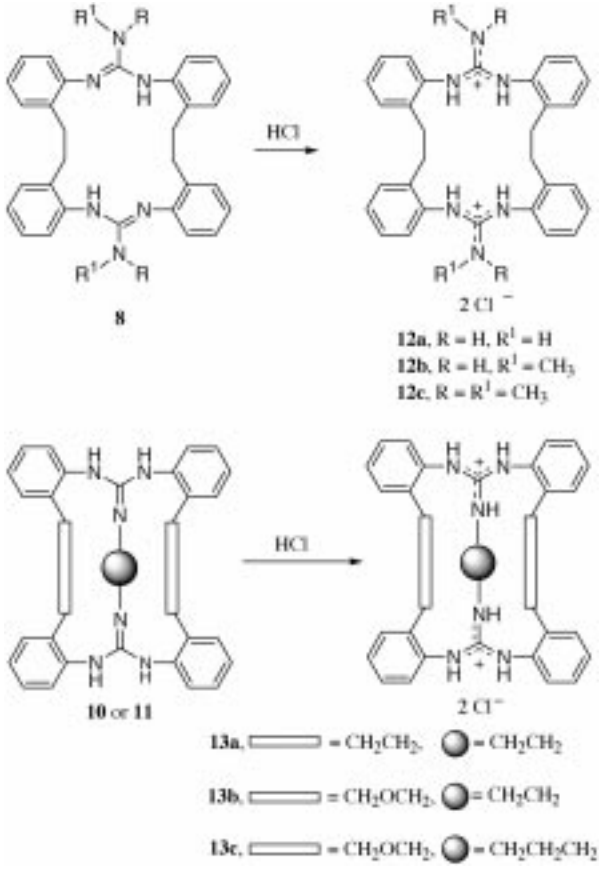


Figure 2. Molecular perspective showing the ring puckering. Some atom labels are shown for reference.

Scheme 3



spectra of **12** and **13** showed sharp and well-defined signals. As expected, in the ^{13}C NMR spectra the guanidinium carbon atom (155−159 ppm) appeared at lower field than in compounds **10** and **11** (148−151 ppm) (Scheme 3).

Some preliminary experiments on the anion complexation properties of the bis(guanidinium) salts **12** and **13** have been performed for the carboxylate anion by liquid−liquid single extraction experiments. Sodium *p*-nitrobenzoate was quantitatively extracted from water by a chloroform solution of **12c**. Despite its ionic structure, no trace of **12c** was found in the aqueous layer, and the chloroform extract was composed exclusively of the bis-

(guanidinium) bis(*p*-nitrobenzoate) salt, which was isolated as a crystalline solid.

Although some differences in chemical shift were observed in the ^{1}H NMR ($CDCl_3$) spectra on going from **8f**·2(*p*-$O_2N-C_6H_4-COOH$) to **12c** ($\Delta\delta CH_2 = +0.16$; $\Delta\delta CH_3 = -0.38$) and between the triethylammonium *p*-nitrobenzoate and the salt **8f**·2(*p*-$O_2N-C_6H_4-COOH$) ($\Delta\delta H_{ortho} = -0.19$; $\Delta\delta H_{meta} = -0.17$), they are not conclusive to elucidate if a complex of well-defined geometry has been formed, which involves some kind of recognition of the guest by the bis(guanidinium) cation.

In an analogous experiment, 2 equiv of sodium *p*-nitrobenzoate was quantitatively extracted from water by a chloroform solution of the bis(guanidinium) salt **13b**. The ^{1}H NMR (DMSO-d_6) spectra of **11a**·2(*p*-$O_2N-C_6H_4-COOH$**)** revealed significant shifts for most signals of both ions. For instance, in the ^{1}H NMR spectrum of this complex, two of the NH guanidinium protons appeared included in the multiplet at δ 7.22−7.46 ppm, corresponding to the aromatic protons of the guanidinium ion, whereas the remaining four NH protons appeared as a broad singlet centered at δ 9.22 ppm. In the salt **13b** these protons appeared as three singlets, each integrating as 2H, centered at δ 7.74, 8.85, and 9.54 ppm.

The $ArCH_2O$ protons were diastereotopic in the salt **13b**, appearing as a set of four doublets at δ 4.29 (J = 11.3 Hz), 4.40 (J = 11.0 Hz), 4.73 (J = 11.0 Hz), and 4.79 (J = 11.3 Hz). However, in the guanidinium salt **11a**·2(*p*-$O_2N-C_6H_4-COOH$**)**, these protons appeared as a complex multiplet centered at δ 4.37−4.83 ppm. The CH_2N protons also appeared as a complex multiplet in the salt **11a**·2(*p*-$O_2N-C_6H_4-COOH$**)** at δ 3.19−3.62 ppm, whereas in the salt **13b** these protons appeared as two multiplets at δ 3.35−3.43 and 4.00−4.09 ppm.

On the other hand, in the ^{1}H NMR spectra the difference in chemical shifts for the protons of the *p*-nitrobenzoate ion on going from triethylammonium *p*-nitrobenzoate (DMSO-d_6) in **11a**·2(*p*-$O_2N-C_6H_4-COOH$**)** was $\Delta\delta H_{ortho} = -0.14$, and $\Delta\delta H_{meta} = -0.03$ ppm, whereas when both ^{1}H NMR spectra were registered in $CDCl_3$ these differences were notably higher, $\Delta\delta H_{ortho} = -0.46$, and $\Delta\delta H_{meta} = -0.20$ ppm.

Concluding Remarks

In conclusion, we have developed a simple and efficient method for the preparation of a new type of macrocyclic bis(guanidine) of varying ring size and complexity.

Due to the easy access of the starting *C,C*-bis(iminophosphoranes), the good yields in the formation of the macrocyclic bis(carbodiimides) as well as in the amination step, and the simplicity of the experimental procedure, the investigated reactions provide a method for the preparation of relatively complex and unreported macrocyclic bis(guanidines) not available by those previously reported methods.

Experimental Section

General Methods. General experimental conditions and spectroscopic instrumentation used have been described.[13]

Crystal Structure of 10a. A summary of the crystallographic work is given in Table 1. The X-ray data were collected at 200 K. The structure was solved by direct methods and refined by weighted full-matrix least squares analysis on F^2. All hydrogen atoms were easily located on the difference map and included in the refinement as isotropic contributors. Slight secondary extinction effects were corrected during the last cycles of refinement.

Table 1. Crystal Data for Compound 10a

Crystal Data	
formula	$C_{32}H_{32}N_6$
crystal habit	colorless prisms
crystal size (mm)	0.3 × 0.2 × 0.2
symmetry	monoclinic $P2_1/a$
wavelength (Å), T (K)	1.5418, 200
unit cell deter.	least squares fit from 52 refl (θ < 30°)
unit cell dimen	a = 9.022(1) Å, b = 28.646(3) Å, c = 10.012(1) Å, β = 91.36(1)°
packing: V (Å^3), Z	2586.8(5), 4
M, D_c (g cm^{-3}), F(000)	500.64, 1.296, 1064
absorption coeff (mm^{-1})	0.609
Experimental Data	
technique	four-circle diffractometer, SEIFERT XRD-3000S bisecting geometry, graphite-oriented monochromator $\omega/2\theta$ scans, scan width (deg) 1.5 + 0.15 tan θ detector apertures 1 × 1°, reference reflections, 2; no decay
no. meas reflct	4065
no. indep reflct	3849
R_{int}	0.010
index ranges	$0 < h < 10$, $0 < k < 32$, $-11 < l < 11$
θ range	3−60°
Refinement Data	
method	full-matrix least squares on F^2
data/paramtr	3849/542
hydrogen atoms	located on the difference map and refined isotropically
goodness of fit on F^2	1.178
final R indices [$I > 2\sigma(I)$]	R = 0.0544, R_w = 0.0774
R indices (all data)	R = 0.0668, R_w = 0.0810
extinction coefficient[14]	0.0024(2)
largest diff peak and hole	0.20 and −0.20 e Å^{-3}
computing programs	XRAY76,[15] SIR92,[16] SHELX93[17]
scattering factors	*International Tables for X-ray Crystallography*[18]

Bis(guanidines) 8 and 9. General Procedure. To a solution of the appropriate bis(carbodiimide) **6** or **7** (0.34 mmol) in anhydrous dichloromethane (15 mL) was added the corresponding amine (1.02 mmol). The resultant mixture was stirred at room temperature for 15−30 min and then the solvent was removed under reduced pressure, and the solid residue was treated with diethyl ether, filtered, and air-dried to give the corresponding bis(guanidine) **8** or **9**, which was recrystallized from the adequate solvent. In the case of

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(18) *International Tables for X-ray Crystallography*, Kynoch Press: Birmingham, 1974; Vol. IV, p 72.

reaction with ammonia, it was bubbled through a solution of the appropriate bis(carbodiimide) in anhydrous dichoromethane at room temperature for 20−30 min and worked up similarly.

8a: 98% yield; mp 173−175 °C, colorless prisms (chloroform); IR (Nujol) 1644, 1632, 1586, 1567, 1483 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.79 (s, 8H), 4.50 (s, 4H), 6.91−7.12 (m, 14H), 7.25 (d, 4H, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$) δ 34.5, 122.6, 123.0, 126.8, 129.5, 136.0, 142.7, 150.9; mass spectrum (relative intensity) 474 (M^+, 7), 221 (14), 212 (53), 106 (100). Anal. Calcd for $C_{30}H_{30}N_6$: C, 75.92; H, 6.37; N, 17.71. Found: C, 75.77; H, 6.21; N, 17.82.

8b: 99% yield; mp 288−290 °C, white prisms (dichloromethane); IR (Nujol) 1665, 1487, 1454, 1395, 751 cm^{-1}; ^1H NMR ($CDCl_3/CF_3CO_2H$) δ 2.84 (s, 6H), 2.94−3.02 (m, 8H), 6.42 (s, br, 1H), 7.15−7.38 (m, 18H), 8.47 (s, br, 1H); ^{13}C NMR ($CDCl_3$ / CF_3CO_2H) δ 28.9, 32.0 (br), 128.0, 128.9, 130.5, 131.0, 138.9 (br), 156.3, one quaternary carbon was not observed; mass spectrum (FAB^+) (relative intensity) 504 (37), 503 (M^+ + 1, 100), 502 (19), 176 (56). Anal. Calcd for $C_{32}H_{34}N_6$: C, 76.45; H, 6.82; N, 16.73. Found: C, 76.28; H, 6.91; N, 16.82.

8c: 89% yield; mp 242−244 °C, colorless prisms (dichloromethane/diethyl ether); IR (Nujol) 1639, 1596, 1515, 1490, 748 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.97 (d, 12H, J = 3.4 Hz), 2.82 (s, 8H), 3.41−3.63 (m, 4H), 6.98−7.23 (m, 18H); ^{13}C NMR ($CDCl_3$) δ 23.0, 32.7 (br), 43.5 (br), 123.2 (br), 126.9, 129.3, 136.0, 142.9 (br), 149.3 (br); mass spectrum (relative intensity) 558 (M^+, 5), 221 (59), 219 (96), 131 (87), 106 (100). Anal. Calcd for $C_{36}H_{42}N_6$: C, 77.37; H, 7.58; N, 15.05. Found: C, 77.25; H, 7.67; N, 15.10.

8d: 80% yield; mp 185−187 °C, colorless prisms (dimethyl sulfoxide); IR (Nujol) 1639, 1632, 1591, 1523, 1494 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.67 (s, 8H), 4.25 (s, 4H), 5.44 (s, br, 2H), 6.69−7.18 (m, 28H); ^{13}C NMR (DMSO-d_6) δ 31.4, 44.6, 122.5 (br), 123.4 (br), 126.3, 126.3, 127.1, 127.8, 128.7 (br), 135.5 (br), 140.6, 148.7, 157.3; mass spectrum (FAB^+) (relative intensity) 656 (45), 655 (M^+ + 1, 100), 654 (63), 653 (22). Anal. Calcd for $C_{44}H_{42}N_6$: C, 80.69; H, 6.47; N, 12.84. Found: C, 80.74; H, 6.36; N, 12.99.

8e: 90% yield; mp 193−195 °C, colorless prisms (chloroform); IR (Nujol) 1632, 1589, 1519, 1485, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.31 (d, 6H, J = 6.5 Hz), 2.33−2.70 (m, 8H), 3.90−3.96 (m, 2H), 5.06 (s, br, 2H), 6.73−7.25 (m, 28H); ^{13}C NMR ($CDCl_3$) δ 21.7, 31.6, 49.5 (br), 123.2 (br), 126.0, 126.2, 126.6, 126.9, 127.9, 128.8 (br), 136.2, 142.6, 144.8, 147.6 (br); mass spectrum (FAB^+) (relative intensity) 685 (52), 684 (100), 683 (M^+ + 1, 54), 219 (34). Anal. Calcd for $C_{46}H_{46}N_6$: C, 80.90; H, 6.79; N, 12.31. Found: C, 81.03; H, 6.54; N, 12.44.

8f: 88% yield; mp 180−182 °C, colorless prisms (benzene/*n*-hexane); IR (Nujol) 1618, 1586, 1570, 1491, 1459 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.17 (s, 4.6H), 2.69−2.89 (m, 15.4H), 6.75−7.21 (m, 18H); ^{13}C NMR ($CDCl_3$) δ 32.5 (br), 33.7 (br), 38.4 (br), 39.21 (br), 121.8 (br), 122.3 (br), 126.9 (br), 129.2 (br), 135.5 (br), 144.2 (br), 155.9 (br); mass spectrum (relative intensity) 530 (M^+, 9), 266 (23), 221 (43), 46 (100). Anal. Calcd for $C_{34}H_{38}N_6$: C, 76.94; H, 7.22; N, 15.84. Found: C, 77.03; H, 7.18; N, 15.78.

9a: 90% yield; mp 310−312 °C, colorless prisms (dichloromethane/diethyl ether); IR (Nujol) 3362, 1666, 1639, 1591, 1570 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.55 (s, 8H), 4.77 (s, br, 4H), 6.91−7.30 (m, 18H); ^{13}C NMR ($CDCl_3$) δ 72.0, 122.4, 128.5 (br), 129.7, 131.1, 144.3 (br), 148.9, one quaternary carbon was not observed; mass spectrum (FAB^+) (relative intensity) 508 (38), 507 (M^+ + 1, 100), 307 (36), 176 (28). Anal. Calcd for $C_{30}H_{30}N_6O_2$: C, 71.11; H, 5.97; N, 16.60. Found: C, 70.98; H, 5.85; N, 16.73.

9b: 90% yield; mp 234−237 °C, colorless prisms (dichloromethane/diethyl ether); IR (Nujol) 3384, 1644, 1597, 1515, 1484 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.16−3.38 (m, 12H), 3.38−3.46 (m, 2H), 3.81−4.82 (m, 10H), 6.42−7.26 (m, 18H); (DMSO-d_6) δ (r.t.): 1.20−1.24 (m, 12H), 3.95 (m, 2H), 4.31 (s, br, 8H), 5.48 (s, br, 1H), 6.09 (s, br, 1H), 6.54−7.24 (m, 18H); (DMSO-d_6) δ (90 °C): 1.19 (d, 12H, J = 6.3 Hz), 3.95−3.99 (m, 2H), 4.22 (s, br, 8H), 5.20 (s, br, 2H), 6.52−7.16 (m, 18H); ^{13}C NMR (DMSO-d_6) δ 22.4, 42.4, 65.5 (br), 69.4 (br), 121.6 (br), 128.2 (br), 129.1 (br), 131.2 (br), 141.9 (br), 147.0, 145.9 (br); HRMS calcd for $C_{36}H_{42}N_6O_2$ (M^+): 590.336925. Found: 590.335570. Anal. Calcd for $C_{36}H_{42}N_6O_2$: C, 73.18; H, 7.17; N, 14.23. Found: C, 73.43; H, 7.03; N, 14.10.

9c: 87% yield; mp 98−100 °C, white prisms (diethyl ether/*n*-hexane); IR (Nujol) 1647, 1604, 1509, 741, 701 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.35−1.60 (m, 6H), 3.37−5.23 (m, 12H), 6.34−7.52 (m, 28H); ^{13}C NMR ($CDCl_3$) δ 22.7, 50.4 (br), 67.7, 69.3, 69.6, 71.7, 117.4, 120.5, 122.1, 122.9, 126.9, 128.3, 129.1, 129.9, 130.3, 131.9, 132.0, 132.1, 132.2, 140.4, 141.9, 144.3, 145.0, 145.6, 146.3, 147.6, 149.2; mass spectrum (FAB^+) (relative intensity) 716 (51), 715 (M^+ + 1, 100), 714 (14), 358 (10). Anal. Calcd for $C_{46}H_{46}N_6O_2$: C, 77.28; H, 6.49; N, 11.76. Found: C, 77.47; H, 6.35; N, 11.87.

Bis(guanidines) 10 and 11. General Procedure. To a stirred solution of the appropriate bis(carbodiimide) **6** or **7** (0.45 mmol) in anhydrous dichloromethane (75 mL) was added dropwise a solution of the α,ω-diamino compound (0.45 mmol) in the same solvent (30 mL) at room temperature under nitrogen for 7 h. After the addition, the solvent was removed under reduced pressure and the crude product was either chromatographed on a silica gel column or recrystallized from the appropriate solvent to give **10** or **11**.

10a: (silica gel, ethanol/ammonium hydroxide 30:1); 88% yield; mp 319−321 °C, colorless prisms (dimethyl sulfoxide); IR (Nujol) 1633, 1596, 1575, 1527, 1485 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.42−3.21 (m, 10H), 3.94−4.22 (m, 4H), 5.42 (s, br, 2H), 6.97−7.30 (m, 16H); ^{13}C NMR ($CDCl_3$) δ 32.4 (br), 40.9 (br), 122.2 (br), 123.3 (br), 127.2, 128.6 (br), 135.6 (br), 136.1 (br), 139.7 (br), 147.8 (br), 150.1; mass spectrum (relative intensity) 500 (M^+, 3), 220 (59), 219 (100), 174 (58). Anal. Calcd for $C_{32}H_{32}N_6$: C, 76.77; H, 6.44; N, 16.79. Found: C, 76.58; H, 6.54; N, 16.87.

10b: (silica gel, ethanol/ammonium hydroxide 40:1); 80% yield; mp 292−294 °C, colorless prisms; IR (Nujol) 1650, 1634, 1591, 1575, 1542 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.30−1.65 (m, br, 2H), 2.42−3.60 (m, br, 12H), 5.20 (s, br, 2H), 6.70−7.40 (m, 18H); ^{13}C NMR ($CDCl_3$) δ 27.3 (br), 31.7 (br), 41.2 (br), 121.4 (br), 123.5 (br), 126.1, 129.3, 135.9 (br), 138.4 (br), 148.4 (br); mass spectrum (FAB^+) (relative intensity) 516 (50), 515 (M^+ + 1, 100), 514 (22), 307 (22). Anal. Calcd for $C_{33}H_{34}N_6$: C, 77.01; H, 6.66; N, 16.33. Found: C, 77.10; H, 6.72; N, 16.17.

10c: (silica gel, ethanol/ammonium hydroxide 60:1); 74% yield; mp 253−255 °C (dec), white prisms; IR (Nujol) 1639, 1590, 1514, 1481, 1455 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.27−2.46 (m, br, 2H), 2.60−2.78 (m, br, 4H), 3.06−3.58 (m, br, 14H), 4.28−4.67 (m, br, 2H), 6.83−7.40 (m, 18H); ^{13}C NMR ($CDCl_3$) δ 31.0 (br), 41.3 (br), 69.8, 70.2, 123.3 (br), 123.9 (br), 127.0 (br), 129.6 (br), 136.1, 148.6 (br), one quaternary carbon was not observed; mass spectrum (FAB^+) (relative intensity) 590 (50), 589 (M^+ + 1, 100), 588 (39), 587 (16). Anal. Calcd for $C_{36}H_{40}N_6O_2$: C, 73.44; H, 6.85; N, 14.27. Found: C, 73.58; H, 6.80; N, 14.11.

11a: 94% yield; mp 296−298 °C, colorless prisms (acetonitrile); IR (Nujol) 1660, 1651, 1644, 1597, 1506 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.94−3.08 (m, 2H), 3.27−3.42 (m, 2H), 4.24 (d, 2H, J = 8.6 Hz + 2 NH), 4.52 (d, 2H, J = 10.2 Hz), 4.79 (d, 2H, J = 8.6 Hz), 4.80 (d, 2H, J = 10.2 Hz), 6.87 (d, 2H, J = 7.3 Hz), 6.96−7.04 (m, 4H), 7.24−7.37 (m, 8H), 7.49 (s, 2H), 7.77 (d, 2H, J = 7.6 Hz); ^{13}C NMR ($CDCl_3$) δ 46.2, 71.9, 73.3, 122.7, 123.0, 123.4, 127.8, 127.9, 129.3, 130.3, 130.8, 131.0, 132.0, 140.3, 149.7, 151.0; mass spectrum (FAB^+) (relative intensity) 534 (55), 533 (M^+ + 1, 100), 532 (12), 280 (11). Anal. Calcd for $C_{32}H_{32}N_6O_2$: C, 72.16; H, 6.06; N, 15.78. Found: C, 72.55; H, 6.21; N, 15.32.

11b: (silica gel, ethanol/ammonium hydroxide 40:1), 77% yield; mp 246−248 °C, colorless prisms (acetonitrile); IR (Nujol) 3410, 1649, 1633, 1591, 1543 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.45−1.49 (m, 2H), 3.08−3.12 (m, 2H), 3.34−3.62 (m, 4H), 3.96 (d, 2H, J = 8.1 Hz), 4.44 (d, 2H, J = 12.7 Hz), 4.79 (d, 2H, J = 8.1 Hz), 5.13 (d, 2H, J = 12.7 Hz), 6.75−7.01 (m, 10H), 7.19−7.41 (m, 6H), 8.01 (d, 2H, J = 7.3 Hz); ^{13}C NMR ($CDCl_3$) δ 28.4, 37.8, 70.5, 73.1, 121.0, 121.4, 122.5, 123.0, 125.2, 129.3, 129.9, 130.1, 131.2, 132.5, 139.6, 147.7, 149.1; mass spectrum (FAB^+) (relative intensity) 548 (M^+, 43), 547 (M^+ + 1, 100),

329 (11), 307 (22). Anal. Calcd for $C_{33}H_{34}N_6O_2$: C, 72.50; H, 6.27; N, 15.37. Found: C, 72.67; H, 6.15; N, 15.48.

11c: (silica gel, ethanol/ammonium hydroxide 60:1), 77% yield; mp 320−324 °C, colorless prisms (chloroform); IR (Nujol) 1639, 1595, 1520, 1493, 1336 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.02−3.90 (m, 12H), 4.10−4.77 (m, 10H), 6.72−7.39 (m, 18H); ^{13}C NMR ($CDCl_3$) δ 41.8, 69.5, 70.2, 70.4, 123.3 (br), 128.8, 129.3, 132.0 (br), 148.4, one methine carbon and one quaternary carbon were not observed; mass spectrum (FAB^+) (relative intensity) 623 (9) 622 (42), 621 ($M^+ + 1$, 100), 620 (8). Anal. Calcd for $C_{36}H_{40}N_6O_4$: C, 69.66; H, 6.50; N, 13.54. Found: C, 69.79; H, 6.41; N, 13.31.

Macrocyclic Bis(guanidinium) Salts 12 and 13. Method A. A stream of dry HCl was bubbled through a solution of the appropriate bis(guanidine) **8** or **11** (0.2 mmol) in anhydrous dichloromethane (30 mL) at room temperature for 15 min. After cooling at 0 °C the precipitated solid was separated by filtration, washed with diethyl ether, and air-dried to give **12** or **13**, which was recrystallized fron the adequate solvent.

12a: 78% yield; mp >350 °C, colorless prisms (dichloromethane/diethyl ether); IR (Nujol) 3329, 3138, 1654, 1639, 1580 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.95 (s, 8H), 7.13−7.49 (m, 20H), 9.91 (s, 4H); ^{13}C NMR ($CDCl_3$) δ 31.1, 127.5, 127.9, 128.0, 130.4, 133.2, 138.4, 155.6; mass spectrum (FAB^+) (relative intensity) 476 (34), 475 ($M^+ + 1 - 2HCl$, 86), 474 (13), 307 (26). Anal. Calcd for $C_{30}H_{32}Cl_2N_6$: C, 65.81; H, 5.89; N, 15.35. Found: C, 65.53; H, 5.72; N, 15.02.

12c: 80% yield; mp >350 °C, colorless prisms (dichloromethane/diethyl ether); IR (Nujol) 3373, 3171, 1634, 1597, 1575 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.74 (s, 8H), 3.09 (s, 12H), 7.12−7.16 (m, 18H), 10.47 (s, br, 2H); ^{13}C NMR ($CDCl_3$) δ 31.9 (br), 40.7, 127.5 (br), 127.3, 127.6, 129.8 (br), 134.8, 135.3, 156.4; mass spectrum (relative intensity) 531 (30), 530 ($M^+ - 2HCl$, 77), 487 (52), 486 (100). Anal. Calcd for $C_{34}H_{40}Cl_2N_6$: C, 67.65; H, 6.68; N, 13.92. Found: C, 67.44; H, 6.72; N, 14.05.

13c: 81% yield; mp 272−274 °C, colorless prisms (dichloromethane); IR (Nujol) 1655, 1634, 1586, 1533, 1507 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.67−1.82 (m, 2H), 2.89−3.15 (m, 4H), 4.47−4.82 (m, 8H), 7.34−7.55 (m, 18H), 9.80 (s, 4H); ^{13}C NMR (DMSO-d_6) δ 25.9, 39.9, 69.3, 127.9, 128.1, 129.5, 131.2, 134.2, 134.8, 154.7; mass spectrum (FAB^+) (relative intensity) 549 (9), 548 (40), 547 ($M^+ + 1 - 2HCl$, 100), 307 (11). Anal. Calcd for $C_{33}H_{36}Cl_2N_6O_2$: C, 63.97; H, 5.86; N, 13.56. Found: C, 64.13; H, 5.90; N, 13.74.

Method B. To a solution of the corresponding bis(guanidine) **8**, **10**, or **11** (0.015 mmol) in dry chloroform (19 mL) was added concentrated hydrochloric acid (1 mL). The mixture was stirred at room temperature for 1 h and the precipitated solid was collected by filtration, washed with diethyl ether, and recrystallized from the adequate solvent.

12b: 91% yield; mp 338−340 °C, colorless prisms (dichloromethane); IR (Nujol) 3207, 3110, 1650, 1630, 1603 cm^{-1}; ^1H NMR (CD_3OD) δ 2.84 (s, br) + 3.22 (s, br) (=14H), 7.32−7.58 (m, 16H); ^{13}C NMR (CD_3OD) δ 29.9 (br), 34.58 (br), 129.5, 130.1, 130.9, 132.4 (br), 134.5 (br), 141.2 (br), 157.9 (br); mass spectrum (FAB^+) (relative intensity) 503 (42), 502 ($M^+ + 1 - 2HCl$, 100), 501 (11), 221 (11). Anal. Calcd for $C_{32}H_{36}N_6Cl_2$: C, 66.78; H, 6.30; N, 14.60. Found: C, 66.91; H, 6.18; N, 14.41.

13a: 89% yield; mp 303−304 °C, colorless prisms (methanol); IR (Nujol) 1635, 1625, 1614, 1594, 1574 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.67−3.42 (m, 10H), 4.29−4.40 (m, 2H), 6.48 (s, br, 1H), 7.32−7.66 (m, 18H), 8.78 (s, 2H), 10.47 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 27.6, 30.6, 31.1, 34.4, 38.5, 41.2, 127.4, 127.8, 128.3, 128.7, 128.9, 129.4, 129.6, 130.0, 130.5, 130.9, 131.7, 131.7, 133.5, 139.3, 139.4, 140.2, 140.9, 154.2, 154.8; mass spectrum (FAB^+) (relative intensity) 502 (38), 501 ($M^+ + 1 - 2HCl$, 100), 500 (11), 329 (8). Anal. Calcd for $C_{32}H_{34}Cl_2N_6$: C, 67.01; H, 5.97; N, 14.65. Found: C, 67.17; H, 5.79; N, 14.39.

13b: 92% yield; mp 276−278 °C, colorless prisms (dichloromethane); IR (Nujol) 1649, 1627, 1612, 1581, 1453 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.35−3.43 (m, 2H), 4.00−4.09 (m, 2H), 4.29 (d, 2H, J = 11.3 Hz), 4.40 (d, 2H, J = 11.0 Hz), 4.73 (d, 2H, J = 11.0 Hz), 4.79 (d, 2H, J = 11.3 Hz), 7.36−7.54 (m, 16H), 7.72−7.77 (m, br, 2H), 8.85 (s, 2H), 9.54 (s, 2H); ^{13}C NMR (DMSO-d_6) δ 41.2 (br), 68.9, 69.1, 128.1, 128.2, 128.4, 129.0, 129.1, 129.9, 130.0, 132.5, 133.0, 134.3, 134.8, 136.7, 154.9; mass spectrum (FAB^+) (relative intensity) 535 (11), 534 (50), 533 ($M^+ + 1 - 2HCl$, 100), 280 (97). Anal. Calcd for $C_{32}H_{34}Cl_2N_6O_2$: C, 63.47; H, 5.66; N, 13.88. Found: C, 63.29; H, 5.74; N, 13.59.

Extraction Experiments. To a solution of the bis(guanidine) salt **12c** or **13b** (0.051 mmol) in chloroform (1 mL) was added a solution of sodium *p*-nitrobenzoate (0.103 mmol) in water (1 mL). The resultant mixture was well-stirred at room temperature for 8 h and then the organic layer was separated and the aqueous one was well-washed with chloroform. The combined organic layers were dried over anhydrous $MgSO_4$, and the solvent was removed under reduced pressure to give the corresponding bis(guanidinium) salt **8f**·2(*p*-$O_2N-C_6H_4-$COOH) or **11a**·2(*p*-$O_2N-C_6H_4-$COOH).

8f·2(*p*-$O_2N-C_6H_4-$COOH): 95% yield; mp 169−171 °C, colorless prisms (dimethyl sulfoxide); IR (Nujol) 1646, 1632, 1601, 1540, 1515, 1340 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.74 (s, 12H), 2.94 (s, 8H), 7.13−7.38 (m, 20H), 7.99 (d, 4H, J = 8.7 Hz), 8.16 (d, 4H, J = 8.7 Hz); ($CDCl_3$) δ: 2.71 (s, 12H), 2.90 (s, 8H), 7.04−7.27 (m, 20H), 8.02 (d, 4H, J = 8.4 Hz), 8.10 (d, 4H, J = 8.4 Hz); ^{13}C NMR (DMSO-d_6) δ 31.3, 39.1, 122.9, 123.7, 125.1, 127.0, 129.8, 130.1, 135.3, 138.8, 142.3, 148.6, 154.8, 167.6; ($CDCl_3$) δ: 31.6, 40.0, 123.1, 125.4 (br), 126.9 (br), 127.9, 130.4, 131.3, 135.7 (br), 136.2, 142.6, 149.2, 158.1, 170.9; mass spectrum (relative intensity) 532 (2), 531 (60), 530 (29), 487 (32), 486 (100). Anal. Calcd for $C_{48}H_{48}N_8O_8$: C, 66.64; H, 5.60; N, 12.96. Found: C, 67.01; H, 5.58; N, 12.69.

11a·2(*p*-$O_2N-C_6H_4-$COOH): 92% yield; ^1H NMR (DMSO-d_6) δ 3.19−3.62 (m, 4H), 4.37−4.83 (m, 8H), 7.22−7.46 (m, 18H), 7.97 (d, 4H, J = 8.8 Hz), 8.20 (d, 4H, J = 8.8 Hz), 9.22 (s, br, 4H); ^{13}C NMR (DMSO-d_6) δ 41.9, 69.4, 123.1, 126.6, 130.3, 131.7, 134.4, 137.6, 142.5, 148.7, 153.7, 167.3.

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Supporting Information Available: Summary of crystal data and structure refinement, atomic coordinates, bond lengths, bond angles, anisotropic displacement parameters, and hydrogen coordinates for compound **10a** (26 pages). This material is contained in libraries on microfiche, inmediately follows 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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