Design, Synthesis, and Characterization of Tyrosinophanes, a Novel Family of Aromatic-Bridged Tyrosine-Based Cyclodepsipeptides

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A simple two-step design strategy has been developed for the synthesis of a large variety of a new class of tyrosine-based aromatic (Ph or Pyr) bridged cyclodepsipeptides (tyrosinophanes). The design is flexible with respect to the size of the ring and the nature of the bridging unit and permits the incorporation of a variety of amino acid residues inside or outside or both inside and outside the ring as illustrated here with the preparation of tyrosine-based macrocycles with aromatic (Ph or Pyr), cage-like alicyclic (adamantane) or simple polymethylene bridging units in ring sizes varying from 26-membered to 78-membered and containing leucine residues as part of the ring or as pendants on the exterior or both inside and outside the macrocyclic ring. ^{1}H NMR, FT-IR, and CD studies have indicated open-ring structures for these macrocycles. A noteworthy feature of the strategy is the formation of the 1 + 1 + 1 + 1 catenane arising from the interlocking of sebacoyl-bridged tyrosine rings. The potential of tyrosinophanes to serve as simple aromatic hosts in the study of π-cation type interactions was illustrated with Pyr-bridged macrocycles (**6b**−**8b**) using *N*-methylacridinium hexafluorophosphate as the pyridinium guest. The K_{assoc} value with **6b** was found to be 8.95×10^3 M^{-1}.

Introduction

Creation of new molecules architecturally beautiful and of potential importance in the context of designing simple models for studying biomolecular interactions continues to stimulate the imagination of synthetic chemists.[1] Cyclic peptides[2] form an attractive class of compounds with multiple and varied biological functions. Recently,[3] cyclic peptides constructed from an even number of D and L amino acids have been shown to self-assemble in tube-like structures through which ions and neutral molecules can be transported across lipid bilayers. An important structural feature of these peptides is the presence of a hollow interior with side chains projecting outward.

Large macrocyclic peptides with open pores are rarely seen in nature.[4] More often, the interior of the macrocycle collapses to some minimum space accompanied by folding of the backbone and formation of intramolecular hydrogen bonds.[5]

Design of cyclic peptides wherein amino acid side chains would form part of the cyclic backbone[6] appeared to us an attractive proposition for creating large rings with open pores useful for studying host−guest chemistry or as transport vehicles for biologically important ions or neutral molecules. The design strategy envisaged the use of conformationally rigid, aromatic (Ph or Pyr)[7] or

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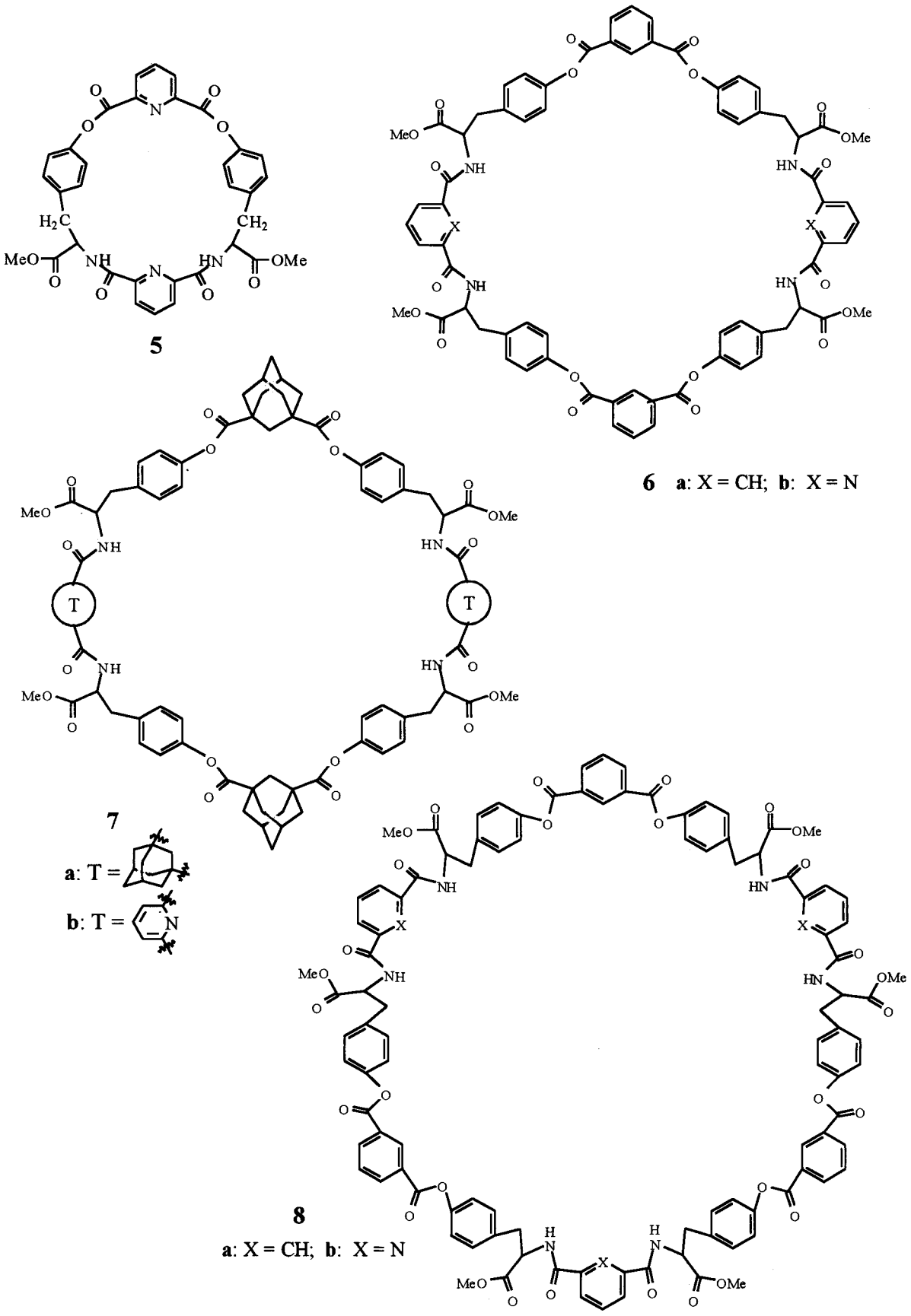
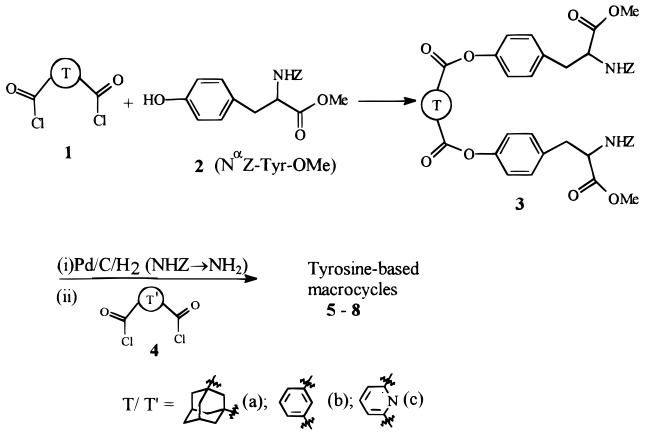


Figure 1.

polycyclic cage-like (Adm)[8] units in conjunction with amino acids with functionalized side chains for crafting the cyclic backbone.

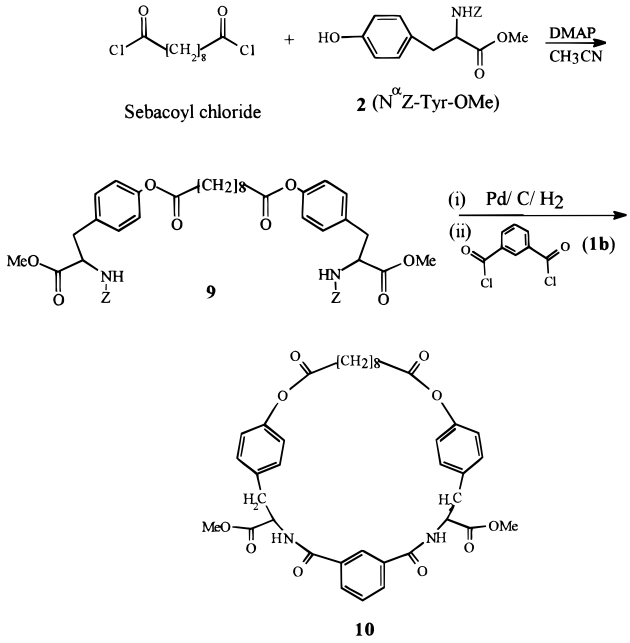
As a first illustration of this strategy, we had recently[9] described the preparation of a large variety of Ser-based macrocyclic peptides with Ser CH_2OH side chain as part

Scheme 1



Step 1	Step 2	Macrocycle (Yield %)			
T	T'	(1+1)	(2+2)	(3+3)	([1+1+1+1] catenane)
1b	**4b**	–	**6a** (23)	**8a** (17)	–
1b	**4c**	–	**6b** (18)	**8b** (23)	–
1c	**4c**	**5** (23)	–	–	–
1a	**4a**	–	**7a** (25)	–	–
1a	**4c**	–	**7b** (20)	–	–
1b	**4a**	–	–	–	–

Scheme 2



of the cyclic backbone. Several of these cyclic peptides were demonstrated to act as efficient carriers of alkali metal ions across lipid bilayer membranes. Solution (^{1}H NMR, FT-IR, and CD spectroscopy) as well as solid state (X-ray crystallography) studies[10] clearly ruled out the presence of open pores in larger (24−26-membered) Ser-based macrocycles. The 18-membered macrocycles containing an alternating sequence of L-serine and aromatic (Ph or Pyr) units were, however, demonstrated to adopt relatively flat ring conformation and formed tubular structures using aromatic $\pi-\pi$ interaction as the main organizing force.[11]

We demonstrate herein the effectiveness of tyrosine side chain in creating large, (26−78-membered) macrocyclic peptides with rigid cyclic backbone and open-ring structures. Tyrosine was considered particularly attractive because of the presence of a phenolic OH in its side chain, suitable for depsi bond formation, and a phenyl ring whose incorporation into the cyclic backbone would not only provide the conformational rigidity most desirable for open pore formation but would also impart required lipophilicity for membrane penetration. A large family of tyrosine-based cyclodepsipeptides, namely, aromatic-bridged macrocycles with the general structure (-Ar-COO-Tyr-NHCO-)$_n$ (Ar = Ph or Pyr unit; Tyr = tyrosine; n = 2, 4, and 6; **5**, **6a**−**b**, **8a**−**b**, Figure 1), adamantane-bridged macrocycles with structure (-Adm-COO-Tyr-NHCO-)$_4$ and (-Adm-COO-Tyr-NHCO-Pyr-CO-NH-Tyr)$_2$ (**7a** and **7b**, respectively, in Figure 1), sebacoyl-bridged regioisomeric cyclic monomers (-(CH$_2$)$_8$-COO-Tyr-NH-CO-Ar-CONH-Tyr-OCO-) (**10**, Scheme 2) and (-Ar-COO-Tyr-NHCO-(CH$_2$)$_8$-CONH-Tyr-OCO-) (**11**, Scheme 3), and the topologically interesting interlocked molecule, the 1 + 1 + 1 + 1 catenane (**12**, Scheme 3), were prepared and examined for conformational preferences by ^{1}H NMR, FT-IR, and CD studies. In another series, leucine residue was incorporated inside the ring, outside the ring, and both inside/outside the ring (**15**−**17**, Figure 2) to provide tyrosine macrocycles with increasing lipophilicity and improved capability for membrane penetration. The 42-membered all-Tyr cyclodepsipeptide **18** was also crafted with the same goal in mind.

The 26−78-membered tyrosinophanes with electron rich phenyl rings (of tyrosine) provided attractive models for host−guest studies with electron-deficient substrates. The aromatic-bridged macrocycles **6**−**8** were particularly chosen for molecular recognition studies with *N*-methylacridinium hexafluorophosphate as the guest. The adamantane-bridged, Leu-containing macrocycles (**15**−**18**) were examined for membrane ion-transport properties.

Results and Discussion

The two-step synthetic strategy (Scheme 1) for the aromatic or nonaromatic-bridged tyrosinophanes involved first the condensation of an N, C protected tyrosine (**2**) with 1,3-dicarbonyl dichloride **1** [T = phenyl (Ph) or pyridyl (Pyr) or adamantyl (Adm) unit] to give bis-Tyr derivative **3** (Z = COOCH$_2$Ph) which in the second step was N-deprotected and coupled with another molecule of the same (**1**) or a different template (**4**) under high dilution conditions to give tyrosine macrocycles **5**, **6a**−**b**, and **8a**−**b** (Figure 1) containing alternating repeats of Tyr and Ar units in 26-, 52-, and 78-membered rings, respectively. The ring size of the macrocycle could be controlled through 1 + 1, 2 + 2 or 3 + 3 cyclizations by selecting an appropriate template (T/T′). For example, while with T as Ph and T′ as Ph or Pyr, the reaction yielded a mixture of 52-membered [2 + 2] and 78-membered [3 + 3] macrocycles, the 26-membered [1 + 1] macrocycle (**5**) was the only product obtained when Pyr unit was used for both T and T′ in **1** and **4**. The influence of an aromatic template on the ability to control

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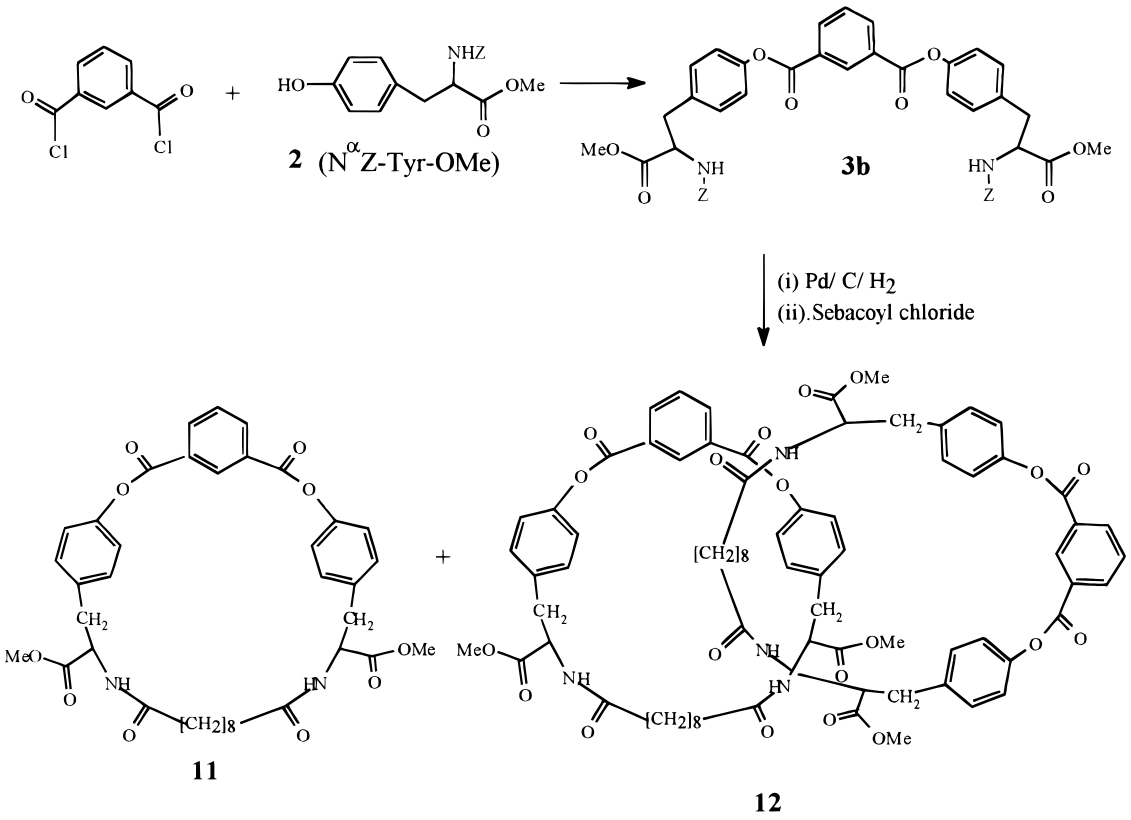
Scheme 3

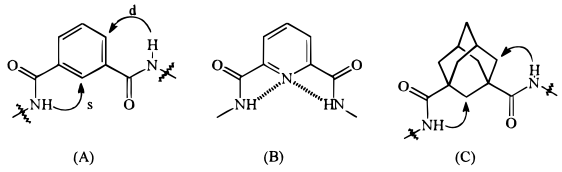


the ring size was clearly brought out when a nonaromatic template was used in the reaction. For example, replacement of Ph or Pyr in **1** and **4** with an adamantyl unit (**1**, **4**, T = T′ = Adm) resulted in the sole formation of [2 + 2] macrocycle **7a**. The [2 + 2] cyclization persisted even with Pyr for T′ in the final step (**1**, T = Adm; **4**, T′ = Pyr). The details of products obtained under different conditions are listed in Scheme 1. All the products were fully characterized by spectroscopic and analytical data. The FAB MS spectra (Supporting Information) confirmed the cyclic oligomeric nature of the products.

The highly symmetrical nature of 2 + 2 and 3 + 3 macrocycles in pairs **6a**/**8a** and **6b**/**8b** was evident from the appearance of a single set of resonances for Tyr and Ar (Ph in **a** and Pyr in **b** series) units in their ^{1}H and ^{13}C NMR spectra. The chemical shifts were almost identical in 2 + 2 and 3 + 3 macrocycles, suggesting similar conformations for these molecules. A comparison of the ^{1}H NMR (400 MHz, $CDCl_3$) spectra of **6a**/**8a** and **6b**/**8b** is provided in Supporting Information.

While molecules of the **a** series (**6a**−**8a**) have their amide NHs almost free as indicated by their normal chemical shifts and relatively larger temperature coefficients ($d\delta/dT$ = −5 to −7 ppb/K) in $CDCl_3$, the **b** macrocycles (**5b**−**8b**) show low-field NHs (downfield shifted by ∼1.5−2.0 ppm) and comparatively low $d\delta/dT$ values (∼ −1 to −3 ppb/K). suggesting involvement of amide NHs in intramolecular hydrogen bonding.

Further information about the conformation of macrocycles **5**−**8** was provided by ROESY NMR experiments (Supporting Information). In the case of both **6a** and **8a**, the presence of strong cross-peaks between NH and the aromatic singlet and aromatic doublet indicated anti orientation of isophthaloyl carbonyls (A). In macrocycles **5b**−**8b** containing a pyridyl unit for T′, no such cross-peaks were observed, thus suggesting syn orientation of the 2, 6 amide groups (B). The conformation B is further stabilized by intramolecular hydrogen bonding as indicated by considerable downfield shift and the low $d\delta/dT$ values for the NH protons in **5b**−**8b** (vide supra). The adamantane-containing macrocycle **7a** showed strong cross-peak between NH and adamantane methylenes, supporting anti conformation for adamantane 1, 3 amide groups (C). These conformational preferences suggest an



open-ring structure for tyrosine macrocycles **5**−**8** as also supported by absence of any other significant cross-peaks in their ROESY spectra (Supporting Information). The open-ring conformation was also indicated by similarity in the chemical shifts of Tyr and Ar signals in the ^{1}H NMR spectra of macrocycles **5**−**8** and their corresponding bis Tyr precursor **3**. The CD spectra of **5**−**8** were devoid of any secondary structural features, thus further supporting the open-ring conformation.

Unlike cystinophanes[7] which showed internal ring collapse due to aromatic face-to-face stacking, no indication of any intramolecular aromatic $\pi-\pi$ interaction either face-to-face or edge-to-face was evident from the ^{1}H NMR spectra of tyrosinophanes **6a**−**b**/**8a**−**b**. The smallest 26-membered macrocycle **3**, obtained when T = T′ = Pyr, arises presumably by [1 + 1] ring closure facilitated by reduction of the 120° angle (expected for

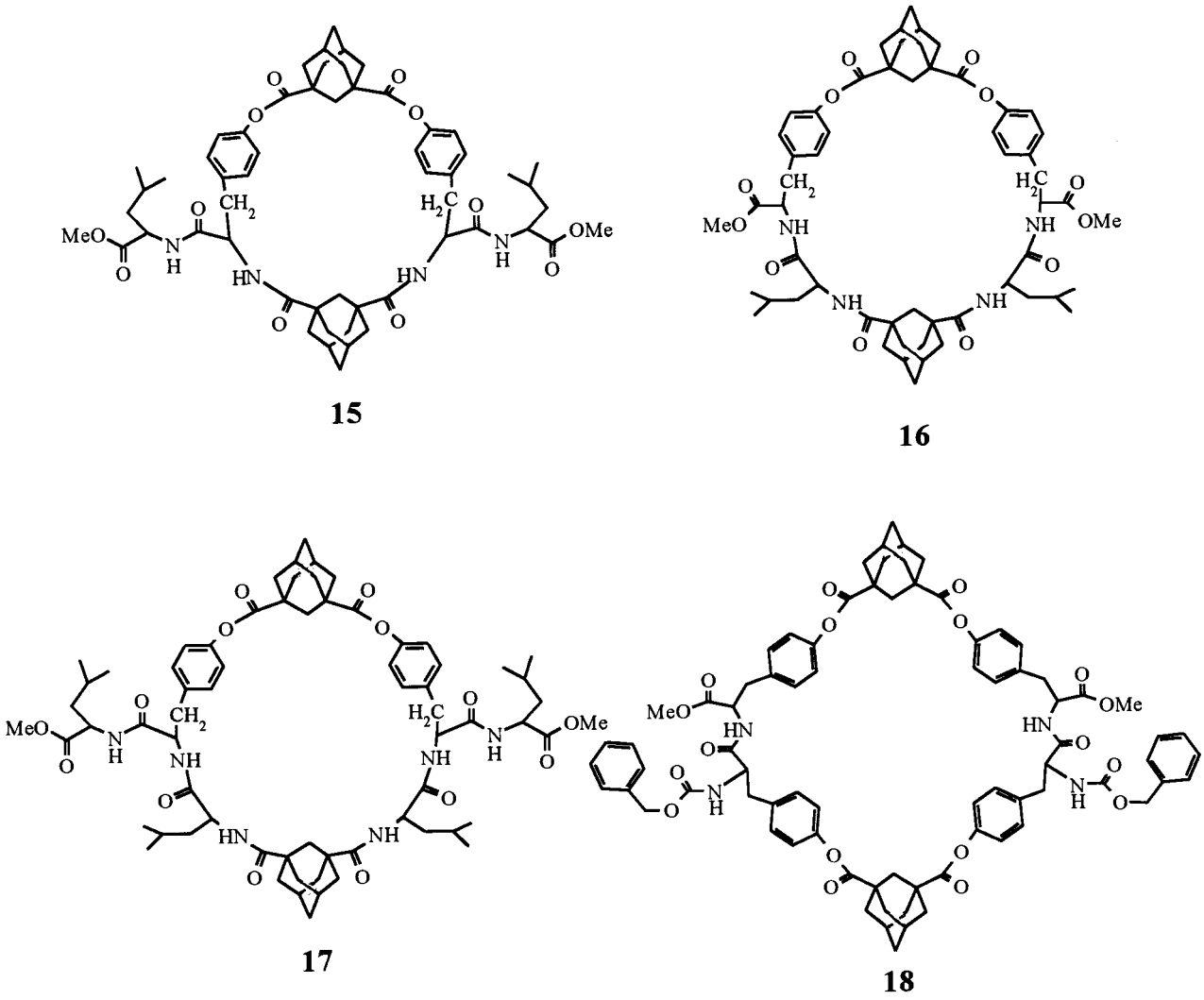


Figure 2.

meta-substituted arenes) to ~96° in the case of 2,6-pyridinedicarboxamide due to internal hydrogen bonds (B).[12]

A recent report[13] of the fortuitous formation of interlocked rings during the reaction of 1,4-bis(aminomethyl)-benzene with isophthaloyl chloride suggested that a similar templating effect may operate during the reaction of isophthaloyl chloride with amino acid tyrosine. In the event, careful examination of ^{1}H NMR and FAB MS spectra of the products obtained in the tyrosine reaction (Scheme 1) showed no evidence of any catenane formation. Prompted by the recent report[14] of the synthesis of amphiphilic benzyl amide catenanes using aliphatic dicarboxylic dichlorides and amide-linked bis diol (prepared from isophthaloyl chloride and 4-(aminomethyl)-phenol), we investigated the reaction of Tyr-based bis amine (generated in situ by the N^{α}Z-deprotection (Pd/C/H_2) of bis-Tyr derivative **9** which in turn was prepared by the coupling of N^{α}-Z-Tyr-OMe with sebacoyl chloride) with isophthaloyl chloride in anhydrous CH_2Cl_2 under high dilution conditions. The reaction, to our surprise, led to the clean formation of only one product, the 1 + 1 macrocycle **10** (Scheme 2) with no trace of any catenated species.

Interestingly, the "reverse reaction" wherein sebacoyl chloride was used in the final step led not only to the 1 + 1 macrocycle **11** but also to the interlocked macrocycle, the 1 + 1 + 1 + 1 catenane **12**, presumably arising from the threading of flexible sebacoyl chloride in the preformed 1 + 1 macrocycle **11** (Scheme 3). However, no 2 + 2 dimer was detected in the reaction mixture. The above results are in agreement with those described for the preparation of sebacoyl-containing amide catenanes and suggest that the mechanism of catenane formation presumably involves nesting of the sebacoyl chloride into the preformed [1 + 1] macrocycle **11** followed by coupling with the diamine of **3b**. The failure of any catenane formation in the reaction where isophthaloyl chloride was used in the final ring closure (Scheme 2) brings out the importance of the length, size, and geometry of the dichloride in determining the threading of the macrocycle. Parenthetically, the above example of tyrosine-based catenane is the first report of interlocked rings containing chiral amino acids and to the best of our knowledge constitutes the first example of a peptide catenane synthesized in the laboratory.

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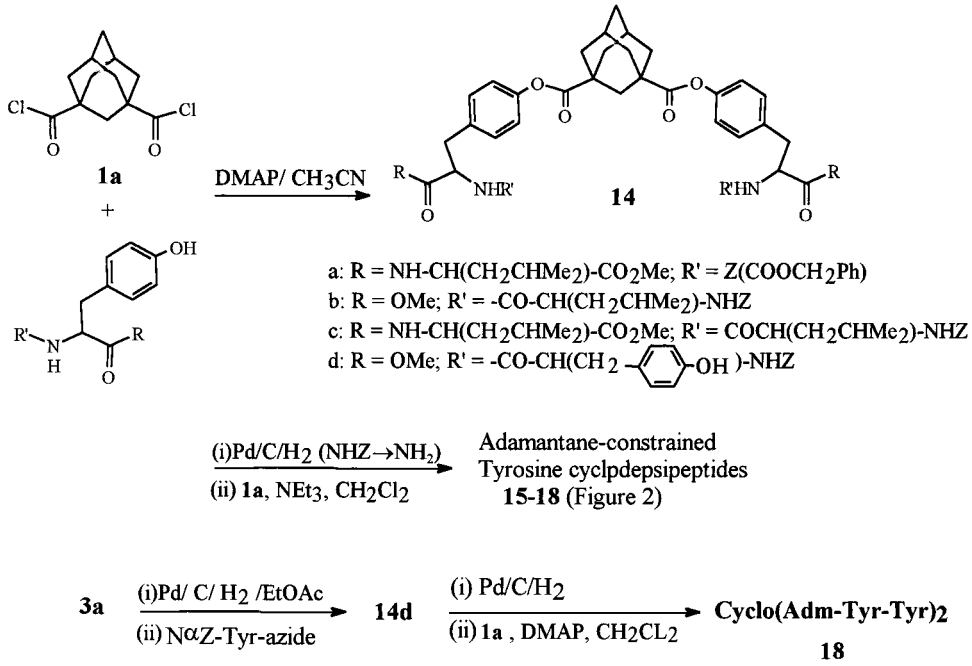
Scheme 4



A comparison of the ^{1}H NMR spectra of the (1 + 1) macrocycle **11** and the (1 + 1 + 1 + 1) catenane **12** (Supporting Information) in $CDCl_3$ indicates the possibility of amide protons in **12** (downfield shifted by ~0.4 ppm) engaged in the hydrogen bonding with the aromatic carbonyl groups. This may be the reason for the slight shielding of the aromatic singlet observed in catenated structure. The other notable differences are in the chemical shifts of the tyrosine $C^{\beta}H_2$ protons and the $C^{\beta}H_2$ protons of the sebacoyl chain, suggesting that these regions are in close proximity to aromatic rings in **12** which cause shielding or deshielding effects. The FAB MS spectrum of **12** (Supporting Information) shows features characteristic of interlocked molecules such as lack of fragmentation between M + H and M/2 peaks.

The versatility of the present strategy was further demonstrated by the preparation of adamantane-constrained leucine-containing, tyrosine-based cyclodepsipeptides **15**−**17** (Figure 2) of varying (26−32-membered) ring sizes. This group of macrocycles was especially designed with the aim of studying ion-transport in bilayer membranes. The incorporation of an increasing number of leucine residues at various locations, for example, as a pair of sidearms on the exterior of the macrocycle **15**, or as part of the macro-ring in **16** or both, as sidearms as well as constituents of the backbone in macrocycle **17**, provided cyclodepsipeptides with increasing lipophilicity most desirable for membrane penetration.

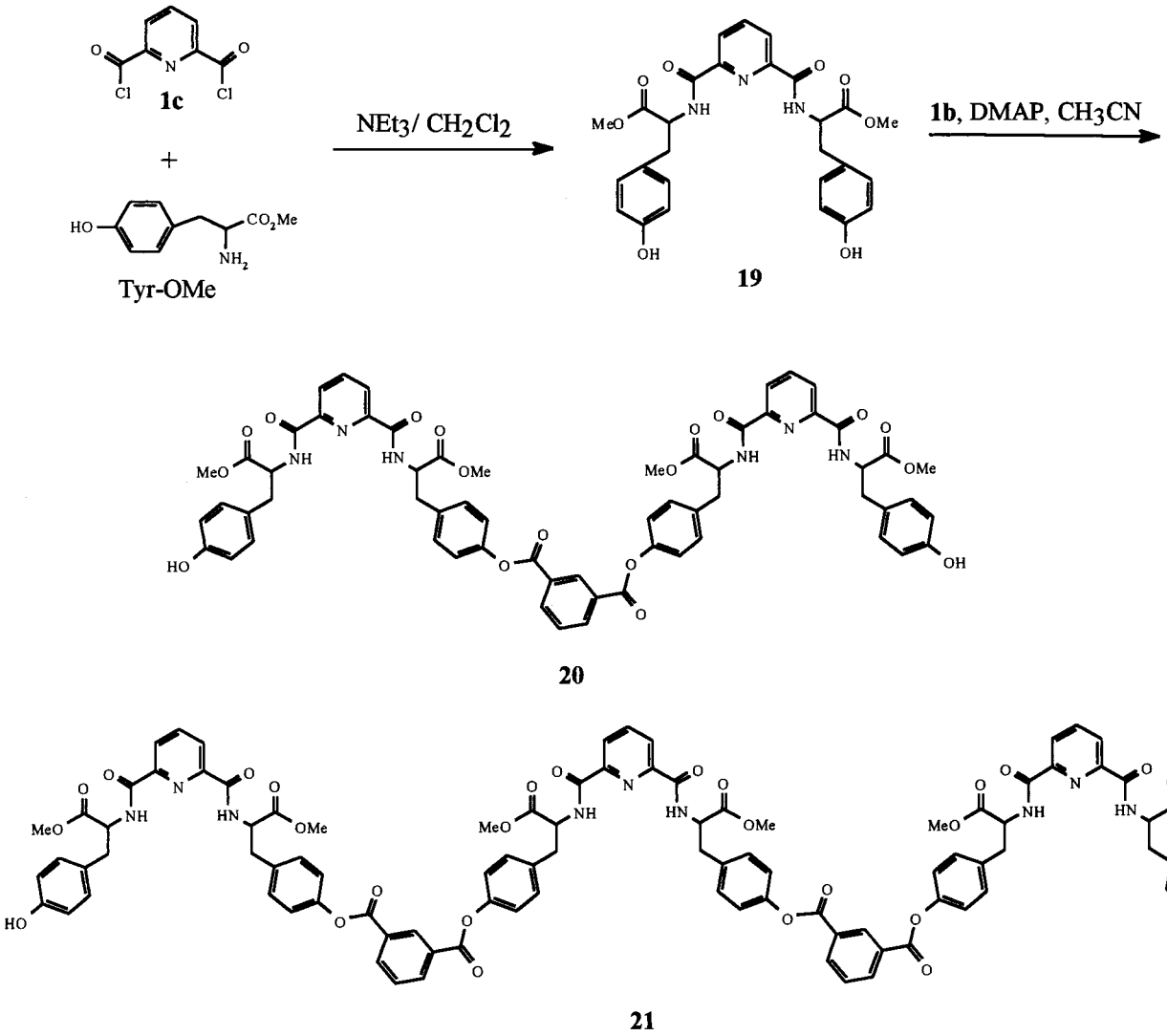
For the preparation of 32-membered macrocycles **16** and **17**, the intermediate bis-depsipeptides **14b** and **14c**—obtained by the direct condensation of tyrosine peptides Z-Leu-Tyr-OMe and Z-Leu-Tyr-Leu-OMe, respectively, with the adamantane template **1a**—were N-deprotected (Pd/C, 5%/H_2) and recoupled with **1a**. The 26-membered cyclodepsipeptide **15** containing a pair of leucine residues symmetrically placed on the exterior of the macrocycle was readily prepared from Z-Tyr-Leu-OMe using essentially the same procedure as for **16** and **17** (Scheme 4). The all-Tyr cyclodepsipeptide **18**, containing 42 atoms in the ring, was synthesized using a two-step sequence involving first the conversion of **3a** into **14d** (by N-deprotection followed by azide coupling with Z-Tyr-hydrazide) and the subsequent depsi coupling of **14d** with adamantane template **1a** (Scheme 4). The alternate route of one-step condensation of **1a** with Z-Tyr-Tyr-OMe led to a mixture of products containing macrocycle **18** only in trace amounts. The macrocycle **18** endowed with two pairs of built-in handles (in the form of protected NH_2 and COOH groups)—that can be ligated via peptide chemistry to a variety of subunits—provides attractive template for novel artificial protein design.

In another series of experiments, with the aim of simplifying the macrocycle formation by avoiding N-protection and deprotection steps, direct condensation of Tyr-OMe free base with 2,6-pyridinedicarbonyl dichloride (**1c**) afforded the bis-Tyr amide **19** in 50% yield. Trace amounts of O-acylated product could easily be removed by dilute acid wash. Attempted depsi coupling of 2,6-pyridine-supported bis-Tyr amide with the template **1b** in the presence of DMAP and under high dilution conditions yielded a mixture of products which were identified as linear oligomers **20** and **21** incorporating one and two isophthaloyl units, respectively, in the linear chain composed of 7 and 11 aromatic rings (Scheme 5). Interestingly, no trace of any cyclized product was isolated in this reaction, suggesting that macrocyclization is possible only with amide bond formation as the final step. The failure of cyclization also indicated extended conformations for these oligomers.

With a variety of tyrosinophanes in hand, we set out to measure the capability of these molecules to act as hosts for ions and neutral guests.

The leucine-containing macrocycles **15**−**18** appeared particularly attractive as potential ion carriers in membranes. Using the fluorescent dye method[8] with valinomycin as standard reference, it was found that while the aromatic or adamantane-bridged macrocycles **5**−**8** showed near absence of any ion-transport capability, the leucine-containing macrocycle **16** showed only modest (1/50th of valinomycin) transport of Na^+/K^+ ions across model membranes (small unilamellar vesicles).

Scheme 5



The presence of unusually large (eight to twelve) numbers of aromatic units in tyrosine macrocycles **6**−**8** suggested that these molecules may be useful as simple synthetic hosts for studying cation−π interaction, known to play an important role in protein structure, binding, and catalysis. Fluorescence titrations were carried out in methanol with *N*-methylacridinium hexafluorophosphate as the guest and macrocycles **6b** and **8b** as the aromatic hosts. Assuming the host−guest (H−G) complex to be nonfluorescent, the percentage quenching of the guest fluorescent intensity with progressive addition of the respective host would give a quantitative estimation of the complex formation. The results have shown strong interactions of pyridinium guest (50% quenching at a host/guest concentration of 0.39 and 0.33, respectively) with both **6b** and **8b**. The adamantane-bridged host **7a** showed only weak quenching (~5% for $C_H/C_G = 1$) of fluorescence, thus indicating that all-aromatic hosts **6b** and **8b** contribute stronger π interactions with pyridinium guest. The K_{assoc} value with **6b** was found to be 8.95×10^3 M^{-1} (Supporting Information).

Regardless of the exact nature of interaction, the above preliminary study has clearly brought out the promise of tyrosinophanes to serve as model aromatic hosts in the study of π−cation interactions.

Conclusion

A simple two-step synthetic strategy, based on the use of tyrosine side chain, for creating aromatic-bridged cyclodepsipeptides with large open pore structures is described. The design is flexible with respect to the nature of the bridging unit and size of the ring and permits the incorporation of a variety of amino acid residues on both the interior and exterior of the ring as illustrated with the preparation of a large number of tyrosine-based, aromatic (Ph or Pyr) or cage-like alicyclic (adamantane) or simple polymethylene-bridged macrocycles with ring sizes varying from 26- to 78-membered. The present study has shown that macrocyclization is possible only through amide bond formation. Attempted cyclization through ester bond formation (in the final step) led only to linear oligomers. The formation of catenane **12**, observed only with sebacoyl-bridged macrocycles, brings out the importance of flexibility required for nesting of the intermediate chains in the preformed rings.

The promise of tyrosinophanes to serve as simple aromatic hosts in the model studies for evaluating cation−π interactions has been demonstrated with 52-membered macrocycle **6b**. The tyrosinophane **6b** containing a pair of Ph and Pyr each as bridging units was found

to serve as an effective host ($K_{assoc} = 8.95 \times 10^3\ M^{-1}$) for *N*-methylacridinium hexafluorophosphate as the pyridinium cationic guest. Further aspects related to the functional properties of tyrosinophanes are under study.

Experimental Section

All amino acids used were of L-configuration. Melting points are uncorrected. ^{1}H NMR ROESY experiments were performed using 0.2 s mixing time with pulsed spin locking with 30° pulses and 2 kHz spin locking field. FAB MS was obtained using *m*-nitrobenzyl alcohol as the matrix. Reactions were monitored wherever possible by TLC. Silica gel G (Merck) was used for TLC, and column chromatography was done on silica gel (100−200 mesh) columns, which were generally made from a slurry in hexane or a mixture of hexane and ethyl acetate. Products were eluted with either a mixture of ethyl acetate/hexane or chloroform/methanol.

General Procedure for the Preparation of 1,3-Adamantane (1a), 1,3-Benzene (1b), or 2,6-Pyridine (1c) Bis Tyr Depsipeptides 3a−c Listed in Scheme 1. A solution of 1,3-dicarbonyl dichloride **1a−c** (1 mmol) in dry CH_2Cl_2 (10 mL) was added dropwise over a period of 0.5 h to a well-stirred and ice-cooled solution of N^{α}-Z-Tyr-OMe (2 mmol) in dry CH_3-CN (30 mL) containing *N*,*N*′-dimethyl-4-aminopyridine (DMAP, 2 mmol) and the mixture stirred at room temperature for 12 h. Solvents were removed in vacuo, the residue was triturated in EtOAc (∼100 mL), the extract was washed sequentially with 20 mL each of ice cold 2 N H_2SO_4 (except in the case of **1c**), H_2O, and 5% aqueous $NaHCO_3$, and the organic layer was dried over anhydrous $MgSO_4$ and evaporated in vacuo. The residue was purified on a short column of silica gel using a mixture of EtOAc/hexane as eluent to afford the template-supported bis-Tyr peptides **3a−c** in nearly quantitative yields.

3a: yield 95%; hygroscopic solid; $[\alpha]^{26}_D$ +40.44 (*c* 3.03, $CHCl_3$); IR (KBr) 3374, 1750, 1726, 1703, 1655 (sh), 1617, 1541 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.72−2.36 (m, 14H), 3.10 (m, 4H), 3.70 (s, 6H), 4.63 (m, 2H), 5.08 (s, 4H), 5.24 (d, J = 8.5 Hz, 2H), 6.97 (d, J = 8.5 Hz, 4H), 7.10 (d, J = 8.5 Hz, 4H), 7.34 (s, 10H); FAB MS (*m*/*z*) 847 $(MH)^+$. Anal. Calcd for $C_{48}H_{50}N_2O_{12}$: C, 68.08; H, 5.91; N, 3.30. Found: C, 68.34; H, 5.71; N, 3.59.

3b: yield 97%; mp 86−87 °C; $[\alpha]^{26}_D$ +47.79 (*c* 2.33, $CHCl_3$); IR (KBr) 3330, 1746, 1699, 1609 (sh), 1543 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.13 (m, 4H), 3.73 (s, 6H), 4.65 (m, 2H), 5.10 (s, 4H), 5.23 (d, J = 8.0 Hz, 2H), 7.15 (s, 8H), 7.32 (s, 10H), 7.68 (t, J = 7.8 Hz, 1H), 8.43 (d, J = 8.0 Hz, 2H), 8.97 (s, 1H); FAB MS *m*/*z* 789 $(MH)^+$. Anal. Calcd for $C_{44}H_{40}N_2O_{12}$: C, 67.00; H, 5.07; N, 3.55. Found: C, 66.82; H, 5.32; N, 3.67.

3c: yield 87%; mp 50−51 °C; $[\alpha]^{26}_D$ +39.39 (*c* 6.35, $CHCl_3$); IR (KBr) 3339, 1739, 1698, 1538 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.11 (m, 4H), 3.71 (s, 6H), 4.66 (m, 2H), 5.11 (s, 4H), 5.31 (d, J = 8.8 Hz, 2H), 7.15 (s, 8H), 7.33 (s, 10H), 8.13 (t, J = 8.8 Hz, 1H), 8.46 (d, J = 8.8 Hz, 2H). Anal. Calcd for $C_{43}H_{39}N_3O_{12}$: C, 65.39; H, 4.94; N, 5.32. Found: C, 65.45; H, 4.81; N, 5.63.

Preparation of Cyclodepsipeptides 5−8 (Figure 1). General Procedure: (a) N-Deprotection of Template-Supported Bis-N^{α}-Z-Tyr-depsipeptides 3a−c. A solution of bis N^{α}-Z-peptide **3a−c** (1 mmol) in dry ethyl acetate (∼10 mL) was admixed with 5% Pd/C (peptide/catalyst 1:0.5 w/w) and hydrogenolyzed using a Parr hydrogenation apparatus. After complete N^{α}-deprotection (TLC), the reaction mixture was filtered through a sintered funnel, the residue was washed with dry ethyl acetate (3 × 5 mL), and the filtrate was directly used for the coupling reaction in the next step.

(b) Condensation of N^{α}-Deprotected 1,3-Ar or Adm Bis-Tyr-depsipeptides 3a−c with 1,3-Ar or Adm dicarbonyl dichloride (4a−c). To a well-stirred and ice-cooled solution of N^{α}-deprotected bis-Tyr-depsipeptide (1 mmol in ∼100 mL of dry EtOAc) containing 2 mmol of triethylamine was added dropwise a solution of 1,3-Ar or Adm dicarbonyl dichloride (**4a−c**; 1 mmol in ∼50 mL of dry CH_2Cl_2) over a period of 0.5 h, and the mixture was stirred at room temperature for 12 h. The solvents were removed in vacuo, and the residue was taken up in CH_2Cl_2 (∼100 mL) and washed, sequentially, with 20 mL each of the ice-cold 2 N H_2SO_4, H_2O, and 5% aqueous $NaHCO_3$. The organic layer was dried over anhydrous $MgSO_4$ and evaporated in vacuo and the residue purified on a column of silica gel using either a mixture of EtOAc/hexane or $CHCl_3$/MeOH as eluent to afford template-constrained Tyr cyclodepsipeptides **5−8** in moderate yields.

5: mp 250−251 °C; $[\alpha]^{26}_D$ +328.34 (*c* 0.58, $CHCl_3$); IR (KBr) 3360, 1748, 1698, 1666, 1594, 1576, 1539 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.09 (dd, J = 5.1, 13.7 Hz, 2H), 3.45 (dd, J = 3.5, 13.7 Hz, 2H), 3.78 (s, 6H), 5.36 (m, 2H), 7.12−7.25 (m, 8H), 8.07 (m, 2H), 8.35 (dd, J = 1.2, 7.7 Hz, 2H), 8.44 (dd, J = 1.2, 7.7 Hz, 2H), 8.50 (d, J = 10.0 Hz, 2H); FAB MS *m*/*z* 653 $(MH)^+$. Anal. Calcd for $C_{34}H_{28}N_4O_{10}$: C, 62.57; H, 4.29; N, 8.58. Found: C, 62.89; H, 4.40; N, 8.35.

6a: mp 177−179 °C; $[\alpha]^{26}_D$ +111.81 (*c* 1.25, $CHCl_3$); IR (KBr) 3300, 1750, 1680, 1650, 1550 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.21 (dd, J = 5.9, 13.9 Hz, 4H), 3.31 (dd, J = 5.9, 13.9 Hz, 4H), 3.72 (s, 12H), 5.10 (dt, J = 7.7, 5.9 Hz, 4H), 6.95 (d, J = 7.7 Hz, 4H), 7.12−7.17 (m, 16H), 7.50 (t, J = 7.7 Hz, 2H), 7.61 (t, J = 7.7 Hz, 2H), 7.93 (dd, J = 1.4, 7.9 Hz, 4H), 8.12 (t, J = 1.6 Hz, 2H), 8.36 (dd, J = 1.6, 7.7 Hz, 4H), 8.80 (t, J = 1.6 Hz, 2H); FAB MS *m*/*z* 1301 $(MH)^+$. Anal. Calcd for $C_{72}H_{60}N_4O_{20}$: C, 66.46; H, 4.61; N, 4.30. Found: C, 66.73; H, 4.59; N, 4.52.

6b: mp 283−284 °C; $[\alpha]^{25}_D$ +122.44 (*c* 0.92, $CHCl_3$); IR (KBr) 3419, 1748, 1681, 1612, 1512 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.19 (dd, J = 6.8, 13.7 Hz, 4H), 3.30 (dd, J = 5.3, 13.7 Hz, 4H), 3.62 (s, 12H), 5.09 (m, 4H), 7.13−7.22 (m, 16H), 7.65 (t, J = 7.7 Hz, 2H), 8.04 (t, J = 7.7 Hz, 2H), 8.30 (d, J = 8.6 Hz, 4H), 8.37 (d, J = 7.7 Hz, 4H), 8.40 (dd, J = 1.6, 7.7 Hz, 4H), 8.90 (t, J = 1.6 Hz, 2H); FAB MS *m*/*z* 1303 $(MH)^+$. Anal. Calcd for $C_{70}H_{58}N_6O_{20}$: C, 64.51; H, 4.45; N, 6.45. Found: C, 64.65; H, 4.52; N, 6.80.

7a: mp 134−135 °C; $[\alpha]^{25}_D$ +57.66 (*c* 2.25, $CHCl_3$); IR (KBr) 3412, 1751, 1662, 1512 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.61−2.26 (m, 56H), 3.03 (dd, J = 6.0, 13.9 Hz, 4H), 3.16 (dd, J = 5.8, 13.9 Hz, 4H), 3.71 (s, 12H), 4.82 (m, 4H), 6.06 (d, J = 7.7 Hz, 4H), 6.96−7.05 (m, 16H); FAB MS *m*/*z* 1533 $(MH)^+$. Anal. Calcd for $C_{88}H_{100}N_4O_{20}$: C, 68.92; H, 6.52; N, 3.65. Found: C, 69.10; H, 6.60; N, 3.52.

7b: mp 280−282 °C; $[\alpha]^{25}_D$ +77.09 (*c* 0.70, $CHCl_3$); IR (KBr) 3419, 1749, 1685, 1514 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.73 (s, 4H), 1.99 (m, 16H), 2.23 (s, 8H), 3.16 (dd, J = 6.5, 13.9 Hz, 4H), 3.24 (dd, J = 6.0, 13.9 Hz, 4H), 3.69 (s, 12H), 5.02 (m, 4H), 6.99−7.17 (m, 16H), 8.02 (d, J = 7.8 Hz, 4H), 8.03 (t, J = 7.8 Hz, 2H), 8.33 (d, J = 7.8 Hz, 4H); FAB MS *m*/*z* 1419 $(MH)^+$. Anal. Calcd for $C_{78}H_{78}N_6O_{20}$: C, 66.00; H, 5.50; N, 5.92. Found: C, 65.95; H, 5.42; N, 6.10.

8a: mp 105−107 °C; IR (KBr) 3369, 1751, 1738, 1666, 1570, 1525 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.20 (dd, J = 6.1, 14.0 Hz, 6H), 3.30 (dd, J = 5.8, 14.0 Hz, 6H), 3.71 (s, 18H), 5.08 (m, 6H), 6.90 (d, J = 7.7 Hz, 6H), 7.11−7.17 (m, 24H), 7.47 (t, J = 7.7 Hz, 3H), 7.61 (t, J = 7.7 Hz, 3H), 7.89 (dd, J = 1.6, 7.8 Hz, 6H), 8.13 (t, J = 1.6 Hz, 3H), 8.36 (dd, J = 1.6, 7.8 Hz, 6H), 8.89 (t, J = 1.6 Hz, 3H); FAB MS *m*/*z* 1951 $(MH)^+$, 1301 (M of **6a** + H)$^+$. Anal. Calcd for $C_{108}H_{90}N_6O_{30}$: C, 66.46; H, 4.61; N, 4.30. Found: C, 66.81; H, 4.73; N, 4.25.

8b: mp 136−137 °C; $[\alpha]^{25}_D$ +61.23 (*c* 0.80, $CHCl_3$); IR (KBr) 3415, 1747, 1683, 1523 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.23 (dd, J = 6.5, 13.9 Hz, 6H), 3.27 (dd, J = 5.8, 13.9 Hz, 6H), 3.66 (s, 18H), 5.04 (m, 6H), 7.13−7.19 (m, 24H), 7.61 (t, J = 7.7 Hz, 3H), 8.02 (t, J = 7.7 Hz, 3H), 8.17 (d, J = 8.3 Hz, 6H), 8.32 (d, J = 7.7 Hz, 2H), 8.35 (dd, J = 1.6, 7.7 Hz, 6H), 8.86 (t, J = 1.6 Hz, 1H); FAB MS *m*/*z* 1955 $(M + 2)^+$, 1303 (M of **6b** + H)$^+$. Anal. Calcd for $C_{106}H_{88}N_8O_{30}$: C, 65.16; H, 4.50; N, 5.73. Found: C, 64.95; H, 4.43; N, 5.90.

Synthesis of Sebacoyl-Based [1 + 1] Tyrosine Cyclodepsipeptides 10 and 11 and [1 + 1 + 1 + 1] Catenane 12. Preparation of Cyclo(sebacoyl-Ser-isophthaloyl-Ser-) (10). (a) Preparation of the Precursor 1,ω-Sebacoyl Bis-Tyr-depsipeptide (9). A solution of freshly prepared 1,ω-sebacoyldicarbonyl dichloride (1 mmol in 10 mL of dry CH_2Cl_2) was added dropwise over a period of 0.5 h to a well-stirred and ice-cooled solution of N^{α}-Z-Tyr-OMe (**2**, 2 mmol in 30 mL

of dry CH_3CN containing 2 mmol of DMAP, and the reaction mixture was stirred for 12 h at room temperature. Workup as for **3a**−**c** and purification of the residue on a short column of silica gel using EtOAc/hexane as eluent afforded the titled bis Tyr compound **9** in 82% yield.

9: mp 110−112 °C; IR (KBr) 3345, 1751, 1700, 1534 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.38−1.74 (m, 12H), 2.54 (m, 4H), 3.10 (m, 4H), 3.71 (s, 6H), 4.65 (m, 2H), 5.09 (s, 4H), 5.23 (d, J = 7.8 Hz, 2H), 6.98 (d, J = 8.3 Hz, 4H), 7.09 (d, J = 8.3 Hz, 4H), 7.34 (brs, 10H).

(b) Condensation of N^{α}-Deprotected 1,ω-Sebacoyl Bis-Tyr derivative 9 with 1,3-Benzenedicarbonyl Dichloride (1b). To a well-stirred and ice-cooled solution of N^{α}-deprotected bis Tyr derivative (1 mmol in ∼100 mL of dry EtOAc) containing 2 mmol of triethylamine was added dropwise a solution of 1,3-benzenedicarbonyl dichloride (1 mmol in 50 mL of dry CH_2Cl_2) over a period of 0.5 h, and the mixture was stirred at room temperature for 12 h. Workup as for macrocycles **5**−**8** and purification of the residue on a short column of silica gel using EtOAc/hexane as eluent afforded the sebacoyl-bridged macrocycle 10 in 30% yield; mp 102−104 °C; IR (KBr) 3371, 1752, 1671, 1648, 1538 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.37 (m, 6H), 1.72 (m, 6H), 2.50 (m, 4H), 3.09 (m, 2H), 3.44 (dd, J = 4.5, 9.7 Hz, 2H), 3.83 (s, 6H), 5.11 (m, 2H), 6.83 (d, J = 7.6 Hz, 2H), 6.97 (d, J = 8.5 Hz, 4H), 7.14 (d, J = 8.5 Hz, 4H), 7.44 (t, J = 7.7 Hz, 1H), 7.85 (dd, J = 1.7, 6.0 Hz, 2H), 8.05 (t, J = 1.6 Hz, 1H); FAB MS m/z 687 $(MH)^+$. Anal. Calcd for $C_{38}H_{42}N_2O_{10}$: C, 66.47; H, 6.12; N, 4.08. Found: C, 66.19; H, 5.91; N, 3.92.

Reverse Addition Reaction: Preparation of Sebacoyl Cyclic Amide 11 and Catenated Molecule 12. A solution of 1,ω-sebacoyldicarbonyl dichloride (1 mmol) in dry CH_2Cl_2 (50 mL) was added dropwise to a well-stirred and ice-cooled solution of N-deprotected (Pd/C, 5%, H_2) 1,3-benzene bis-Tyr-depsipeptide (**3b**, 1 mmol) in dry ethyl acetate (100 mL) containing 2 mmol of triethylamin, and the reaction mixture was stirred for 12 h. The solvents were removed in vacuo, and the residue was dissolved in CH_2Cl_2 (100 mL), washed with 5% $NaHCO_3$ (20 mL), dried (anhydrous $MgSO_4$), and evaporated in vacuo. The residue showing two spots on TLC was chromatographed on a column of silica gel. Elution with a mixture of $CHCl_3$/MeOH yielded two compounds, identified as a [1 + 1] cyclization product (**11**) and [1 + 1 + 1 + 1] catenane (**12**).

11: yield 25%; mp 286−288 °C; IR (KBr) 3307, 1741, 1655, 1546 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.20 (s, 8H), 1.41 (m, 4H), 2.06 (m, 4H), 2.94 (m, 2H), 3.33 (dd, J = 4.7, 9.1 Hz, 2H), 3.80 (s, 6H), 4.93 (m, 2H), 5.77 (d, J = 8.3 Hz, 2H), 7.19 (s, 8H), 7.69 (t, J = 7.9 Hz, 1H), 8.42 (dd, J = 1.7, 6.2 Hz, 2H), 9.06 (s, 1H); FAB MS m/z 687 $(MH)^+$.

12: yield 5%; mp 208−210 °C; IR (KBr) 3308, 1747, 1649, 1621, 1601 (sh), 1541 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.25 (m, 16H), 1.40 (m, 4H), 1.57 (m, 4H), 2.10 (m, 8H), 2.94 (m, 2H), 3.08 (m, 2H), 3.21 (m, 2H), 3.33 (m, 2H), 3.74 (s, 6H), 3.80 (s, 6H), 4.91 (m, 4H), 5.74 (d, J = 8.4 Hz, 2H), 6.02 (d, J = 7.9 Hz, 2H), 7.09 (s, 8H), 7.19 (m, 8H), 7.68 (m, 2H), 8.42 (d, J = 6.5 Hz, 4H), 8.95 (s, 1H), 9.07 (s, 1H); FAB MS m/z 1395 (M + Na^+), 1373 $(MH)^+$, 709 (M/2 + Na^+), 687 (M/2 + $H)^+$.

General Procedure for the Preparation of 1,3-Adamantane-Bridged Leu-Containing Tyrosine Cyclodepsipeptides 15−18. (a) Preparation of Precursor 1,3-Adamantane Bis-Tyr-depsipeptides 14a−d Listed in Scheme 4. A solution of 1,3-adamantanedicarbonyl dichloride (**1a**, 1 mmol) in dry CH_2Cl_2 (10 mL) was added dropwise over a period of 0.5 h to a well-stirred and ice-cooled solution of N^{α}-Z-Tyr-OMe or its di- or tripeptide (2 mmol) in dry CH_3CN (30 mL) containing DMAP (2 mmol), and the reaction mixture was stirred at room temperature for 12 h. Solvents were removed in vacuo, the residue was triturated with ethyl acetate (∼100 mL), the extract was washed sequentially with 20 mL each of ice cold 2 N H_2SO_4, H_2O, and 5% aqueous $NaHCO_3$, and the organic layer was dried over anhydrous $MgSO_4$ and evaporated in vacuo. The residue was purified on a column of silica gel using a mixture of $CHCl_3$/MeOH as eluents to afford the bis-Tyr-depsipeptides **14a**−**d** in good yields.

14a: yield 88%; syrup; $[\alpha]^{30}_D$ +4.48 (c 0.54, $CHCl_3$); IR (neat) 3324, 1735, 1702, 1671, 1648, 1620, 1557 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (d, J = 3.7 Hz, 12H), 1.50−2.37 (m, 20H), 3.07 (m, 4H), 3.70 (s, 6H), 4.43 (m, 2H), 4.54 (m, 2H), 5.08 (s, 4H), 5.40 (d, J = 7.6 Hz, 2H), 6.29 (d, J = 7.2 Hz, 2H), 6.97 (d, J = 8.2 Hz, 4H), 7.20 (d, J = 7.8 Hz, 4H), 7.33 (brs, 10H); FAB MS m/z 1073 $(MH)^+$.

14b: yield 78%; mp 40−42 °C; $[\alpha]^{30}_D$ +14.14 (c 1.52, $CHCl_3$); IR (KBr) 3333, 1751, 1673, 1555 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.99 (d, J = 4.5 Hz, 12H), 1.50−2.41 (m, 20H), 3.18 (m, 4H), 3.80 (s, 6H), 4.22 (m, 2H), 4.93 (m, 2H), 5.19 (brs, 6H), 6.57 (brd, 2H), 7.02 (d, J = 8.4 Hz, 4H), 7.17 (d, J = 7.4 Hz, 4H), 7.43 (brs, 10H); FAB MS m/z 1073 $(MH)^+$.

14c: yield 85%; mp 146−148 °C; $[\alpha]^{30}_D$ −37.26 (c 1.0, $CHCl_3$); IR (KBr) 3320, 1756, 1749, 1714, 1668, 1652, 1584, 1544 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.97 (d, J = 4.5 Hz, 24H), 1.57−2.44 (m, 26H), 3.15 (m, 4H), 3.79 (s, 6H), 4.21 (m, 2H), 4.61 (m, 2H), 4.74 (m, 2H), 5.17 (m, 6H), 6.50 (br, 2H), 6.77 (br, 2H), 7.00 (d, J = 8.4 Hz, 4H), 7.28 (d, J = 8.1 Hz, 4H), 7.42 (brs, 10H); FAB MS m/z 1299 $(MH)^+$.

14d: yield 32%; sticky solid; IR (KBr) 3486, 3347, 3041, 1734, 1702, 1678, 1614, 1557, 1534 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.76−2.38 (m, 14H), 2.99 (brm, 8H), 3.68 (brs, 6H), 4.57 (m, 4H), 4.99 (brs, 4H), 5.38 (br, 2H), 5.81 (br, 2H), 6.69 (d, J = 7.8 Hz, 8H), 6.90 (d, J = 8.0 Hz, 8H); 7.31 (brs, 10H), 7.83 (br, 2H).

(b) Condensation of N^{α}-Deprotected 1,3-Adamantane Bis-Tyr-depsipeptides 14a−d with 1,3-Adamantanedicarbonyl Dichloride (1a). To a well-stirred and ice-cooled solution (1 mmol in ∼100 mL of dry EtOAc) of N^{α}-deprotected **14a**−**c** (Pd/C/H_2 as described for **5**−**8**) containing 2 mmol of triethylamine was added dropwise a solution of freshly prepared 1,3-adamantanedicarbonyl dichloride (1 mmol in 50 mL of dry CH_2Cl_2) over a period of 0.5 h, and the mixture was stirred at room temperature for 12 h. Workup as described for **5**−**8** and purification of the residue on a column of silica gel using a mixture of $CHCl_3$/MeOH as eluent afforded adamantane-constrained Tyr cyclodepsipeptides **15**−**18** in low to moderate yields.

15: yield 10%; mp 145−146 °C; $[\alpha]^{30}_D$ +2.10 (c 0.21, $CHCl_3$); IR (KBr) 3314, 1751, 1701, 1680, 1643, 1574, 1552 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.89 (m, 12H), 1.25−2.30 (m, 34H), 2.97 (m, 2H), 3.21 (dd, J = 4.3, 10.1 Hz, 2H), 3.75 (s, 6H), 4.58 (m, 4H), 5.96 (d, J = 7.3 Hz, 2H), 6.73 (d, J = 7.9 Hz, 2H), 7.00 (d, J = 8.3 Hz, 4H), 7.10 (d, J = 8.3 Hz, 4H); FAB MS m/z 993 $(MH)^+$. Anal. Calcd for $C_{56}H_{72}N_4O_{12}$: C, 67.74; H, 7.25; N, 5.64. Found: C, 67.53; H, 7.03; N, 5.39.

16: yield 20%; mp 108−110 °C; $[\alpha]^{30}_D$ −15.82 (c 0.3, $CHCl_3$); IR (KBr) 3384, 3323, 1752, 1670, 1648, 1551 (sh) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.88 (d, J = 6.6 Hz, 12H), 1.25−2.33 (m, 34H), 2.90 (m, 2H), 3.30 (dd, J = 4.0, 10.4 Hz, 2H), 3.79 (s, 6H), 4.44 (m, 2H), 4.86 (m, 2H), 5.67 (d, J = 8.4 Hz, 2H), 6.59 (d, J = 7.8 Hz, 2H), 6.99 (d, J = 8.4 Hz, 4H), 7.12 (d, J = 8.5 Hz, 4H); FAB MS m/z 993 $(MH)^+$. Anal. Calcd for $C_{56}H_{72}N_4O_{12}$: C, 67.74; H, 7.25; N, 5.64. Found: C, 68.03; H, 7.35; N, 5.83.

17: yield 32%; mp 210−212 °C; $[\alpha]^{30}_D$ −31.40 (c 1.0, $CHCl_3$); IR (KBr) 3323, 1755, 1673 (sh), 1656, 1561 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.89 (m, 24H), 1.36−2.40 (m, 40H), 2.99 (dd, J = 4.6, 9.8 Hz, 2H), 3.25 (m, 2H), 3.72 (s, 6H), 4.25 (m, 2H), 4.61 (m, 2H), 4.79 (m, 2H), 5.66 (d, J = 6.7 Hz, 2H), 6.34 (d, J = 8.6 Hz, 2H), 6.79 (d, J = 8.4 Hz, 2H), 6.95 (d, J = 8.4 Hz, 4H), 7.16 (d, J = 8.4 Hz, 4H); FAB MS m/z 1219 $(MH)^+$. Anal. Calcd for $C_{68}H_{94}N_6O_{14}$: C, 66.99; H, 7.71; N, 6.89. Found: C, 67.13; H, 7.92; N, 6.82.

18: yield 10%; sticky solid; ^1H NMR (300 MHz, $CDCl_3$) δ 1.56−2.36 (m, 28H), 2.99−3.08 (m, 8H), 3.71 (s, 6H), 4.56 (m, 2H), 4.74 (m, 2H), 5.08 (brs, 4H), 5.27 (d, J = 8.17 Hz, 2H), 5.84 (br, 2H), 6.70 (d, J = 8.0 Hz, 4H), 6.92 (d, J = 8.1 Hz, 4H), 7.35 (brs, 10H); FAB MS m/z 1361 $(MH)^+$.

Reaction of 2,6-Pyridine-Supported Bis-Tyr-amide (19) with 1,3-Benzenedicarbonyl D. Reverse reaction

(Attempted Formation of Depsi Linkage in Step II). (a) Preparation of 2,6-Pyridine-Supported Bis-Tyr-amide (19). A solution of 2,6-pyridinedicarbonyl dichloride (**1c**, 1 mmol) in dry CH_2Cl_2 (~10 mL) was added dropwise to a well-stirred and ice-cooled solution of tyrosine methyl ester (2 mmol in 50 mL of CH_2Cl_2) containing 2 mmol of triethylamine, and the reaction mixture was stirred for 12 h. Workup involved washing the dichloromethane solution sequentially, with 20 mL each of ice cold 2 N H_2SO_4, H_2O, and 5% aqueous $NaHCO_3$ and evaporation of the organic solvent in vacuo to afford 50% of the bisamide **19** as hygroscopic solid: IR (KBr) 3399, 3324, 1750, 1669, 1619, 1600 (sh), 1555 (sh), 1533 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.11 (m, 4H), 3.78 (s, 6H), 4.99 (m, 2H), 6.74 (d, J = 8.3 Hz, 4H), 6.92 (d, J = 8.3 Hz, 4H), 7.90 (d, J = 8.3 Hz, 2H), 7.97 (m, 3H), 8.28 (d, J = 7.8 Hz, 2H); FAB MS m/z 522 $(MH)^+$.

Coupling of 2,6-Pyridine-Supported Bis-Tyr-amide (19) with 1,3-Benzenedicarbonyl Dichloride (1b). Formation of Tyr-Based Linear Oligomers 20 and 21. A dilute solution of 1,3-benzenedicarbonyl dichloride (**1b**, 1 mmol in 50 mL of dry CH_2Cl_2) was added dropwise over a period of 0.5 h to a well-stirred and ice-cooled solution of the bis-Tyr-amide **19** (1 mmol in 100 mL of dry CH_2Cl_2) containing DMAP (2 mmol), and the reaction mixture after 12 h of stirring at room temperature was worked up as for **19**. The residue was chromatographed on a column of silica gel and eluted with a mixture of ethyl acetate/hexane to give two products which were identified as linear oligomers **20** and **21** incorporating one and two isophthaloyl units, respectively, in the linear chains composed of 7 and 11 aromatic rings.

20: yield 40%; mp 110−112 °C; IR (KBr) 3414 (br), 1749, 1684, 1523 cm^{-1}; ^1H NMR (400 MHz. $CDCl_3$) δ 3.13 (m, 6H), 3.28 (dd, J = 5.4, 8.3 Hz, 2H), 3.72 (s, 6H), 3.81 (s, 6H), 5.04 (m, 4H), 6.11 (s, 2H), 6.76 (d, J = 8.3 Hz, 4H), 6.95 (d, J = 8.8 Hz, 4H), 7.18 (m, 8H), 7.64 (t, J = 7.8 Hz, 1H), 7.92 (d, J = 7.9 Hz, 2H), 8.01 (m, 4H), 8.31 (m, 4H), 8.39 (dd, J = 1.9, 5.8 Hz, 2H), 8.90 (s, 1H); FAB MS m/z 1173 $(MH)^+$.

21: yield 3%; mp 128−130 °C; IR (KBr) 3412 (br), 1750, 1688, 1669 (sh), 1615 (sh), 1542 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.22 (m, 12H), 3.70 (s, 12H), 3.71 (s, 6H), 5.05 (m, 6H), 6.29 (s, 2H), 6.75 (d, J = 8.3 Hz, 4H), 6.95 (d, J = 8.3 Hz, 4H), 7.18 (m, 16H), 7.64 (t, J = 7.8 Hz, 2H), 7.94 (d, J = 8.3 Hz, 2H), 8.01 (m, 5H), 8.25 (d, J = 7.8 Hz, 2H), 8.31 (m, 6H), 8.38 (m, 4H), 8.89 (s, 2H); FAB MS m/z 1957 $(M + Cs^+)$.

Fluorescence Titration Experiment of *N*-Methylacridinium Hexafluorophosphate (Guest) with Host 6b. In a representative example, 700 μL of the guest solution (1.476×10^{-4} M) was taken in a microcuvette, and its emission spectra were recorded in the range of 420−550 nm with an excitation wavelength of 279 nm. The fluorescence intensity at 490 nm was monitored. The host solution (3.49×10^{-3} M) was added in portions with the final concentration varying from 2.47×10^{-5} to 3.58×10^{-4}. The results showed 50% quenching of the guest fluorescence at a C_H/C_G of 0.39 (Supporting Information). The K_{assoc} constant was calculated[15] from the graph plot (Supporting Information) as 8.95×10^3 M^{-1}.

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Supporting Information Available: ^1H NMR spectra of **5**, **7a**, **7b**, **10**, **15**−**17**, 2**0**, and **21**, comparison of ^1H NMR of **6a**/**8a** and **6b**/**8b** and of **11** and **12**, ROESY NMR spectra of **6a**, **6b**, **7a**, **8a**, **8b**, and **15**−**17**, FAB MS of **5**, **6b**, **7a**, **7b**, **8a**, **8b**, **1**−**12**, **15**−**17**, **19**, **20**, and **21**, fluorescence titration of **6b** with acridinium guest, and plot for K_{assoc}. This material is available free of charge via the Internet at http://pubs.acs.org.

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