Modular Synthesis of π-Acceptor Cyclophanes Derived from 1,4,5,8-Naphthalenetetracarboxylic Diimide and 1,5-Dinitronaphthalene

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Three neutral cyclophanes were synthesized, and their association with indole, an aromatic π-donor, was studied. The cyclophanes were designed to contain a rigid, hydrophobic binding cavity with 1,4,5,8-naphthalenetetracarboxylic diimide or 1,5-dinitronaphthalene as the π-acceptor. Two of the cyclophanes also contain a (*S*)-(valine-leucine-alanine) tripeptide unit to provide chiral hydrogen bonding interactions with guest molecules. Despite the fact that these cyclophanes contain a hydrophobic binding cavity of appropriate dimensions, their association with indole is very weak. In the case of cyclophanes derived from 1,5-dinitronaphthalene, steric interactions force the nitro groups out of the plane of the naphthalene ring, diminishing their effectiveness as π-acceptors. A simple UV−visible titrimetric method, using *N*,*N*,*N*′,*N*′-tetramethyl-1,4-phenylenediamine (TMPD) as a π-donor, was used to rank the π-acceptor strength of these and other aromatic units. These titrations show that 1,4,5,8-naphthalenetetracarboxylic diimide and 1,5-dinitronaphthalene derivatives are weaker π-acceptors than viologens, which make good π-acceptor cyclophanes. Methyl viologen is in turn a weaker π-acceptor than anthaquinone disulfonate, suggesting that the latter may serve as a useful building block for π-accepting cyclophane hosts.

Introduction

Cyclophanes, which are bridged aromatic molecules, have interesting properties as synthetic receptors.[1] As cyclic hosts, they are preorganized for binding guests of appropriate dimensions. The aromatic groups that encircle their binding cavities are often benzene rings, but they can also be condensed, and heteroaromatics that impart particular molecular recognition properties. The size, shape, charge, hydrophobicity, and π-donor/acceptor properties of these cavities are thus synthetically tunable, and so cyclophane hosts have been designed for a great variety of molecular guests.[2,3]

We have studied cyclophanes and nonannular π-accepting aromatic molecules as hosts for shape-selective molecular recognition in the solid state.[4,5] Cationic aromatic hosts are easily intercalated into α-zirconium phosphate (α-ZrP), a high surface area lamellar cation exchanger. In the case of chiral host molecules, the resulting solids can be used in batch mode for preparative-scale chiral separations.[6] Recently we reported the synthesis and molecular recognition properties of chiral cyclophane **1**, which contains a π-accepting 4,4′-bipyridium unit bridged by a tripeptide loop.[7] This molecule is a relative of the bipyridinium cyclophane **2**, which has been studied extensively by Stoddard and co-workers.[8] In water/acetone mixtures, **1** showed an (*R*)/(*S*) enantioselectivity ratio of 13 for association with [3-(3,4-dihydroxyphenyl)-DL-alanine] (DOPA), a π-donating cationic guest. Unfortunately, intercalation of **1**, **2**, and related bipyridinium cyclophanes into α-ZrP diminished their affinity for π-donor guest molecules, and their intercalation compounds were therefore not effective as chiral separations media.

We hypothesized that close association of the negatively charged α-ZrP sheets reduces the π-acidity of the 4,4′-bipyridium unit in **1** and **2**, making them poorer hosts for π-donating guests. To overcome this problem,

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(2) For reviews and recent examples of cyclophane host−guest chemistry, see: (a) Cram, D. J. *From Design to Discovery*; Seeman, J. I., Ed.; American Chemical Society: Washington, DC, 1990. (b) Wilcox, C. S.; Glagovich, N. M.; Webb, T. H.; *ACS Symp. Ser.* **1994**, 568, 282−90. (c) Webb, T. H.; Wilcox, C. S. *Chem Soc. Rev.* **1993**, 22, 383−395. (d) Torneiro, M.; Still, W. C. *J. Am. Chem. Soc.* **1995**, *117*, 5887. (e) Helgeson, R. C.; Knobler, C. B.; Cram, D. J. *J. Am. Chem. Soc.* **1997**, *119*, 3229. (f) Boulas, P. L.; Gomez-Kaifer, M.; Echegoyen, L., *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 216.

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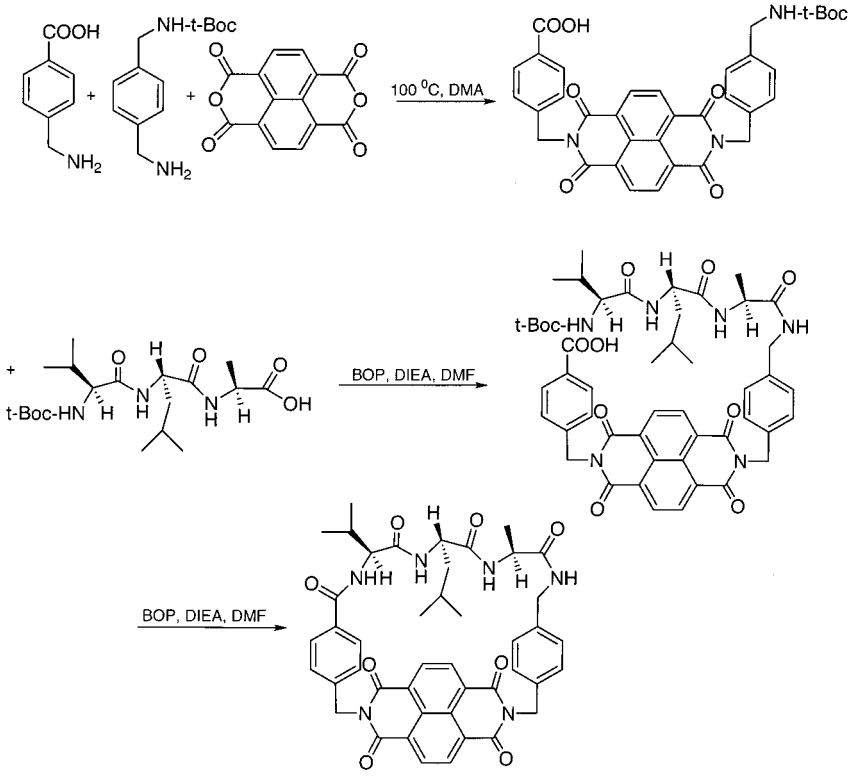
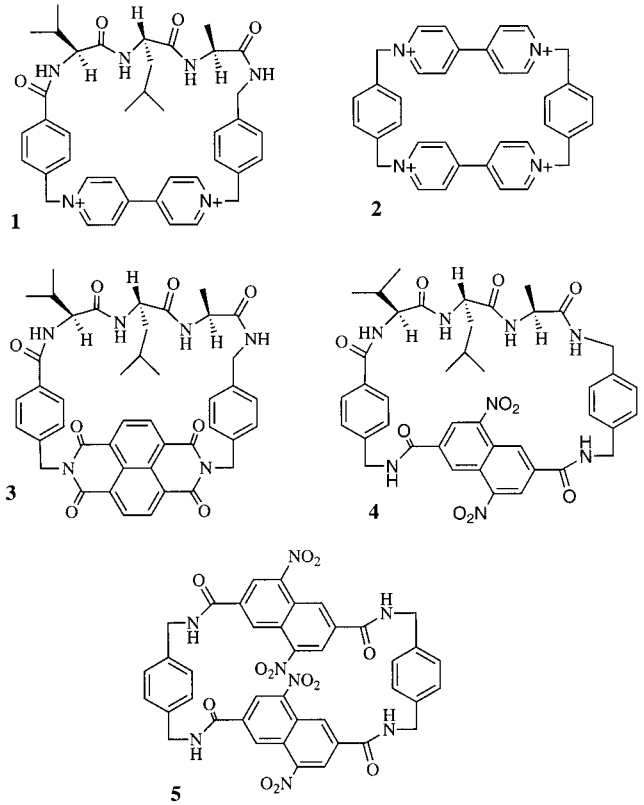
Scheme 1. Synthesis of Cyclophane 3



3

we are designing neutral hosts, including cyclophanes **3**−**5**. In principle, hosts of this type can be functionalized with cationic groups that are remote from the binding site, to provide the necessary charge for intercalation into α-ZrP. This strategy was successful with Pirkle-type hosts based on 3,5-dinitrobenzoyl-L-leucine, which retained their π-acceptor strength and enantioselectivity in intercalation compounds.[10]



1 **2** **3** **4** **5**

Cyclophanes **3** and **4** are structurally similar to **1**. Cyclophane **5** is the symmetric analogue of **4**. These cyclophanes were designed to have a neutral, rigid, hydrophobic pocket that is capable of binding stereoelectronically complementary guest molecules. The tripeptide unit provides chirality, hydrogen bonding positions, and (in principle, by varying the amino acid sequence) structural diversity. We report here the synthesis of these cyclophanes and their solution complexation with a strong π-donating guest, indole.

Results and Discussion

Synthesis. The synthesis of cyclophane **3** is represented in Scheme 1. The diimide portion of the molecule was synthesized in a "one-pot" procedure using a standard imide synthesis for coupling amines and anhydrides. Naphthalenetetracarboxylic dianhydride was heated with 4-aminomethyl benzoic acid and 4-[[(1,1-dimethylethoxy)-carbonyl]amino] benzylamine in *N*,*N*-dimethylacetamide (DMA). The product, which was precipitated with diethyl ether, contains the bifunctional diimide along with both symmetric diimides. The product was then separated on a silica gel column using $CHCl_3$/MeOH/Et_3N as the eluent. Removal of the solvent from the second fraction gave the bifunctional diimide in 26% yield. Attempts to improve the yield by only coupling one amine at a time resulted in poorer yields.

The synthesis of cyclophane **4** is represented in Scheme 2. The dinitronaphthalene portion of the molecule was

(9) (a) Chen, E. C. M.; Wentworth, W. E. *J. Chem. Phys.* **1975**, *63*, 3183. (b) Kondratov, V. K.; Lipatova, L. F.; Karpin, G. M. *Zhurnal Obshchei Khimii* **1979**, *49*, 2342.

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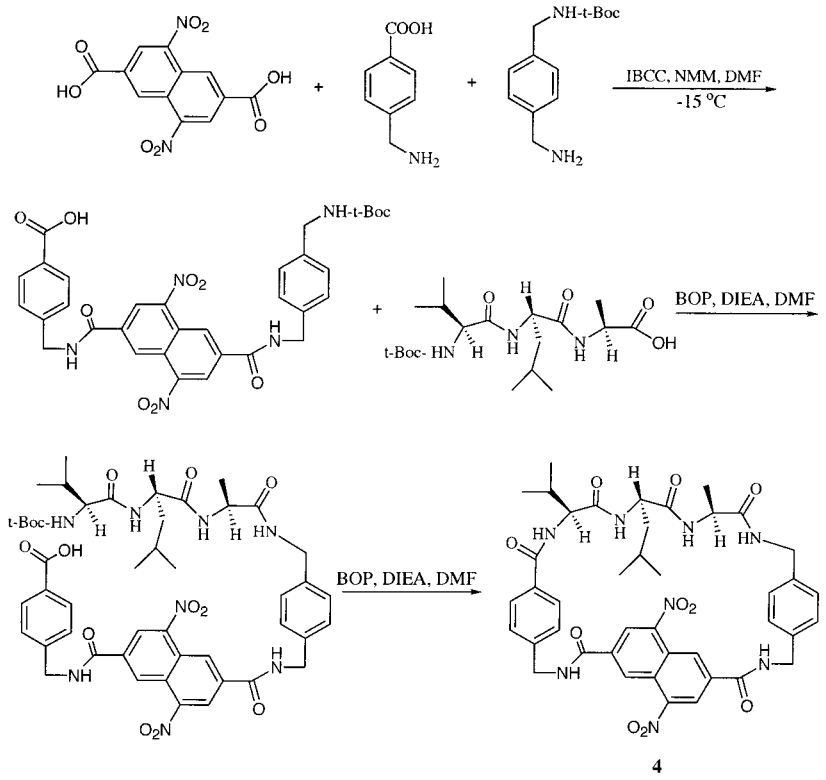
Scheme 2. Synthesis of Cyclophane 4



4

synthesized from the dicarboxylic acid and 4-aminobenzoic acid and 4-[[(1,1-dimethylethoxy)carbonyl]amino]-benzylamine using amino acid coupling chemistry in *N*,*N*-dimethylformamide (DMF). Isobutyl chloroformate (IBCC) was used as the coupling agent in a two-step process, which first couples 4-[[(1,1-dimethylethoxy)carbonyl]amino]benzylamine to the dicarboxylic acid and then 4-aminobenzoic acid. Only 1 equiv of IBCC was added at each step to promote the formation of the bifunctional product. After silica gel chromatography, the bifunctional product was isolated in 20% yield.

The tripeptide unit was synthesized using standard solid-phase peptide synthesis procedures. The first *N*-t-BOC amino acid was converted to its cesium salt and coupled to Merrifield resin. Subsequent *N*-t-BOC amino acids were coupled to the first by using in situ neutralization. The *N*-t-BOC amino acid on the resin was deprotected with trifluoroacetic acid (TFA) and neutralized with diisopropylethylamine (DIEA), and then the next *N*-t-BOC amino acid was coupled with 1,3-diisopropylcarbodiimide (DIC)/1-hydroxybenzotriazole (HOBt) in DMF. The method was particularly convenient since it only required 10 min per coupling step. The tripeptide with the *N*-t-BOC protecting group was cleaved from the resin with the aid of a phase transfer catalyst.

The tripeptide unit was coupled to the π-accepting unit of cyclophanes **3** and **4** with benzotriazol-1-yloxytris-(dimethylamino)phosphonium hexafluorophosphate (BOP) and DIEA in dry DMF. The *N*-t-BOC protecting group on the π-accepting unit was removed with TFA in chloroform. The carboxylic group on the tripeptide unit was activated with BOP in DMF, and the deprotected π-accepting unit in DMF was slowly added to the activated solution. Cyclophanes **3** and **4** were then produced in good yield by deprotecting the tripeptide with TFA in chloroform and performing another BOP coupling reaction at moderate dilution, to avoid polymeric species, in DMF.

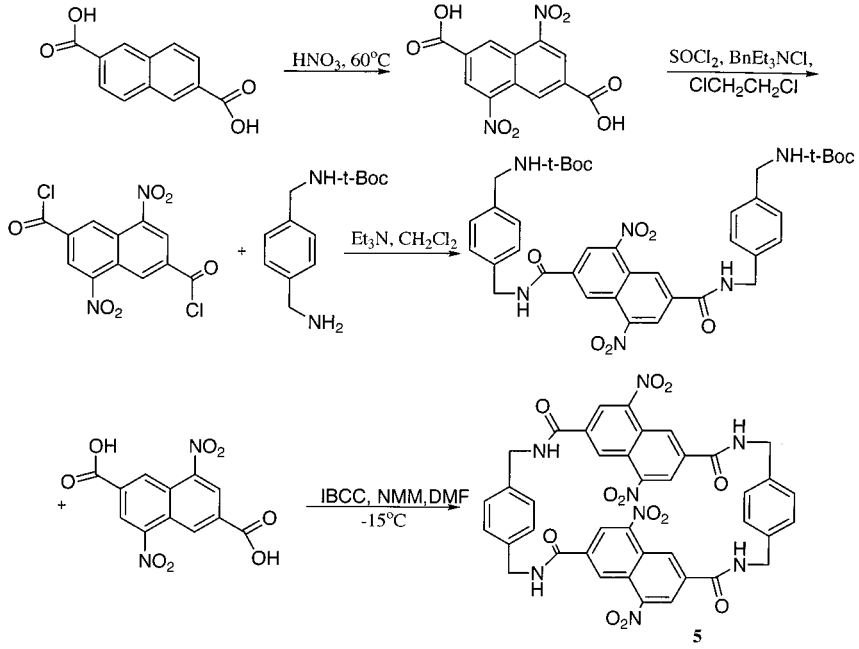
The synthesis of cyclophane **5** is represented in Scheme 3. The first portion of the cyclophane was synthesized by reacting 1,5-dinitronaphthalene-3,7-dicarbonyl dichloride with 4-[[(1,1-dimethylethoxy)carbonyl]amino]benzylamine. The monoprotection of the diamine ensures that no polymeric species form during this step. The *N*-t-Boc groups were deprotected with TFA in chloroform, and the dinitronaphthalene dicarboxylic acid was coupled to the molecule with IBCC to form the cyclophane.

Determination of Association Constants. UV−visible binding titrations were performed with cyclophane **3** and indole in chloroform. A charge-transfer band was observed with a cyclophane concentration of 0.1 mM and an indole concentration range of 20−100 mM (Figure 1). An association constant of 13 ± 1 M^{-1} was determined for cyclophane **3** with indole.

Because of their low solubility, cyclophanes **4** and **5** could not be tested in low dielectric solvents, such as $CHCl_3$, which stabilize π-donor/acceptor complexes. ^1H NMR binding titrations in DMSO-d_6 were performed with cyclophanes **4** and **5** at concentrations of 0.3 mM and 0.2 mM, respectively, and an indole concentration range of 0.2− 0.5 M. There was no detectable shift in the host proton peaks in this range, indicating that in this medium the association constant was <1 M^{-1}. No charge-transfer band was observed in the UV−visible spectra of cyclophanes **4** and **5** with indole in the same concentration range.

The low affinity of cyclophanes **3**−**5** for indole, a good π-donor, is somewhat surprising considering that naphthalenetetracarboxylic dianhydride (with an electron affinity of 2.28 eV) is considered a strong π-acceptor and aromatic nitro compounds, in general, are also.[9] The strength of the cyclophane−guest interaction depends on

Scheme 3. Synthesis of Cyclophane 5



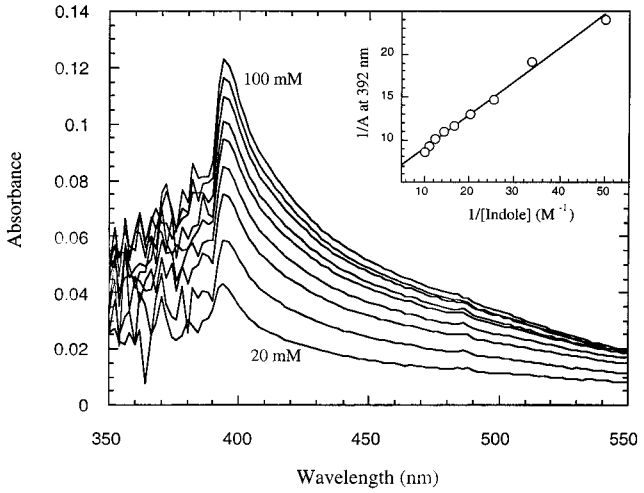


Figure 1. UV−visible titration of cyclophane **3** with indole. The cyclophane concentration was 0.5 mM, and the indole concentration range was 20−100 mM. Inset shows a double reciprocal plot, from which the association constant was determined.

several factors. The first is the stereoelectronic complementarity between host and guest, which permits favorable π-donor/acceptor, hydrogen bonding, and other interactions. The second is the preorganization of the host, i.e., the existence of a rigid binding pocket that does not require loss of entropy to accommodate the guest.[5] Energy-minimized (MM2 force field) space-filling models of hosts **3**−**5** (Figure 2) show that they do in fact contain preorganized binding pockets of the appropriate size to bind small aromatic guests such as indole.

In an effort to understand the weak π-acceptor character of cyclophanes **3**−**5**, relative to viologen hosts **1** and **2**, we studied the association of model π-acceptor units with *N*,*N*,*N*′,*N*′-tetramethyl-1,4-phenylenediamine (TMPD), a strong π-electron donor. There are several advantages to studying aromatic model compounds, instead of complete cyclophane hosts, in this way as π-acceptors. The most obvious is that one can screen available π-acceptors without the effort of synthesizing the complete host. A second advantage is that this procedure helps minimize the effects of solvation and steric complementarity on the host−guest interaction. With hydrophobic cyclophane binding cavities and guests in polar solvents such as water, changes in solvation can dominate the free energy of association. Thus, specific solvation effects can mask the strength of π-donor/acceptor interactions if one varies the structure of the host, or if one varies substituent groups on aromatic guests complexed by a single host.[10] In nonpolar solvents, this effect is smaller, particularly if substituents that reside outside the binding cavity are varied.[11] However, steric and specific solvation effects of the cyclophane can be more easily minimized by eliminating the cavity entirely. In this case, it is important to use nonpolar solvents and a particularly strong donor, so that the π-donor/acceptor interaction can be observed even for weak acceptors.

Table 1 gives the results of these experiments. Titrations were performed in chloroform, acetonitrile, and acetone with a constant π-acceptor concentration and a range of TMPD concentrations. Association constants were determined by monitoring the resulting charge-transfer band with a UV−vis spectrometer or proton shift in the ^{1}H NMR spectrum and applying the Benesi−Hildebrand method.[12] The association constant for the naphthalenediimide derivative **6** is low compared to the corresponding dianhydride **7**, which binds TMPD with an association constant of 5 ± 1 M^{-1}. In the case of the model compound **6** and cyclophane **3**, the π-accepting power of the host is diminished by electron-donating nitrogen atoms. Jazwinski et al. found that a symmetric cyclophane containing the naphthalenediimide group forms an inclusion complex with nitrobenzene, a π-acceptor, in the solid state.[13] Again, this is consistent with the weak π-acceptor character of **6**. **3** is a slightly better host for indole ($K_a = 13 \pm 1$ M^{-1} in $CHCl_3$) than **6** ($K_a =$

(11) Ferguson, S. B.; Diederich, F. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 5, 1127.
(12) Benesi, H.; Hildebrand, J. H. *J. Am. Chem. Soc.* **1949**, *71*, 2703.

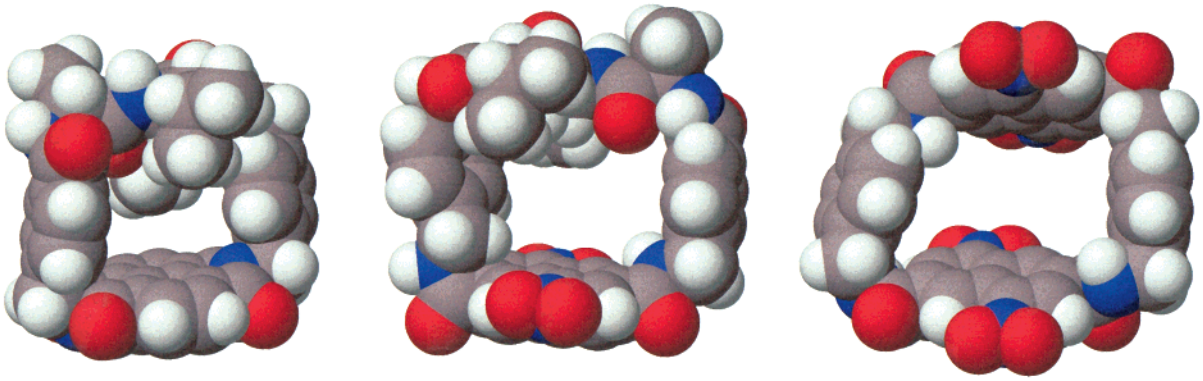
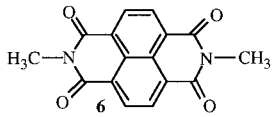
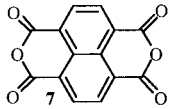
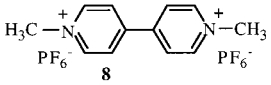
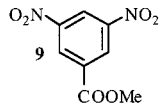
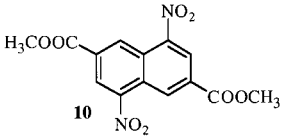
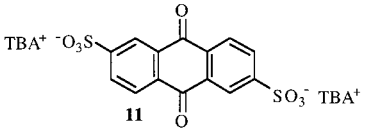


Figure 2. Space-filling models of cyclophanes **3**−**5**.

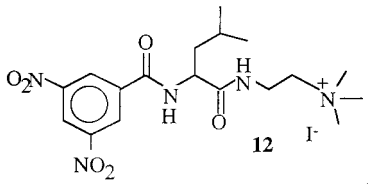
Table 1. Results of UV−Visible Titrations between Various π-Acceptors and TMPD[a]

Compound	Solvent	K(M^{-1})
 **6**	$CDCl_3$	<1
 **7**	Acetone	5 ± 1
 **8**	MeCN	5 ± 1
 **9**	$CHCl_3$ MeCN	28 ± 4 2 ± 1
 **10**	$CHCl_3$	*
 **11**	MeCN	37 ± 7

[a] (*) indicates no charge-transfer band observed.

3 ± 1 under the same conditions). The low association constant of **3** with indole, relative to viologen-containing hosts such as **1** and **2**,[9,11,14] is consistent with the observation that the naphthalene diimide unit in **3** and **6** is a weaker π-acceptor than methyl viologen (**8**).

Compound **9** is a model π-acceptor for Pirkle-type chiral selectors which have been used extensively in enantioseparations of π-donors.[15] Titrations with TMPD in $CHCl_3$ and CH_3CN rank this compound as a much better π-acceptor than **6**, and slightly weaker than **8**. The lower association constant found for **9** in CH_3CN can be understood in terms of weaker electrostatic interaction in the higher dielectric solvent. Consistent with this observation, we find $K_a = 4 \pm 2\ M^{-1}$ for complexation of *S*-**12** with chiral π-donor *S*-**13** in acetontrile, whereas Pirkle and Pochapsky measured $K_a = 88\ M^{-1}$ for *S*-**14**/*S*-**13** in $CHCl_3$.[19b]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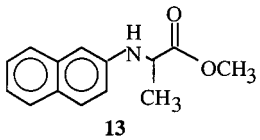
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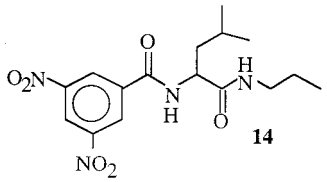
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A remaining question is why cyclophanes **4** and **5**, which contain binding cavities of similar dimensions to **1** and **2**, respectively, are poor hosts. Titration with TMPD in $CHCl_3$ shows that model compound **10** is a far weaker π-acceptor than either **8** or **9**, despite the fact that the former contains two nitro groups. The crystal structure of 1,5-dinitronaphthalene shows that the nitro groups are rotated 49° out of the aromatic plane, because of steric interactions with hydrogen atoms in the 4- and 8-positions.[16] Although energy minimization of the conformations of **10**, **4**, and **5**, using an MM2 force field, gives coplanar nitro groups (Figure 3), we believe that this is an artifact of the parametrization. The lowest energy π−π* absorption band of **10** is at 348 nm, whereas that of 2,6-naphthalenedicarboxylic acid dimethyl ester is at 349 nm. This indicates that the nitro groups, rotated out of the plane, are very weakly coupled to the naphthalene π-system. Rotation of the nitro groups also prevents guest

(13) Jazwinski, J.; Blacker, A. J.; Lehn, J.; Cesario, M.; Guilhem, J.; Pascard, C. *Tetrahedron Lett.* **1987**, *28*, 6057.
(14) Bernardo, A. R.; Stoddart, J. F.; Kaifer, A. E. J. *Am. Chem. Soc.* **1992**, *114*, 10624.
(15) (a) Pirkle, W. H.; Pochapsky, T. *Chem. Rev.* **1989**, *89*, 347. (b) Pirkle, W. H.; Pochapsky, T. *J. Am. Chem. Soc.* **1987**, *109*, 5975.
(16) Trotter, J. *Acta Crystallogr.* **1960**, *13*, 95.
(17) Rathore, R.; Lindeman, S. V.; Kochi, J. K. *J. Am. Chem. Soc.* **1997**, *119*, 9393.
(18) Smith, J.; Liras, J. L.; Schneider, S. E.; Anslyn, E. V. *J. Org. Chem.* **1996**, *61*, 8811.
(19) Cammarata, U.; Atanasoska, L.; Miller, L. L.; Kolaskie, C. J.; Stallman, B. J. *Langmuir* **1992**, *8*, 876.

molecules from approaching close enough to the aromatic plane of **10**, **4**, and **5** for effective binding. Similar steric inhibition of π-complexation by aliphatic substituents on good π-donors has been recently documented by Kochi and co-workers.[17]

Interestingly, the anthraquinonedisulfonate model compound **11** appears to be a better π-acceptor than both **8** and **9**. This suggests that cyclophanes derived from anthraquinone and structurally similar aromatic compounds may make interesting π-acceptor cyclophanes.

Summary and Conclusions

We have synthesized new symmetric and chiral cyclophanes based on naphthlalenediimide and 1,5-dinitronaphthalene aromatic units. Because of its electron-donating nitrogen atoms, the naphthlalenediimide cyclophane **3** complexes very weakly with strong π-donors in chloroform. Cyclophanes **4** and **5** derived from 1,5-dinitronaphthalene are very poor hosts because steric interactions force the nitro groups out of the aromatic plane. In the course of these studies, we have generalized a technique for the cyclization of asymmetric cyclophanes through amide coupling. A method was devised for ranking as π-acceptors different aromatic groups that might be used as components of related cyclophanes. These studies help rationalize the molecular recognition properties of these and previously synthesized hosts, and suggest that anthraquinone groups with electron-withdrawing substituents should be strong π-acceptors. We are currently investigating the molecular recognition properties of various anthraquinones, phenanthraquinones, and fluorenones, and cyclophanes derived from them.

Experimental Section

General. All starting materials were purchased from Aldrich Chemical Co., Milwaukee, WI, or VWR Scientific Products, West Chester, PA, and used as received. ^{1}H NMR was carried out on a Bruker AC-E-200, AMX-360, or PRX-400 spectrometer. ^{13}C NMR was carried out on a Bruker AMX-360 spectrometer. UV−visible spectra were obtained on a Hewlett-Packard 8452A Diode Array Spectrophotometer. Molecular mechanics calculations were performed with CAChe Ltd. software, which uses MM2 force fields and conjugate gradient optimization to find the minimum energy conformations of molecules. Elemental analysis (CHN) was performed by Atlantic Microlabs, Inc., P.O. Box 2288, Norcross, GA 30091.

Synthesis. 4-[[(1,1-Dimethylethoxy)carbonyl]amino]-benzylamine. The compound was prepared as described in the literature with modifications noted below.[18] To a solution of *p*-xylylenediamine (11.90 g, 87.4 mmol) in chloroform (100 mL) cooled in an ice bath, a solution of di-*tert*-butyl carbonate (9.17 g, 42.0 mmol) in chloroform (200 mL) was added dropwise over a period of 4 h. The mixture was stirred for 20 h under Ar. A white solid was filtered from the solution and washed with cold chloroform (2 °C, 100 mL). The chloroform was removed under reduced pressure. To the remaining oil, dichloromethane (DCM) (200 mL) and water (200 mL) were added. The layers were separated, and the aqueous layer was extracted with DCM (3 × 100 mL). The extracts were combined and dried over Na_2SO_4. The solvent was removed under reduced pressure to leave an off-white solid. The solid was mixed with diethyl ether (150 mL) and filtered. Removal of the solvent from the filtrate under reduced pressure resulted in the white solid product (6.24 g, 30%): ^{1}H NMR ($CDCl_3$) δ 7.25 (m, 4H), 4.85 (br, 1H), 4.26 (d, 2H, J = 8.0 Hz), 3.83 (s, 2H), 1.49 (s, 2H), 1.43 (s, 9H).

{***N*-[(*p*-Carboxyphenyl)methyl]-*N*′-[(*p*-(*N*-t-BOC-aminomethyl)phenyl)methyl]-1,4,5,8-naphthalenetetracarboxylic diimide}.** The diimide was synthesized based on a literature procedure.[19] 1,4,5,8-Naphthalenetetracarboxylic dianhydride (1.50 g, 5.6 mmol) was dissolved in DMA (80 mL) and heated (100 °C) under Ar. 4-Aminomethyl benzoic acid (0.84 g, 5.6 mmol) was then added in small portions to the heated solution. After 6 h, 4-[[(1,1-dimethylethoxy)carbonyl]amino]benzylamine (1.32 g, 5.6 mmol) was added at one time to the solution. Heating was continued for an additional 12 h. The solution was cooled to room temperature and filtered to remove some precipitate, and the filtrate was poured into diethyl ether (300 mL). The solid was filtered and washed with diethyl ether (200 mL). The mixture was separated on a silica gel column with Et_3N/MeOH/$CHCl_3$ (1:4:35). The second fraction was collected and the solvent removed under reduced pressure to yield a yellow solid. The solid was washed with diethyl ether and dried in air to yield the product (0.90 g, 26%): ^{1}H NMR (DMSO-d_6) δ 8.69 (s, 4H) (naphthalene), [7.88 (d, 2H, J = 6.0 Hz), 7.50 (d, 2H, J = 6.0 Hz), 7.35 (d, 3H, J = 14.0 Hz), 7.15 (d, 2H, J = 12.0 Hz)] (phenyls and NHCO), 5.28 (d, 4H, J = 26.0 Hz) (methylene groups next to imides), 4.05 (d, 2H, J = 10.0 Hz) (CH_2NH), 1.35 (s, 9H) (BOC).

{***N*-[(*p*-(*N*-t-BOC-aminomethyl)phenyl)methyl]-*N*′-[(*p*-carboxyphenyl)methyl]-1,5-dinitronaphthalene-3,7-diamide}.** 1,5-Dinitronaphthalene-3,7-dicarboxylic acid was prepared according to the procedure in the literature.[20] In a 1 L three-neck flask under Ar were added 1,5-dinitronaphthalene-3,7-dicarboxylic acid (3.06 g, 10 mmol) and DMF (280 mL). The solution was then cooled to −15 °C. A solution of *N*-methylmorpholine (1.1 mL, 10 mmol) in DMF (200 mL) was added dropwise followed by a solution of IBCC (1.3 mL, 10 mmol) in DMF (50 mL). Then a solution of 4-[[(1,1-dimethylethoxy)carbonyl]amino]benzylamine (2.36 g, 10 mmol) in DMF (50 mL) was added in the same manner. The mixture was allowed to warm to room temperature and stirred for 12 h. The reaction was again cooled to −15 °C, and the procedure was repeated with 4-aminomethyl benzoic acid (1.50 g, 10 mmol). After stirring for an additional 24 h, the solvent was removed by evaporation at 50 °C at atmospheric pressure. The residue was washed with 1 N HCl, water, and DCM. The solid was purified by silica gel column chromatography $CHCl_3$/MeOH/Et_3N (10:1:1) to yield a yellow product (1.32, 20%): ^{1}H NMR (DMSO-d_6) δ [9.20 (m, 2H), 8.92 (m, 2H)] (naphthalene), [7.90 (d, 2H, J = 8.3 Hz), 7.45 (d, 2H, J = 8.3 Hz), 7.25 (dd, 4H, J = 14.8 Hz, 8.3 Hz)] (phenyls), [4.65 (m, 2H), 4.55 (m, 2H)] (methylenes next to naphthalene), 4.08 (d, 2H, J = 5.8 Hz) (−CH_2NH), 1.35 (s, 9H) (BOC); positive ion FABMS: $C_{33}H_{31}N_5O_{10}$ $[M + H]^+ = 658$. Anal. Calcd (found): C, 60.27% (59.56%); H, 4.72% (4.52%); N, 10.65% (10.26%).

(*S*)-Val(*N*-t-BOC)-Leu-Ala. [(*S*)-Ala-*N*-t-BOC]$^-$Cs$^+$ was synthesized and coupled to Merrifield peptide resin by a standard literature procedure.[21] (*S*)-Alanine-*N*-t-BOC (5.0 g, 26 mmol) was dissolved in EtOH/water (40 mL, 2:1). Aqueous cesium carbonate was added to pH 7, and the solvent was removed by rotary evaporation. The white solid was then dried under vacuum. Merrifield resin (5 g, 2.3 mmol Cl$^-$/g) and [(*S*)-Ala-*N*-t-BOC]$^-$Cs$^+$ (5.54 g, 17 mmol) were combined in a flask with DMF (50 mL). The mixture was heated at 50 °C with stirring overnight. The mixture was filtered, and the solid was washed with DMF, DMF/water (9:1), DMF, and MeOH. (*S*)-Leu-*N*-t-BOC and (*S*)-Val-*N*-t-BOC were coupled to the resin using in situ neutralization.[22] (*S*)-Leu-*N*-t-BOC (10.6 g, 46 mmol) was activated for 30 min with DIC (7.2 mL, 46 mmol) and 0.4 M HOBt in DMF (115 mL). The resin-(*S*)-Alanine-*N*-t-BOC was deprotected with pure TFA (2 × 1 min) and washed with DMF (1 min). The deprotected resin was then added to the activated amino acid solution with DIEA (3 mL). The mixture was allowed to react for 10 min with occasional stirring. The resin was filtered and washed with DMF (1 min). A ninhydrin test

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(21) Gisin, B. F. *Helv. Chim. Acta* **1973**, *56*, 1476.
(22) Schnolzer, M.; Alewood, P.; Jones, A.; Alewood, D.; Kent, S. B. H. *Int. J. Pept. Protein Res.* **1992**, *40*, 180.

was performed to ensure complete coupling.[23] The procedure was repeated for (*S*)-Val-*N*-t-BOC. After the DMF wash, the resin was washed with MeOH and allowed to air-dry. The BOC-protected tripeptide was cleaved from the resin by potassium carbonate with a phase transfer reagent.[24] (*S*)-Val-(*N*-t-BOC)-Leu-Ala (2.70 g, yield 40%) was isolated as described previously:[11] ^{1}H NMR (DMSO-d_6) δ [8.13 (d, 1H, J = 6.7 Hz), 7.75 (d, 1H, J = 7.9 Hz), 6.75 (d, 1H, J = 8.2 Hz)] (three NHCO), [4.38 (m, 1H), 4.15 (m, 1H), 3.73 (m, 1H)] (CH amino acid chiral centers), 1.90 (m, 1H) (CH valine), 1.62 (m, 1H) (CH leucine), 1.45 (m, 2H) (CH_2 valine), 1.33 (s, 9H) (BOC), 1.22 (d, 3H, J = 7.0 Hz) (CH_3 alanine), 0.81 (m, 12H) (two CH_3 valine and two CH_3 leucine); ^{13}C NMR (DMSO-d_6) δ [174.02, 171.82, 171.21, 155.58] (carbonyl), [78.23, 28.33] (BOC carbons), [60.13, 50.57, 47.58] (chiral center carbons), [24.08, 23.32, 21.72, 19.42, 18.38, 17.23] (amino acid side chains). Anal. Calcd (found): C, 56.91% (57.05%); H, 8.73% (8.78%); N, 10.47% (10.38%)

{*N*-[(*p*-Carboxyphenyl)methyl]-*N*′-[(*p*-((*S*)-Val(*N*-t-BOC)-Leu-Ala-aminomethyl)phenyl)methyl]-1,4,5,8-naphthalenetetracarboxylic diimide}. (*S*)-Val-Leu-Ala-*N*-t-BOC was coupled to {*N*-[(*p*-carboxyphenyl)methyl]-*N*′-[*p*-(*N*-t-BOC-aminomethyl)phenyl)methyl]-1,4,5,8-naphthalenetetracarboxylic diimide} using a modified amino acid coupling procedure.[25] {*N*-[(*p*-Carboxyphenyl)methyl]-*N*′-[*p*-(*N*-t-BOC-aminomethyl)phenyl)methyl]-1,4,5,8-naphthalenetetracarboxylic diimide} (0.63 g, 1.0 mmol) was dissolved in TFA/$CHCl_3$ (15 mL, 1:3) and stirred for 45 min. The solvent was removed under vacuum. The residue was washed with hexane (15 mL × 3) which was removed under vacuum. The deprotected diimide was dissolved in DMF (50 mL), and DIEA (0.348 mL, 2.0 mmol) was added. In a separate flask under Ar, (*S*)-Val(*N*-t-BOC)-Leu-Ala (0.40 g, 1.0 mmol) was dissolved in DMF (20 mL). DIEA (0.174 mL, 1.0 mmol) and BOP (0.442 g, 1.0 mmol) were added, and the solution was allowed to react for 20 min. The deprotected diimide solution was then added dropwise to the activated (*S*)-Val(*N*-t-BOC)-Leu-Ala solution, and the solution was stirred for 6 h. The solvent was removed by evaporation at 50 °C at atmospheric pressure. The residue was washed with MeCN, water, and acetone and dried under vacuum to yield a yellow powder (0.471 g, 52%): ^{1}H NMR (DMSO-d_6) δ 8.69 (s, 4H) (naphthalene), [8.25 (m, 1H), 7.94 (m, 1H), 7.78 (m, 1H), 6.70 (m, 1H)] (four NHCO), [7.87 (d, 2H, J = 8.2 Hz), 7.50 (d, 2H, J = 8.3 Hz), 7.32 (d, 2H, J = 8.1 Hz), 7.17 (m, 2H)] (phenyls), 5.28 (d, 4H, J = 30.5 Hz) (methylene groups next to imides), 4.21 (m, 4H) (CH_2NH and two amino acid chiral centers), 3.70 (m, 1H) (amino acid chiral center), 1.84 (m, 1H) (CH valine), 1.55 (m, 1H) (CH leucine), 1.40 (m, 2H) (CH_2 valine), 1.32 (s, 9H) (BOC), 1.17 (d, 3H, J = 7.2 Hz) (CH_3 alanine), 0.78 (m, 12H) (two CH_3 valine and two CH_3 leucine); ^{13}C NMR (DMSO-d_6) δ [172.37, 172.21, 172.08, 156.01] (carbonyl), 167.49 (carboxylic), [163.30, 163.20] (carbonyl), [142.43, 138.91, 135.85, 131.28, 130.15, 129.98, 128.18, 127.75, 127.59, 126.96, 126.89] (phenyl and naphthalene rings), 48.73 (−CH_2NH), 43.81 (two methylenes next to imides), 28.66 (BOC carbons), [24.56, 23.40, 22.16, 19.64, 18.75, 18.48] (amino acid side chains); positive ion MALDI: $C_{49}H_{54}O_{11}N_6$ $[M + Na]^+$ = 925.

Cyclophane 3. {*N*-[(*p*-Carboxyphenyl)methyl]-*N*′-[(*p*-((*S*)-Val(*N*-t-BOC)-Leu-Ala-aminomethyl)phenyl)methyl]-1,4,5,8-naphthalenetetracarboxylic diimide} (0.345 g, 0.38 mmol) was deprotected as described above. It was then dissolved in DMF (50 mL) and transferred to a syringe. In a separate flask under Ar, BOP (0.252 g, 0.57 mmol) and DIEA (0.199 mL, 1.1 mmol) were combined with DMF (250 mL). The diimide solution was then added to the BOP solution via a syringe pump (4.2 mL/h). The solution was stirred for 4 d. The solvent was removed by rotary evaporation. The residue was washed with aqueous $NaHCO_3$ and water. It was then dissolved in $CHCl_3$, filtered to remove the insoluble solid, and dried over Na_2SO_4. Removal of the solvent resulted in an orange solid. The solid was purified by silica gel chromatography (MeOH/$CHCl_3$, 1:9). Removal of the solvent gave an orange-yellow product (0.224 g, 76%). ^{1}H NMR showed minor impurities in the range 2.3−2.8 ppm (see Supporting Information). ^{1}H NMR (DMSO-d_6) δ 8.64 (br, 4H) (naphthalene), [8.41 (m, 1H), 8.13 (m, 2H), 7.80 (m, 1H)] (four NHCO), [7.19−7.40 (br, 4H), 7.10 (m, 4H)] (phenyls), 5.46−5.28 (br, 4H)) (methylene groups next to imides), 4.52−3.71 (br, 5H) (CH_2NH and three amino acid chiral centers), 2.08 (m, 1H) (CH valine), 1.40−1.10 (br, 6H) (CH leucine, CH_2 valine, CH_3 alanine), 0.87−0.52 (br, 12H) (two CH_3 valine and two CH_3 leucine); ^{13}C NMR (DMSO-d_6) δ [171.89, 171.80, 171.64, 170.23, 166.81] (carbonyl), [138.96, 138.72, 134.64, 131.12, 129.46, 128.97, 128.11, 127.98, 127.73, 127.36, 126.64] (phenyl and naphthalene rings), [59.53, 51.98, 50.21] (chiral carbon centers), 48.65 (−CH_2NH), 42.53 (two methylenes next to imides), [24.11, 23.21, 21.84, 19.82, 18.45, 18.11] (amino acid side chains); positive ion MALDI HRMS: $C_{44}H_{44}O_8N_6$ MH^+ = 785.3299 ± 10 ppm. Anal. Calcd (found): C, 67.33% (64.22%); H, 5.65% (6.06%); N, 10.71% (10.55%).

{*N*-[(*p*-((*S*)-Val(*N*-t-BOC)-Leu-Ala-aminomethyl)phenyl)-methyl]-N′-[(*p*-carboxyphenyl)methyl]-1,5-dinitronaphthalene-3,7-diamide}. {*N*-[(*p*-(*N*-t-BOC-aminomethyl)phenyl)-methyl]-*N*′-[(*p*-carboxyphenyl)methyl]-1,5-dinitronaphthalene-3,7-diamide} (1.10 g, 1.67 mmol) was dissolved in TFA/$CHCl_3$ (15 mL, 1:3) and stirred for 45 min. The solvent was removed under vacuum. The residue was washed with hexane (15 mL × 3) which was removed under vacuum. The deprotected dinitronaphthalene was dissolved in DMF (50 mL), and DIEA (0.295 mL, 1.6 mmol) was added. In a separate flask under Ar, (*S*)-Val(*N*-t-BOC)-Leu-Ala (0.65 g, 1.62 mmol) was dissolved in DMF (50 mL). DIEA (0.582 mL, 3.2 mmol) and BOP (0.723 g, 1.64 mmol) were added, and the solution was allowed to react for 20 min. The deprotected dinitronaphthalene solution was then added dropwise to the activated (*S*)-Val(*N*-t-BOC)-Leu-Ala solution, and the solution was stirred for 6 h. The solvent was removed by evaporation at 50 °C at atmospheric pressure. The residue was washed with 0.5 N $NaHCO_3$, water, MeCN, and hexane to yield a yellow product (1.30 g, 85%): ^{1}H NMR (DMSO-d_6) δ 9.75 (m, 2H) (two −NHCO), [9.18 (m, 2H), 8.90 (m, 2H)] (naphthalene), [8.32 (m, 1H), 8.02 (m, 1H), 7.80 (m, 1H), 6.75 (m, 1H)] (four NHCO], [7.95 (d, 2H, J = 8.3 Hz), 7.50 (d, 2H, J = 8.3 Hz), 7.20 (dd, 4H, J = 13.81 Hz, 8.0 Hz)] (phenyls), [4.65 (d, 2H, J = 4.79), 4.52 (d, 2H, J = 4.33)] (methylenes next to naphthalene), [4.30 (m, 1H), 3.70 (m, 1H), 3.00 (m, 1H)] (CH amino acid chiral centers), 4.20 (m, 2H) (CH_2NH), 1.95 (m,1H) (CH valine), 1.60 (m, 1H) (CH leucine), 1.42 (m, 11H) (CH_2 valine and BOC), 1.17 (d, 3H, J = 7.4 Hz) (CH_3 alanine), 0.80 (m, 12H) (two CH_3 valine and two CH_3 leucine); positive ion MALDI: $C_{47}H_{56}N_8O_{13}$ $[M + Na]^+$ = 963. Anal. Calcd (found): C, 60.0% (58.14%); H, 5.96% (5.95%); N, 11.91% (11.60%).

Cyclophane 4. {*N*-[(*p*-((*S*)-Val(*N*-t-BOC)-Leu-Ala-aminomethyl)phenyl)methyl]-*N*′-[(*p*-carboxyphenyl)methyl]-1,5-dinitronaphthalene-3,7-diamide} (0.455 g, 0.48 mmol) was deprotected as described above. DMF (40 mL) and DIEA (0.085 mL, 0.48 mmol) were added to the deprotected dinitronaphthalene. In a separate flask under Ar, BOP (0.243 g, 0.55 mmol) and DIEA (0.17 mL, 0.96 mmol) were combined with DMF (30 mL) and stirred for 20 min. The deprotected dinitronaphthalene solution was slowly added to the BOP solution and stirred for 24 h. The solvent was removed by evaporation at 50 °C at atmospheric pressure. The residue was washed with 0.5 N $NaHCO_3$, water, MeCN, and hexane. Further purification was carried out by silica gel column chromatography (MeOH/$CHCl_3$, 1:10) to yield a yellow product (0.038 g, 10%): ^{1}H NMR (DMSO-d_6) δ 9.65 (m, 2H) (two NHCO), [9.12 (m, 2H), 8.85 (m, 2H)] (naphthalene), [8.20 (m, 1H), 7.95 (m, 1H), 7.75 (m, 1H), 7.55 (m, 1H)] (four NHCO), [7.50 (m, 4H), 7.25 (dd, 4H, J = 13.8 Hz, 8.0 Hz)] (phenyls), [4.65 (s, 2H), 4.55 (s, 2H)] (methylenes next to naphthalene), 4.40 (m, 2H) (CH_2NH), [4.25 (m, 2H), 3.60 (m, 1H)] (CH amino acid chiral centers), 2.05 (m, 1H) (CH valine), 1.45 (m,1H) (CH leucine), 1.35 (m, 2H) (CH_2 valine), 1.20 (m, 3H) (CH_3 alanine), 0.80 (m, 12H) (two CH_3 valine and two CH_3 leucine); positive ion MALDI HRMS:

(23) Sarin, V. K.; Kent, B. H.; Tam, J. P.; Merrifield, R. B. *Anal. Biochem.* **1981**, *117*, 147.
(24) Anwer, M. K.; Spatola, A. F. *Tetrahedron Lett.* **1992**, *33*, 3121.
(25) Nguyen, D. L.; Seyer, R.; Heitz, A.; Castro, B. *J. Chem. Soc., Perkin Trans. 1* **1985**, 1025.

$C_{42}H_{46}N_8O_{10}$ $MH^+ = 823.3415 \pm 10$ ppm. Anal. Calcd (found): C, 61.30% (61.30%); H, 5.59% (5.44%); N, 13.62% (13.59%).

1,5-Dinitronaphthalene-3,7-dicarbonyl Dichloride. The acyl chloride was made according to a literature procedure.[26] To a dry three neck 50 mL flask under Ar was added 1,5-dinitronaphthalene-3,7-dicarboxylic acid (3.79 g, 12.4 mmol), 1,2-dichloroethane (30 mL), and $BnEt_3NCl$ (0.006 g, 0.024 mmol). The slurry was brought to reflux, and $SOCl_2$ (1.95 mL, 26 mmol) was added all at once. Reflux was maintained for 16 h. The mixture was then cooled and allowed to crystallize. The solid was filtered, washed with diethyl ether, and dried in air to give orange, needle-shaped crystals (3.43 g, 81%): IR (KBr): = 1740 cm^{-1}(s, COCl), 1540(s), 1132(s); ^1H NMR (DMSO-d_6) δ 9.25 (s, 2H), 8.80 (s, 2H); MS(EI): $C_{12}H_4Cl_2N_2O_6$ $[M]^+ = 342$.

[*N*,*N*′-Bis(4-methylbenzylamine)-1,5-dinitronaphthalene-3,7-diamide](CF$_3$COO)$_2$. 1,5-Dinitronaphthalene-3,7-dicarbonyl dichloride (0.519 g, 1.5 mmol), 4-[[(1,1-dimethylethoxy)carbonyl]amino]benzylamine (0.708 g, 3.0 mmol), and Et_3N (0.42 mL, 3.0 mmol) were dissolved in DCM (100 mL) under Ar. A pale yellow solid precipitated immediately. The reaction was stirred for 24 h. The mixture was filtered and washed with DCM. The solid was then dissolved in 25% TFA/DCM solution (20 mL) and stirred for 30 min. The solvent was removed under vacuum, and the residue was washed with diethyl ether. The product was air-dried to yield a yellow product (0.930 g, 84%): ^1H NMR (DMSO-d_6) δ 9.75 (br, 2H) (NHCO), [9.15 (s, 2H), 8.91 (s, 2H)] (naphthalene), 8.20 (br, 2H) (NH_2), 7.40 (m, 8H) (phenyls), 4.58 (m 4H) (methylenes next to naphthalene), 4.02 (m, 4H) (CH_2NH_2); positive ion FABMS: $C_{32}H_{28}F_6N_6O_{10}$ $[M + H]^+ = 543$. Anal. Calcd (found): C, 49.87% (48.58%); H, 3.64% (3.67%); N, 10.90% (10.55%).

(26) Burdett, K. A. *Synthesis* **1991**, 441.

Cyclophane 5. In a 100 mL round-bottom flask, a solution of [*N*,*N*′-bis(4-methylbenzylamine)-1,5-dinitronaphthalene-3,7-diamide]$^{2+}$(CF_3COO^-)$_2$ (0.077 g, 0.10 mmol) in DMF (40 mL) was treated with Et_3N (0.028 mL, 0.20 mmol). In a 250 mL three-neck flask under Ar, 1,5-dinitronaphthalene-3,7-dicarboxylic acid (0.032 g, 0.10 mmol) was dissolved in DMF (50 mL). The solution cooled to −15 °C, and *N*-methylmorpholine (0.0275 mL, 0.25 mmol) was added. Isobutyl chlorocarbonate (0.0324 mL, 0.25 mmol) was added, followed about 1 min later by the [*N*,*N*′-bis(4-methylbenzylamine)-1,5-dinitronaphthalene-3,7-diamide]$^{2+}$(CF_3COO^-)$_2$ solution described above. The mixture was then diluted by DMF (200 mL) and allowed to warm to room temperature. The reaction was stirred for 48 h, and the solvent was removed by evaporation at 50 °C at atmospheric pressure. The residue was washed with DCM and redissolved in DMF (5 mL). The solution was centrifuged to remove a trace solid. After removing the solvent at atmospheric pressure again, the residue was washed with diethyl ether and air died to yield a pale yellow product (0.021 g, 25%): ^1H NMR (DMSO-d_6) δ 9.65 (br, 1H) (−NHCO), [9.18 (s, 4H), 8.85 (s, 4H)] (naphthalene), 7.35 (m, 8H) (phenyls), 4.55 (m, 8H) (methylenes); positive ion FABMS: $C_{40}H_{28}N_8O_{12}$ $MNa^+ = 835.4082 \pm 10$ ppm. Anal. Calcd (found): C, 59.11% (59.16%); H, 3.45% (3.49%); N, 13.79% (13.85%).

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Supporting Information Available: ^1H NMR spectrum of cyclophane **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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