Synthesis of symmetrical N-tosyldiazamacrocycles and complexation properties of their derivatives

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cipitate more solid. The solid was recrystallized from water to give **23** as a white crystalline solid (8.3 g, 66%): mp 192–194 °C (lit.[16b] mp 195–197 °C; ^{1}H NMR (DMSO-d_6) δ 9.03 (t, J = 2 Hz, 1 H), 8.83 (d, J = 3 Hz, 1 H), 8.12 (m, 1 H); ^{19}F NMR (DMSO-d_6) δ 126.8 (dd, J = 8, 2 Hz); IR (KBr) 3067 (s), 2462 (br), 1713 (s) cm^{-1}; MS, m/e 141 (M$^+$).

Methyl 5-Fluoronicotinate (24). A suspension of acid **23** (8.3 g, 0.059 mol) in ether (75 mL) was cooled to 0 °C and an ethereal solution of diazomethane (ca. 0.13 mol) was added dropwise with stirring. The acid gradually dissolved and the solution was allowed to warm to room temperature and stirred overnight. The unreacted starting material (0.2 g) was removed by filtration and the filtrate was concentrated to give a light yellow solid. Recrystallization from hexanes gave the ester **24** as a colorless crystalline solid (8.8 g, 99%): mp 47–48 °C (lit.[24] mp 50.0–50.5 °C); ^{1}H NMR δ 9.13 (m, 1 H), 8.71 (d, J = 3 Hz, 1 H), 8.06 (m, 1 H), 4.02 (s, 3 H); ^{19}F NMR δ 127.1 (dd, J = 8, 2 Hz); IR 1731 (s), 1294 (s) cm^{-1}; MS, m/e 155 (M$^+$).

5-Fluoro-3-pyridylmethanol (25). This was prepared as above for **18** in 70% yield as a colorless liquid: bp 123 °C (0.4 mm) (lit.[25] bp 83–85 °C (0.01–0.05 mm); ^{1}H NMR δ 8.33 (m, 2 H), 7.53 (td, J = 9, 2 Hz, 1 H), 5.02 (s, 1 H), 4.78 (s, 2 H); ^{19}F NMR δ 127.1 (dd, J = 8, 2 Hz); IR 3608 (m), 3271 (br), 1608 (s), 1435 (s) cm^{-1}; MS, m/e 127 (M$^+$).

5-Fluoronicotinaldehyde (26). This was prepared as above for **19** in 91% yield, as a colorless liquid: bp 90 °C (22 mm) (lit.[15] bp 71–76 °C (10 mm)); ^{1}H NMR δ 10.23 (d, J = 2 Hz, 1 H), 8.98 (s, 1 H), 8.79 (d, J = 2 Hz, 1 H), 7.92 (td, J = 9, 2 Hz, 1 H); ^{19}F NMR δ 125.6 (d, J = 7 Hz); IR 3001 (m), 2846 (m), 1704 (s), 1580 (s) cm^{-1}; MS, m/e 125 (M$^+$).

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Supplementary Material Available: The preparations and spectral properties of most of the derivatives **6–8** (39 compounds, 9 pages). Ordering information is given on any current masthead page.

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Reaction of Tosylamide Monosodium Salt with Bis(halomethyl) Compounds: An Easy Entry to Symmetrical *N*-Tosyl Aza Macrocycles

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A one-step, general procedure for a variety of *N*-tosyl aza macrocycles (including aza-crown ethers, pyridino- and bipyridino-aza-crown analogues, and azacyclophanes), by reaction of appropriate bis(halomethyl) precursors with tosylamide monosodium salt (TsNHNa) in *N,N*-dimethylformamide, is described. In polymethyl-substituted 2,11-diaza[3.3]cyclophane systems, the methyl substituents play an important role in inducing stereospecific ring closures. Thus, coupling of 1,4-bis(chloromethyl)-2,5-dimethylbenzene (**15b**) with TsNHNa produced only one of the two possible diastereomeric dimers, to which chiral structure **16db** was assigned by means of the chiral Eu(dcm)$_3$ shift reagent. This stereochemical assignment was confirmed by a single-crystal X-ray study on **16d**. Detosylation of *N*-tosyl aza macrocycles to the free polyamino macrocycles by reductive (Na–NH$_3$) or hydrolytic (90% H_2SO_4) methods, followed by N-methylation (CH_2O–HCO_2H), was also accomplished in excellent yield. The ^{1}H NMR spectra of 2,11-diaza[3.3]cyclophanes and 2,11-diaza[3.3](2,6)pyridinophanes are discussed in terms of conformation and conformational mobility.

Introduction

Synthetic aza macrocycles are well-known for their binding properties toward either inorganic[1] or organic[2] cations, anions,[3] and neutral molecules.[4] Selective binding of certain cations by multifunctional aza macrocycles has resulted in their use as models for carrier molecules in the study of active ion transport phenomena in liquid membrane systems.[5] Furthermore, macrocyclic (poly)amines have been further functionalized to improve ligand–cation binding or change ligand–cation selectivity,[6] provide secondary binding sites,[7] impart biological activity to the macrocycle,[8] and prepare polymer-bound reagents.[9]

Conventional strategies for the preparation of these compounds rely upon the availability of suitable acyclic mono- or polyamino precursors.[10] Lehn[8,11] developed a generally useful procedure for the preparation of diaza macrocycles, which is based on the high-dilution reaction of a diamine with a diacid dichloride to form a macrocyclic

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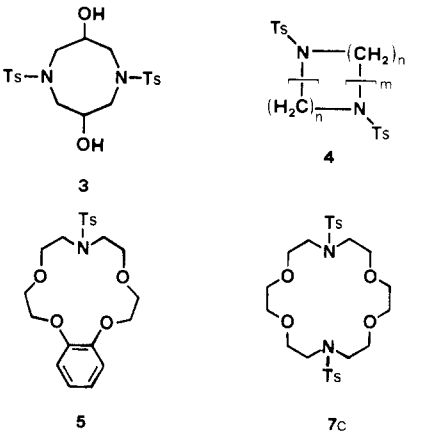
diamide, followed by reduction of the amide carbonyls to yield the corresponding diamino macrocycle. Subsequently Richman and Atkins[12] found that the synthesis of macrocyclic polyamines could be conveniently accomplished by condensation of bis(sulfonamide sodium salts) with compounds having sulfonate ester leaving groups, which facilitate ring closure at high reactant concentrations, thus obviating the need for employing high-dilution or template techniques. Slight modifications of the latter method have been widely used for the synthesis of a variety of aza macrocycles.[13]

A fortuitous synthesis of *N,N'*-ditosyl-2,17-diaza[3.3]-(6,6')-2,2'-bipyridinophane (**23c**)[14] resulted from an attempt to prepare the intermediate *N,N'*-ditosyl-6,6'-bis(aminomethyl)-2,2'-bipyridine by reaction of 6,6'-bis(chloromethyl)-2,2'-bipyridine (**22b**) with tosylamide monosodium salt (TsNHNa) in refluxing absolute EtOH. This finding has prompted us to investigate the synthetic possibilities offered by the one-step condensation of TsNHNa with bis(halomethyl) compounds for producing symmetrical *N*-tosyl aza macrocycles. Consequently, we have examined the condensation of TsNHNa with numerous aliphatic, aromatic, and heteroaromatic bis(halomethyl) derivatives to verify the generality of the reaction, and to determine the efficiency of the cyclizations and product distribution ratios for the formation of small and large rings. This synthetic approach has been the subject of a preliminary communication.[15]

We now report full experimental data concerning this study, which has also been extended to bis(halomethyl)(poly)methylbenzenes in order to evaluate possible steric hindrance effects on the one-pot macrocyclization. Our results have shown that the TsNHNa method provides an easy entry to a variety of symmetrical *N*-tosyl aza macrocycles, including aza-crown ethers, azacyclophanes, and azaheterophanes. Furthermore, stereospecific ring closures have been noticed for sterically hindered (poly)methyl diaza[3.3]cyclophane systems, bringing to light the important role played by substituents in the crucial cyclization step. Besides, suitably substituted diaza[3.3]paracyclophanes, e.g., **16d** and its derivatives, provide a cheap source of optically stable chiral compounds. A dynamic variable temperature (VT) ^{1}H NMR study has shown a hindered rotation of the aryl rings in these systems up to 180 °C. Torsional dissymmetry was ascertained by means of the chiral Eu(dcm)$_3$ shift reagent and confirmed by a single-crystal X-ray structural determination on **16d**.

The viability of reductive or hydrolytic removal of the tosyl functions (depending on the nature of the substrate) to afford polyamino macrocycles, and subsequent N-methylation to provide the hitherto unreported macrocyclic structures, have also been demonstrated.

Chart I



During the completion of this work, Inazu[16] has reported the synthesis of (aza)$_n$[3^n]paracyclophanes by condensation of 1,4-bis(bromomethyl)benzene (**15a**) with tosylamide in the presence of NaH.

Results and Discussion

Tosylamide **1** can be considered as a protected as well as masked NH_3 molecule in which the electron-withdrawing tosyl group plays a dual role: (i) it enhances the acidity of geminal hydrogens, and (ii) it preserves the nitrogen atom from multiple substitution in reactions with electrophilic agents. Thus, alkylation of **1** under basic conditions followed by detosylation of the intermediate *N,N*-dialkyltosylamine **2** is in principle one of the simplest preparative routes to pure symmetrical secondary amines (eq 1). The utilization of bifunctional alkylating agents would ultimately result in the formation, inter alia, of cyclic amines.

$$\underset{\mathbf{1}}{TsNH_2} \xrightarrow{RX,\ B^-} \underset{\mathbf{2}}{TsNR_2} \xrightarrow{\text{detosylation}} HNR_2 \qquad (1)$$

A survey of the literature has shown that **1** has been sporadically used as the nitrogen source in the construction of medium sized and large ring aza macrocycles. Paudler et al.[17] reported the preparation of *cis*- and *trans*-1,5-ditosyl-3,7-dihydroxyoctahydro-1,5-diazocine (**3**) (Chart I) in a 13% total yield by condensation of 1,3-dibromo-2-propanol with **1** in the presence of 2 equiv of KOH. More recently, the synthesis of *N*-tosylazacycloalkanes **4** (n = 10–20; m = 0, 1) has been accomplished in moderate to good yields by catalytic two-phase alkylation of **1** with dibromoalkanes.[18] Besides, subjection of appropriate bis(sulfonate ester) precursors to $TsNH^-$ anion has led to formation of aza-crown ethers **5** (36%)[13b] and **7c** (14.9%).[13d]

From these preliminary remarks, we felt that the one-pot nucleophilic condensation of bis(halomethyl) compounds with 2 equiv of TsNHNa, acting as the nitrogen source and as the base, could offer a cheap, practical, and general route to symmetrical *N*-tosyl aza macrocycles. Our initial experiments were carried out in absolute ethanol. The reactions required extended time and generally resulted in a low yield of the desired *N*-tosyl aza macrocycles, the

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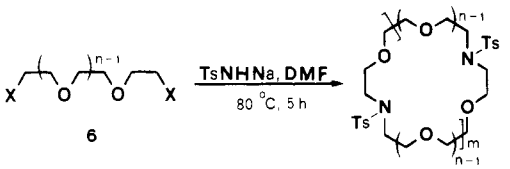
Scheme I



	X	n
6a	I	1
6b	I	2
6c	Br	3

	n	m
7a	1	0
7b	2	0
7c	2	1
7d	3	0

Scheme II

major reaction products being open-chain tosylamino intermediates and unwanted ethoxy derivatives. The use of a dipolar aprotic solvent such as *N*,*N*-dimethylformamide (DMF) instead of ethanol suppressed the latter side reaction, and above all, the one-pot macrocyclization step proceeded quickly and cleanly for all the substrates examined.

The results of the coupling of oligoethylene glycol dihalides **6** (n = 1–3) with TsNHNa (2 equiv) in anhydrous DMF are summarized in Scheme I.

Reaction of TsNHNa with bis(2-iodoethyl) ether (**6a**) gave *N*-tosylmorpholine (**7a**) in a nearly quantitative yield. As expected, the more favorable six-membered ring closure is detrimental to the formation of higher cyclic oligomers.

Treatment of 1,2-bis(2-iodoethoxy)ethane (**6b**) with TsNHNa under standard conditions afforded 1:1 and 2:2 *N*-tosyl-aza-crown ethers **7b** (25%) and **7c** (5%), respectively, while bis[2-(2-bromoethoxy)ethyl] ether (**6c**) gave only the 1:1 macrocycle **7d** (35%).

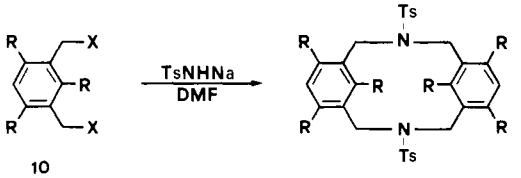
Coupling of 1,2-bis(bromomethyl)benzene (**8**) with TsNHNa produced *N*-tosyldihydroisoindole (**9**) in almost quantitative yield (Scheme II). Similarly, condensation of 1,2,4,5-tetrakis(bromomethyl)benzene with 1 and NaH as the base has been reported to give 1,2,3,5,6,7-hexahydro-2,6-bis(*p*-tolylsulfonyl)benzo[1,2-*c*:4,5-*c*']dipyrrole in 94% yield.[19]

The reaction of 1,3-bis(bromomethyl)benzene (**10a**) with TsNHNa gave the expected *N*,*N*'-ditosyl-2,11-diaza[3.3]metacyclophane (**11a**) in 53% yield (Scheme III). Vögtle previously obtained dimer **11a** in 22% yield by condensing **10a** with 1,3-bis[(tosylamino)methyl]benzene.[20]

In order to verify possible steric hindrance effects of methyl substituents in the dimerization to 2,11-diaza[3.3]metacyclophane systems, we subjected bis(chloromethyl)mesitylene (**10b**) to TsNHNa under standard conditions. The reaction afforded *anti*-*N*,*N*'-ditosyl-5,7,9,14,16,18-hexamethyl-2,11-diaza[3.3]metacyclophane (**11b**) (15%) as the only cyclic product (Scheme III), along with 2,4-bis[(tosylamino)methyl]mesitylene (**12**) (31%).

Polymethylated *N*-tosylazacyclophanes are in general high-melting crystalline materials, which show a low volatility under MS conditions. In addition, the tosyl groups are very labile upon electron impact, so that these compounds very often give a weak parent peak even at low voltage, and in some cases the molecular ion is absent, while the free polyamino cyclophanes and their *N*-methyl derivatives display much more intense molecular ions.[14,21] Therefore, detosylation of these materials to the more volatile polyamino compounds was deemed essential for their structural characterization.

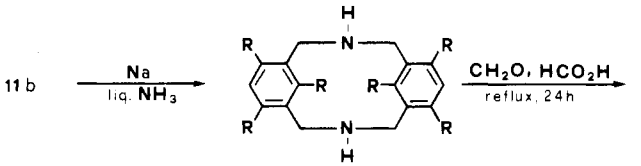
Scheme III

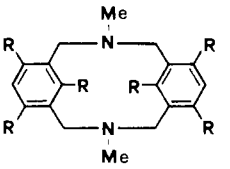


	X	R
10a	Br	H
10b	Cl	Me

	R
11a	R=H
11b	R=Me

Scheme IV





Accordingly, reductive removal of the tosyl groups in **11b** by sodium in liquid ammonia[22] afforded (85%) *anti*-2,11-diaza[3.3]metacyclophane **13**, which was converted to the *N*,*N*'-dimethyl derivative **14** by the Eschweiler–Clarke modification of the Leuckart reaction (Scheme IV).

The ^{1}H NMR spectra of dimers **11b**, **13**, and **14** are characterized by upfield singlets at δ 1.04–1.05 for the intraannular methyl groups and by double doublets (AB systems, J = 13.6–14.4 Hz) for the methylene protons centered at δ 4.29, 3.83, and 3.54 (reminiscent of N-substitution), respectively, which are of diagnostic value for a fixed stepped anti conformation for these compounds. This stereochemical assignment is consistent with the results reported by Sato for the sulfur analogue *anti*-5,7,9,14,16,18-hexamethyl-2,11-dithia[3.3]metacyclophane.[23]

Condensation of 1,4-bis(bromomethyl)benzene (**15a**) with TsNHNa produced a mixture of 2:2, 3:3, and 4:4 *N*-tosyl aza macrocycles **16a–c** (ca. 60% total yield) (Scheme V). The product distribution was quite similar to that reported by Inazu for the reaction of **15a** with 1 and NaH.[16]

In the ^{1}H NMR spectrum of dimer **16a** at room temperature, both methylene and phenyl protons showed up as singlets, indicating rapid conformational equilibration;

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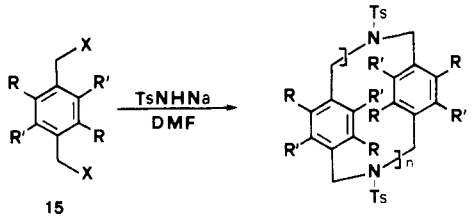
Table I. Coordinates for Cyclophane Tosylate $C_{34}H_{38}N_2O_4S_2$

atom	x	y	z	atom	x	y	z
S	0.65366 (4)	0.68690 (5)	0.13022 (7)	C8	0.5314 (2)	0.6057 (2)	−0.4287 (3)
O1	0.7065 (1)	0.6626 (2)	0.0633 (2)	C9	0.5935 (2)	0.9758 (2)	−0.2344 (4)
O2	0.6179 (1)	0.6170 (2)	0.1830 (2)	C10	0.4634 (2)	0.7690 (2)	−0.5673 (3)
N	0.5995 (1)	0.7436 (2)	0.0243 (2)	C11	0.6853 (1)	0.7633 (2)	0.2574 (3)
C1	0.6264 (1)	0.8124 (2)	−0.0579 (3)	C12	0.7371 (1)	0.8219 (2)	0.2444 (3)
C2	0.5957 (1)	0.8030 (2)	−0.2026 (3)	C13	0.7598 (2)	0.8840 (2)	0.3423 (3)
C3	0.5838 (1)	0.7159 (2)	−0.2560 (3)	C14	0.7326 (2)	0.8883 (2)	0.4554 (3)
C4	0.5456 (1)	0.7014 (2)	−0.3790 (3)	C15	0.6818 (2)	0.8284 (2)	0.4663 (3)
C5	0.5184 (1)	0.7784 (2)	−0.4497 (3)	C16	0.6578 (1)	0.7673 (2)	0.3692 (3)
C6	0.5376 (1)	0.8647 (2)	−0.4026 (3)	C17	0.7568 (2)	0.9557 (2)	0.5606 (3)
C7	0.5770 (1)	0.8793 (2)	−0.2795 (3)				

Scheme V



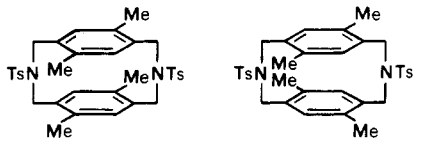
15

	X	R	R'
15a	Br	H	H
15b	Cl	Me	H
15c	Cl	Me	Me

16

	n	R	R'
16a	1	H	H
16b	2	H	H
16c	3	H	H
16d	1	Me	H
16e	2	Me	H
16f	1	Me	Me

Chart II



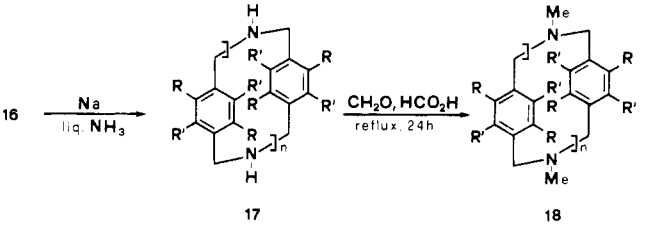
16da: C_{2v} 16db: D_2

however, a low temperature NMR study was precluded by solubility problems. Since ^1H NMR studies[24] and above all the optical resolution of appropriate monosubstituted derivatives[25] have demonstrated a restricted rotation of the benzene rings in hydrocarbon [3.3]paracyclophanes, the structurally related 2,11-diaza[3.3]paracyclophane systems might show analogous properties, by virtue of a C–N bond length comparable to a C–C bond length.

On the assumption of hindered rotation of the aromatic rings with respect to one another, a pair of inconvertible diastereomeric dimers **16da** and **16db** (Chart II) can be expected from the condensation of 1,4-bis(chloromethyl)-2,5-dimethylbenzene (**15b**) with TsNHNa. Their symmetry point groups are shown in Chart II: of **16da** and **16db**, only **16db** is chiral, as it contains only C_2 symmetry elements (torsional dissymmetry).

Contrary to previous observations on structurally related tetrasubstituted 2,11-dithia[3.3]paracyclophane systems,[26]

Scheme VI



17

	n	R	R'
17a	1	Me	H
17b	2	Me	H
17c	1	Me	Me

18

	n	R	R'
18a	1	Me	H
18b	1	Me	Me

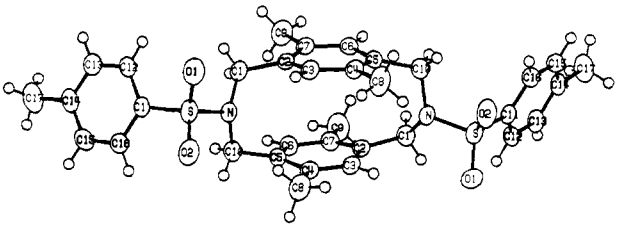


Figure 1. ORTEP drawing and atomic numbering scheme of paracyclophane **16d**.

the coupling reaction of **15b** appeared to be stereospecific since it produced *only* one of the two possible diastereomeric dimers, namely, the less hindered chiral **16db** (35–40%), along with cyclic trimer **16e** (12%). Separation of these compounds was easily achieved by column chromatography. Trimer **16e** was isolated as a 1:1 clathrate with CH_2Cl_2. The solvent was tenaciously held and escaped only at 160–170 °C under very high vacuum (10^{-6}–10^{-7} mmHg). Detosylation of **16d,e** to **17a,b** and subsequent conversion of **17a** to **18a** by the above methods (Scheme VI) were accomplished in excellent yield.

The ^1H NMR spectra of dimers **16db**, **17a**, and **18a** exhibited AB quartets (J_{AB} = 13.4–14.3 Hz) for the methylene protons centered at δ 4.10, 3.78, and 3.37, respectively, which remained unchanged in the temperature range 30–180 °C (DMSO-d_6), thus supporting the above assumption of hindered rotation of the phenyl rings in these systems.

The chiral structure of these dimers was unambiguously assigned by means of the chiral tris(*d,d*-dicampholylmethanato)europium(III) [Eu(dcm)$_3$] shift reagent.[27] In fact, addition of Eu(dcm)$_3$ to a $CDCl_3$ solution of **17a** caused the splitting of methyl (δ 2.22) and aromatic (δ 6.73) proton signals to two pairs of singlets of roughly equal

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(25) Cram, D. J.; Maxwell Cram, J. *Acc. Chem. Res.* **1971**, *4*, 204 and references therein.

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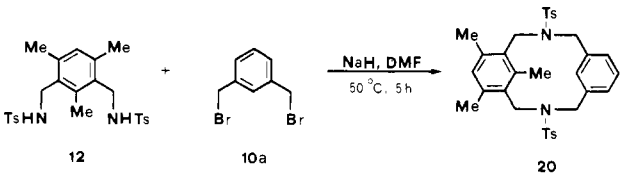
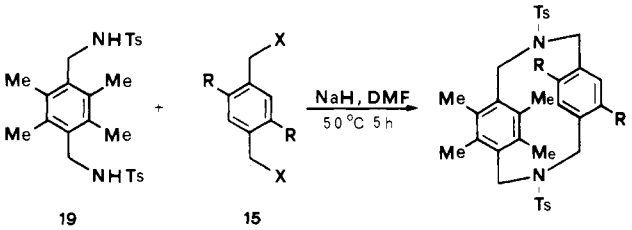
Scheme VII



12 10a 20

Scheme VIII



19 15 21

	X	R
15a	Br	H
15b	Cl	Me

21a R=H

21b R=Me

intensity at δ 2.57 and 2.68, and δ 7.27 and 7.51, respectively, owing to the diastereomeric interaction between the substrate and Eu(dcm)$_3$, while the methylene protons appeared as two broad signals at δ 4.83 and 5.13. Therefore, coupling of appropriately substituted 1,4-bis(halomethyl)benzenes with TsNHNa may provide a good source of optically stable 2,11-diaza[3.3]paracyclophanes.

Chiral structure **16db** was further confirmed by a single-crystal X-ray diffraction study. Coordinates are given in Table I, and the molecule is illustrated in Figure 1. The molecule lies on a crystallographic twofold axis. The cyclophane aromatic rings are slightly nonplanar, having a slightly bowed conformation, in which C(2) and C(5) lie 0.064 (3) and 0.059 (3) Å, respectively, out of the aromatic best plane, toward the interior of the molecule, while C(3), C(4), C(6), and C(7) lie an average of 0.031 Å out of the best plane toward the outside. The two aromatic best planes are parallel, and their centers are separated by 3.179 Å. The S–N bond has length 1.637 (2) Å, and the pyramidal coordination about N is considerably flattened, with angles ranging 116.0 (2)–116.5 (2)°.

The reaction of bis(chloromethyl)durene (**15c**) with TsNHNa produced the fully methyl substituted dimer **16f** (15%) (Scheme V), along with 1,4-bis[(tosylamino)methyl]durene (**19**) (36%). Dimer **16f** was smoothly converted (Na–NH$_3$) to diamino macrocycle **17c** (82%), which upon methylation (CH_2O, HCO_2H) gave derivative **18b** (76%) (Scheme VI).

The ^{1}H NMR spectra of **16f**, **17c**, and **18b** displayed sharp singlets for the methylene protons at δ 4.40, 4.14, and 3.67, respectively, which may indicate for these systems a rapid interconversion at room temperature between the boat and chair conformers.[24c,28]

The ready availability of bis[(tosylamino)methyl] derivatives **12** and **19** led us to make a digression into the synthesis of unsymmetrical 2,11-diaza[3.3]cyclophanes **20** (Scheme VII) and **21** (Scheme VIII). Dropwise addition of a DMF solution of equimolar quantities of **12** and **10a** to a suspension of NaH in anhydrous DMF afforded *syn*-*N*,*N*′-ditosyl-5,7,9-trimethyl-2,11-diaza[3.3]metacyclophane (**20**) in a 75% yield, while the anti stereoisomer was not even detected from the reaction mixture. Similarly, the reaction of **19** with **15** (R = H, CH$_3$) produced *N*,*N*′-ditosyl-2,11-diaza[3.3]paracyclophanes **21a** (52%) and **21b** (60%), respectively.

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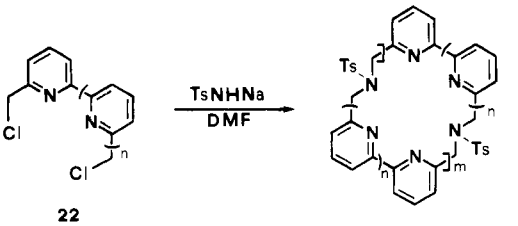
Scheme IX



22

22a n=0

22b n=1

23

	n	m
23a	0	1
23b	0	2
23c	1	1

The ^{1}H NMR spectrum of **20** displayed singlets at δ 2.03 (3 H), 2.09 (6 H), and 2.48 (6 H) for the mesityl and tosyl methyl groups, respectively, a complex eight-line pattern [two distinct AB systems centered at δ 4.05 (J = 14.7 Hz) and 4.39 (J = 13.2 Hz)] for the magnetically nonequivalent methylene protons in the region at δ 3.5–4.7, three broad singlets at δ 6.16 (1 H), 6.40 (1 H), and 6.97 (3 H), which were assigned to C_{18}-H, C_6-H, and C_{14-16}-H protons, respectively, and a double doublet (AA′BB′ system, J = 8.4 Hz) centered at δ 7.61 for the tosyl aromatic protons. These assignments were confirmed by spin-decoupling experiments. This spectral pattern is diagnostic for a fixed syn conformation of **20**, as compared to the anti conformation of **11b**, in which the intraannular methyl groups (δ 1.05) experience a remarkable diamagnetic shielding from the opposing aromatic ring.[29] Furthermore, no syn–anti isomer interconversion occurred in **20**, as suggested by the invariance of its ^{1}H NMR spectrum up to temperatures as high as 180 °C (DMSO-d_6).

Unsymmetrical structures **21** are substantiated by magnetic nonequivalence of the methylene protons, which show up as two singlets at δ 4.05 and 4.45 in **21a** and as two distinct doublets of doublets centered at δ 4.10 (J = 13.2 Hz) and 4.42 (J = 13.9 Hz) in **21b**. It is noteworthy that the signal of the duryl moiety in the latter is split into two singlets at δ 2.27 and 2.29, further confirming the hindered rotation of the phenyl rings in these systems.

The coupling reaction was also extended to the synthesis of pyridino- and bipyridino-aza-crown analogues **23** (Scheme IX). Treatment of 2,6-bis(chloromethyl)pyridine (**22a**) with TsNHNa under standard conditions afforded (66%) *N*,*N*′-ditosyl-2,11-diaza[3.3](2,6)pyridinophane (**23a**) as the major product, along with minor amounts (9%) of the trimer *N*,*N*′,*N*″-tritosyl-2,11,20-triaza[3.3.3](2,6)-pyridinophane (**23b**). Hydrolytic removal of the tosyl groups from these materials (90% H_2SO_4) gave the free polyamino macrocycles **24a** (88%) and **24b** (81%), respectively, which upon treatment with CH_2O–HCO_2H were converted to their *N*-methyl derivatives **25a** (61%) and **25b** (68%) (Scheme X).

As anticipated, when this reaction was applied to 6,6′-bis(chloromethyl)-2,2′-bipyridine (**22b**), dimer **23c**[14,30] was obtained in 46% yield. Subsequent hydrolytic detosylation to diamino macrocycle **24c** followed by N-methylation to derivative **25c** was accomplished in 74% overall yield.

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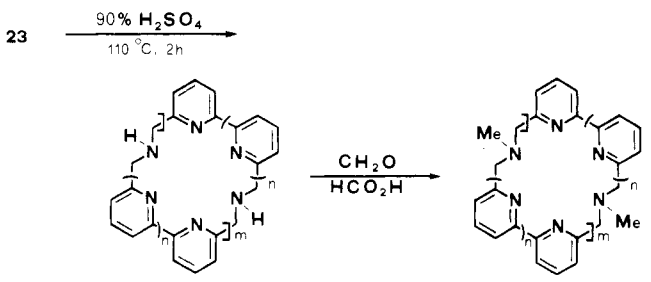
Scheme X



	n	m
24a	0	1
24b	0	2
24c	1	1

	n	m
25a	0	1
25b	0	2
25c	1	1

The ^{1}H NMR spectra of *N*-tosyl compounds **23** displayed complicated patterns in the aromatic region, because of the overlapping of tosyl aromatic protons with those of the pyridine moieties. However, compounds **24** and **25** gave clearer ^{1}H NMR spectra, and the pyridine protons showed up as AB_2 systems in pyridinophanes **24a,b** and **25a,b** and as AMX systems in bipyridinophanes **24c** and **25c**.

In solution, the conformational preference of dimers **24a** and **25a** was easily ascertained by chemical shift comparison of their pyridyl protons with those of the corresponding trimers **24b** and **25b**. On the basis of previous reports on related pyridinophanes,[31] the upfield shift ($\Delta\delta$ = 0.22–0.55 ppm) experienced by the pyridyl protons in **24a** and **25a** was considered supportive of the syn conformation in solution.

In conclusion, we have demonstrated the utility and efficiency of the TsNHNa method for the synthesis of a wide variety of *N*-tosyl aza macrocycles. The procedure overcomes the cumbersome preparation and hazardous handling of suitable aryl and heteroaryl diamino precursors. Furthermore, removal of the tosyl functionalities from these materials affords polyamino macrocycles, which may provide suitable matrixes for more sophisticated macropolycyclic host molecules[32] and for macromolecular systems.[33] Further structural modifications of these compounds for specific applications are in progress.

Experimental Section

General Comments. Melting points were determined on a Kofler apparatus and are uncorrected. Unless otherwise noted, ^{1}H NMR spectra were obtained in $CDCl_3$ with Me_4Si as the internal standard and recorded on a Bruker WP-80 NMR spectrometer. Mass spectra (MS) were determined on a LKB 9000S instrument or a Kratos MS 50 double-focusing mass spectrometer operating at 18 eV; *m/z* values reported include the parent ion peak. Elemental analyses were obtained commercially. Oligoethylene glycol diiodides **6a,b** were obtained from the appropriate dichlorides by the Finkelstein reaction.[34] Dibromide **6c** was synthesized by reaction of tetraethylene glycol with PBr_3.[35] Isomeric α,α'-dibromoxylenes were prepared by bromination of the pure xylenes with NBS in CCl_4. Bis(chloromethyl)mesitylene **10b**,[36] bis(chloromethyl)durene (**15c**),[37] 2,6-bis(chloromethyl)-pyridine (**22a**),[38] and 6,6′-bis(chloromethyl)-2,2′-bipyridine (**22b**)[39] were prepared by literature procedures. 1,4-Bis(chloromethyl)-2,5-dimethylbenzene (**15b**) was obtained from Fluka and used without further purification.

Tosylamide Monosodium Salt (TsNHNa). To a stirred, refluxing solution of freshly prepared NaOEt (23.8 g, 0.35 mol) in absolute EtOH (400 mL) was added solid 1 (60 g, 0.35 mol). The mixture was refluxed for 2 h and then cooled. The insoluble TsNHNa was collected by filtration, washed with absolute EtOH, and dried in vacuo to give >90% yield. This salt was used without further purification and could be stored indefinitely.

Reaction of TsNHNa with Bis(halomethyl) Compounds in DMF. General *N*-Tosyl Aza Macrocycle Preparation. To a stirred solution of TsNHNa (0.965 g, 5 mmol) in anhydrous DMF (100 mL) at 80 °C was added dropwise under a N_2 atmosphere a solution of dihalide (5 mmol) in DMF (10 mL). After 1 h, solid TsNHNa (0.965 g, 5 mmol) was added all at once, and the mixture was stirred at 80 °C for 4 h. On cooling, *N*-tosylazacyclophanes and -azaheterophanes precipitated from the reaction mixture, or crystallized out on evaporation of most of the solvent under reduced pressure. Further purification was achieved by recrystallization or by column chromatography, as noted below. In the case of the more soluble *N*-tosyl-aza-crown compounds, concentration of the reaction mixture to dryness gave an oily residue, which was extracted with chloroform, thoroughly washed with 1 N NaOH, dried (Na_2SO_4), and chromatographed (SiO_2, eluent cyclohexane–AcOEt, 2:1) to afford the desired compound(s).

Reaction of TsNHNa with Bis(2-iodoethyl) Ether (6a). The above general procedure was followed with **6a** (1.63 g, 5 mmol) to give *N*-tosylmorpholine (**7a**) as white needles: 1.19 g, 99%; mp 147–148 °C (MeOH) (lit.[41] mp 147 °C); ^{1}H NMR δ 2.45 (s, Ts CH_3, 3 H), 2.99 (t, J = 4.8 Hz, αCH_2, 4 H), 3.74 (t, J = 4.8 Hz, βCH_2, 4 H), 7.35 (d, J = 8.4 Hz, Ts H, 2 H), and 7.66 (d, J = 8.4 Hz, Ts H, 2 H); MS, *m/z* M^+ 241.

Reaction of TsNHNa with 1,2-Bis(2-iodoethoxy)ethane (6b). The above general procedure was followed except for the substitution of **6b** (1.85 g, 5 mmol); usual workup followed by chromatography (eluent cyclohexane–AcOEt, 2:1) afforded fractions A and B.

Fraction A yielded *N*-tosyl-aza-9-crown-3 (**7b**) as white prisms: 0.36 g, 25%; R_f 0.23; mp 98–100 °C (Et_2O); ^{1}H NMR δ 2.43 (s, Ts CH_3, 3 H), 3.33 (t, J = 4.2 Hz, αCH_2, 4 H), 3.75 (s, γCH_2, 4 H), 3.91 (t, J = 4.2 Hz, βCH_2, 4 H), 7.32 (d, J = 8.4 Hz, Ts H, 2 H), and 7.70 (d, J = 8.4 Hz, Ts H, 2 H); MS, *m/z* M^+ 285. Anal. Calcd for $C_{13}H_{19}NO_4S$: C, 54.72; H, 6.71; N, 4.91. Found: C, 54.55; H, 6.64; N, 4.85.

Fraction B gave *N,N′*-ditosyl-1,10-diaza-18-crown-6 (**7c**) as white needles: 0.071 g, 5%; R_f 0.38 (cyclohexane–AcOEt, 1:1); mp 164–166 °C (MeCN) (lit.[12a] mp 163.5–164.5 °C); ^{1}H NMR δ 2.41 (s, Ts CH_3, 6 H), 3.41 (d, J = 5.5 Hz, αCH_2, 8 H), 3.55 (s, γCH_2, 8 H), 3.62 (d, J = 5.5 Hz, βCH_2, 8 H), 7.34 (d, J = 8.4 Hz, Ts H, 4 H), and 7.73 (d, J = 8.4 Hz, Ts H, 4 H); MS, *m/z* M^+ 570.

Reaction of TsNHNa with Bis[2-(2-bromoethoxy)ethyl] Ether (6c). The general procedure was followed except for the substitution of **6c** (2.5 g, 5 mmol); usual workup followed by chromatography (eluent AcOEt–cyclohexane, 1:1) afforded *N*-tosyl-aza-12-crown-4 (**7d**) as colorless prisms: 0.51 g, 35%; R_f 0.36; mp 63–65 °C (Et_2O); ^{1}H NMR δ 2.42 (s, Ts CH_3, 3 H), 3.33 (t, J = 4.9 Hz, αCH_2, 4 H), 3.64 (t, J = 4.8 Hz, βCH_2, 4 H), 3.82 [t, J = 4.8 Hz, (γ + δ)CH_2, 8 H], 7.30 (d, J = 8.4 Hz, Ts H, 2 H), and 7.72 (d, J = 8.4 Hz, Ts H, 2 H); MS, *m/z* M^+ 329. Anal. Calcd for $C_{15}H_{23}NO_5S$: C, 54.70; H, 7.04; N, 4.25. Found: C, 54.95; H, 6.99; N, 4.16.

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Reaction of TsNHNa with 1,2-Bis(bromomethyl)benzene (8). The general procedure was followed except for the substitution of 8 (1.31 g, 5 mmol); the usual workup gave *N*-tosyldihydroisoindole (**9**) as colorless crystals: 1.34 g, 99%; mp 178–179 °C (MeOH) (lit.[41] mp 176 °C); ^{1}H NMR δ 2.39 (s, Ts CH_3, 3 H), 4.62 (s, CH_2, 4 H), 7.19 (s, Ph H, 4 H), 7.30 (d, J = 8.4 Hz, Ts H, 2 H), and 7.78 (d, J = 8.4 Hz, Ts H, 2 H); MS, m/z M^+ 273.

Reaction of TsNHNa with 1,3-Bis(bromomethyl)benzene (10a). The general procedure was followed except for the substitution of **10a** (1.31 g, 5 mmol). The usual workup yielded *N,N'*-ditosyl-2,11-diaza[3.3]metacyclophane (**11a**) as white prisms: 0.72 g, 53%; mp 266–268 °C (dioxane) (lit.[20] mp 257–259 °C); ^{1}H NMR δ 2.48 (s, Ts CH_3, 6 H), 4.32 (s, CH_2, 8 H), 6.85 (s, external Ph H, 6 H), 7.19 (br s, internal Ph H, 2 H), 7.40 (d, J = 8.4 Hz, Ts H, 4 H), and 7.82 (d, J = 8.4 Hz, Ts H, 4 H); MS, m/z M^+ 546.

Reaction of TsNHNa with Bis(chloromethyl)mesitylene (10b). The general procedure was followed except for the substitution of **10b** (1.08 g, 5 mmol). The reaction produced a white precipitate, which was collected by filtration, thoroughly washed with water, dried, and recrystallized from DMF to give *anti-N,N'*-ditosyl-5,7,9,14,16,18-hexamethyl-2,11-diaza[3.3]metacyclophane (**11b**) as white prisms: 0.25 g, 16%; mp >300 °C; ^{1}H NMR δ 1.05 (s, internal Ar CH_3, 6 H), 1.99 (s, external Ar CH_3, 12 H), 2.47 (s, Ts CH_3, 6 H), 4.29 (AB quartet, J_{AB} = 13.6 Hz, Δν = 46.2 Hz, CH_2, 8 H), 6.58 (br s, Ar H, 2 H), 7.39 (d, J = 8.4 Hz, Ts H, 4 H), and 7.86 (d, J = 8.4 Hz, Ts H, 4 H); MS, m/z M^+ 630. Anal. Calcd for $C_{36}H_{42}N_2O_4S_2$: C, 68.54; H, 6.71; N, 4.44. Found: C, 68.74; H, 6.91; N, 4.71.

Concentration of the mother liquor to a small volume followed by dilution with acetone produced white crystals of 2,4-bis[(tosylamino)methyl]mesitylene (**12**): 0.75 g, 31%; R_f 0.08; mp 211–213 °C; ^{1}H NMR δ 1.93 (s, Ar CH_3, 3 H), 2.07 (s, Ar CH_3, 6 H), 2.41 (s, Ts CH_3, 6 H), 3.97 (d, J = 5.1 Hz, Ar CH_2, 4 H), 4.31 (br t, J = 5.1 Hz, NH, 2 H), 6.72 (br s, Ar H, 1 H), 7.28 (d, J = 8.2 Hz, Ts H, 4 H), and 7.78 (d, J = 8.2 Hz, Ts H, 4 H); MS, m/z M^+ 486. Anal. Calcd for $C_{25}H_{30}N_2O_4S_2$: C, 61.70; H, 6.21; N, 5.76. Found: C, 61.44; H, 6.12; N, 5.71.

Reaction of TsNHNa with 1,4-Bis(bromomethyl)benzene (15a). The general procedure was followed except for the substitution of **15a** (1.31 g, 5 mmol). The usual workup afforded a solid, which was chromatographed (column, SiO_2) by eluting with CH_2Cl_2 to give fractions A–C.

Fraction A afforded *N,N'*-ditosyl-2,11-diaza[3.3]paracyclophane (**16a**) as white crystals: 0.38 g, 28%; R_f 0.49; mp >280 °C (dioxane) (lit.[16] mp 322.1–322.6 °C); ^{1}H NMR δ 2.48 (s, Ts CH_3, 6 H), 4.32 (s, CH_2, 8 H), 6.91 (s, Ar H, 8 H), 7.39 (d, J = 8.4 Hz, Ts H, 4 H), and 7.80 (d, J = 8.4 Hz, Ts H, 4 H); MS m/z M^+ 546.

Fraction B gave *N,N',N''*-tritosyl-2,11,20-triaza[3.3.3]paracyclophane (**16b**) as white crystals: 0.27 g, 20%; R_f 0.21; mp >280 °C (lit.[16] mp 300 °C dec); ^{1}H NMR δ 2.46 (s, Ts CH_3, 9 H), 4.15 (s, CH_2, 12 H), 6.95 (s, Ar H, 12 H), 7.36 (d, J = 8.4 Hz, Ts H, 6 H), and 7.76 (d, J = 8.4 Hz, Ts H, 6 H).

Fraction C yielded *N,N',N'',N'''*-tetratosyl-2,11,20,29-tetraaza[3.3.3.3]paracyclophane (**16c**) as white crystals: 0.16 g, 12%; R_f 0.19; mp > 280 °C (lit.[16] mp 320 °C dec); ^{1}H NMR δ 2.48 (s, Ts CH_3, 12 H), 4.08 (s, CH_2, 16 H), 6.80 (s, Ar H, 16 H), 7.34 (d, J = 8.4 Hz, Ts H, 8 H), and 7.73 (d, J = 8.4 Hz, Ts H, 8 H).

Reaction of TsNHNa with 1,4-Bis(chloromethyl)-2,5-dimethylbenzene (15b). The general procedure was followed except for the substitution of **15b** (1.01 g, 5 mmol). The reaction produced a crystalline precipitate, which was collected by filtration, washed with water, and dried. The filtrate was concentrated in vacuo to a small volume to give a second crop of crystals. The combined solids were chromatographed (column, SiO_2) by eluting with CH_2Cl_2 to afford fractions A and B.

Fraction A gave *N,N'*-ditosyl-5,8,15,18-tetramethyl-2,11-diaza[3.3]paracyclophane (**16d**) as white prisms: 0.53 g, 35%; R_f 0.34; mp 337–338 °C dec (DMF); ^{1}H NMR δ 2.18 (s, Ar CH_3, 12 H), 2.49 (s, Ts CH_3, 6 H), 4.10 (AB quartet, J_{AB} = 13.9 Hz, Δν = 28.6 Hz, CH_2, 8 H), 6.79 (br s, Ar H, 4 H), 7.40 (d, J = 8.1 Hz, Ts H, 4 H), and 7.79 (d, J = 8.1 Hz, Ts H, 4 H); MS, m/z M^+ 602. Anal. Calcd for $C_{34}H_{38}N_2O_4S_2$: C, 67.74; H, 6.35; N, 4.65. Found: C, 67.98; H, 6.29; N, 4.70.

Fraction B yielded *N,N',N''*-tritosyl-5,8,14,17,23,26-hexamethyl-2,11,20-triaza[3.3.3]paracyclophane (**16e**) as white crystals: 0.18 g, 12%; R_f 0.20; mp 286–290 °C dec (dichoromethane); ^{1}H NMR δ 1.98 (s, Ar CH_3, 18 H), 2.46 (s, Ts CH_3, 9 H), 4.05 (br s, CH_2, 12 H), 5.29 (s, CH_2Cl_2, 2 H), 6.80 (s, Ar H, 6 H), 7.36 (d, J = 8.1 Hz, Ts H, 6 H), and 7.76 (d, J = 8.1 Hz, Ts H, 6 H); MS, m/z $(M - Ts)^+$ 749. Anal. Calcd for $C_{51}H_{57}N_3O_6S_3 \cdot CH_2Cl_2$: C, 63.14; H, 6.01; N, 4.25. Found: C, 62.55; H, 6.09; N, 4.46.

From the mother liquor a small amount of 1,4-bis[(tosylamino)methyl]-2,5-dimethylbenzene was also isolated (<1%): ^{1}H NMR δ 2.12 (s, Ar CH_3, 6 H), 2.44 (s, Ts CH_3, 6 H), 4.02 (d, J = 5.9 Hz, CH_2, 4 H), 4.37 [t, J = 5.5 Hz, NH (exchangeable with D_2O), 2 H], 6.85 (s, Ar H, 2 H), 7.31 (d, J = 8.4 Hz, Ts H, 4 H), and 7.76 (d, J = 8.4 Hz, Ts H, 4 H); MS, m/z M^+ 472.

Reaction of TsNHNa with Bis(chloromethyl)durene (15c). The general procedure was followed except for the substitution of **15c** (1.15 g, 5 mmol). The reaction produced a white precipitate, which was collected by filtration, washed with water, dried, and recrystallized to give *N,N'*-ditosyl-5,6,8,9,14,15,17,18-octamethyl-2,11-diaza[3.3]paracyclophane (**16f**) as white microcrystals: 0.25 g, 15%; mp >300 °C (*o*-dichlorobenzene); ^{1}H NMR δ 2.19 (s, Ar CH_3, 24 H), 2.52 (s, Ts CH_3, 6 H), 4.40 (s, CH_2, 8 H), 7.42 (d, J = 8.4 Hz, Ts H, 4 H), and 7.81 (d, J = 8.4 Hz, Ts H, 4 H); MS, m/z M^+ 658. Anal. Calcd for $C_{38}H_{46}N_2O_4S_2$: C, 69.27; H, 7.04; N, 4.25. Found: C, 68.96; H, 6.95; N, 4.16.

Concentration of the mother liquor to a small volume (15 mL) gave a solid, which on recrystallization afforded 1,4-bis[(tosylamino)methyl]durene (**19**) as white crystals: 0.9 g, 36%; mp 306–308 °C dec (DMF–H_2O); ^{1}H NMR (DMSO-d_6) δ 2.02 (s, Ar CH_3, 12 H), 2.40 (s, Ts CH_3, 6 H), 3.88 (d, J = 5.5 Hz, CH_2, 4 H), and 7.3–7.8 (m, Ts H + NH, 10 H); ^{1}H NMR (DMSO-d_6 with added D_2O) δ 2.02 (s, Ar CH_3, 12 H), 2.40 (s, Ts CH_3, 6 H), 3.88 (s, CH_2, 4 H), 7.41 (d, J = 8.4 Hz, Ts H, 4 H), and 7.75 (d, J = 8.4 Hz, Ts H, 4 H); MS, m/z M^+ 500. Anal. Calcd for $C_{26}H_{32}N_2O_4S_2$: C, 62.37; H, 6.44; N, 5.59. Found: C, 62.15; H, 6.39; N, 5.66.

Reaction of TsNHNa with 2,6-Bis(chloromethyl)pyridine (22a). The general procedure was followed except for the substitution of **22a** (0.88 g, 5 mmol). The usual workup afforded a solid, which was chromatographed (column, SiO_2) by eluting with CH_2Cl_2 containing increasing amounts of AcOEt (2–15%) to give two main fractions, A and B.

Fraction A afforded *N,N',N''*-tritosyl-2,11,20-triaza[3.3.3]-(2,6)pyridinophane (**23b**) as white crystals: 0.12 g, 9%; R_f 0.44 (cyclohexane–AcOEt, 1:1); mp >230 °C; ^{1}H NMR δ 2.41 (s, Ts CH_3, 9 H), 4.28 (s, CH_2, 12 H), 7.0–7.4 (m, Ts H + Py H, 10 H), and 7.80 (d, J = 8.4 Hz, Ts H, 4 H); MS, m/z $(M - Ts - TsH)^+$ 511. Anal. Calcd for $C_{42}H_{42}N_6O_6S_3$: C, 61.29; H, 5.14; N, 10.21. Found: C, 61.15; H, 5.12; N, 10.32.

Fraction B gave *N,N'*-ditosyl-2,11-diaza[3.3](2,6)pyridinophane (**23a**) as white scales: 0.90 g, 66%; R_f 0.08 (cyclohexane–AcOEt, 1:1); mp 247 °C dec (dioxane); ^{1}H NMR δ 2.46 (s, Ts CH_3, 6 H), 4.48 (s, CH_2, 8 H), 7.1–7.4 (m, Ts H + Py H, 10 H), and 7.80 (d, J = 8.4 Hz, Ts H, 4 H); MS, m/z M^+ 548. Anal. Calcd for $C_{28}H_{28}N_4O_4S_2$: C, 61.29; H, 5.14; N, 10.21. Found: C, 61.37; H, 5.26; N, 10.32.

Reaction of TsNHNa with 6,6'-Bis(chloromethyl)-2,2'-bipyridine (22b). The general procedure was followed except for the substitution of **22b** (1.26 g, 5 mmol). The solid which deposited by concentration of the reaction mixture to a small volume (15–20 mL) was collected by filtration, washed with water and EtOH, and recrystallized from DMF to give *N,N'*-ditosyl-2,17-diaza[3.3](6,6')-2,2'-bipyridinophane (**23c**) as white prisms (0.80 g, 46%), identical in all respects with an authentic sample.[14,30]

***syn*-*N,N'*-Ditosyl-5,7,9-trimethyl-2,11-diaza[3.3]metacyclophane (20). A General Procedure for the Preparation of Unsymmetrical *N*-Tosylazacyclophanes.** To a stirred suspension of NaH (72 mg, 0.3 mmol) in anhydrous DMF (20 mL) at 50 °C was added a solution of **12** (486 mg, 1 mmol) and **10a** (262 mg, 1 mmol) in DMF (30 mL) over a period of 2 h under nitrogen atmosphere. After additional stirring and heating for 5 h, the reaction mixture was allowed to cool to room temperature, and MeOH (1 mL) was added to quench the reaction. The solvent was evaporated in vacuo, and the residue was partitioned between water and CH_2Cl_2. The organic extract was washed with water, dried over anhydrous Na_2SO_4, and evaporated in vacuo to give a solid, which was chromatographed (column, SiO_2) by eluting with CH_2Cl_2 to afford unsymmetrical dimer **20** as white crystals:

0.44 g, 75%; mp 289–292 °C dec (toluene); ^{1}H NMR δ 2.03 (s, Ar CH_3, 6 H), 2.09 (s, Ar CH_3, 3 H), 2.48 (s, Ts CH_3, 6 H), 4.05 (AB quartet, J_{AB} = 14.7 Hz, Δν = 74.8 Hz, CH_2, 4 H), 4.39 (AB quartet, J_{AB} = 13.2 Hz, Δν = 34.8 Hz, CH_2, 4 H), 6.16 (br s, internal Ph H, 1 H), 6.40 (br s, Ar H, 1 H), 6.97 (br s, external Ph H, 3 H), 7.40 (d, J = 8.4 Hz, Ts H, 4 H), and 7.82 (d, J = 8.4 Hz, Ts H, 4 H); MS, m/z M$^+$ 588. Anal. Calcd for $C_{33}H_{36}N_2O_4S_2$: C, 67.32; H, 6.16; N, 4.76. Found: C, 67.55; H, 6.11; N, 4.63.

***N,N'*-Ditosyl-5,6,8,9-tetramethyl-2,11-diaza[3.3]paracyclophane (21a).** When the above general procedure was followed, the reaction of **19** (0.5 g, 1 mmol) with **15a** (0.262 g, 1 mmol) produced unsymmetrical dimer **21a** in 52% yield: white crystals, mp 320–322 °C dec (DMF); ^{1}H NMR δ 2.15 (s, Ar CH_3, 12 H), 2.50 (s, Ts CH_3, 6 H), 4.05, 4.45 (s, CH_2, 8 H), 6.95 (s, Ph H, 4 H), 7.41 (d, J = 8.4 Hz, Ts H, 4 H), and 7.80 (d, J = 8.4 Hz, Ts H, 4 H); MS, m/z M$^+$ 602. Anal. Calcd for $C_{34}H_{38}N_2O_4S_2$: C, 67.74; H, 6.35; N, 4.65. Found: C, 67.95; H, 6.21; N, 4.78.

***N,N'*-Ditosyl-5,6,8,9,14,17-hexamethyl-2,11-diaza[3.3]paracyclophane (21b).** The reaction of equimolar amounts of **19** and **15b** under the above standard conditions gave unsymmetrical dimer **21b** in 60% yield: white prisms, mp >320 °C dec (DMF); ^{1}H NMR δ 2.13 (s, *p*-xylyl CH_3, 6 H), 2.27, 2.29 (s, duryl CH_3, 12 H), 2.51 (s, Ts CH_3, 6 H), 4.10 (AB quartet, J_{AB} = 13.2 Hz, Δν = 97.1 Hz, CH_2, 4 H), 4.42 (AB quartet, J_{AB} = 13.9 Hz, Δν = 38.9 Hz, CH_2, 4 H), 6.68 (s, Ar H, 2 H), 7.43 (d, J = 8.4 Hz, Ts H, 4 H), and 7.81 (d, J = 8.4 Hz, Ts H, 4 H); MS, m/z M$^+$ 630. Anal. Calcd for $C_{36}H_{42}N_2O_4S_2$: C, 68.54; H, 6.71; N, 4.44. Found: C, 68.26; H, 6.65; N, 4.41.

Reductive Detosylation of *N*-Tosylazacyclophanes. A General Procedure. To a stirred slurry of *N*-tosylazacyclophane (1 mmol) in liquid NH_3 (150 mL) under argon was added a large excess of sodium (1.15 g, 50 mmol) in small portions. The reaction mixture turned dark blue at once. After the mixture was stirred for about 6 h, excess NH_4Cl (2.65 g, 50 mmol) was added (the color turned dark brown), and NH_3 was evaporated. The residue was treated with MeOH (2 mL) and then with 1 N NaOH (10 mL) and extracted with $CHCl_3$ (4 × 10 mL). The $CHCl_3$ extract was dried over anhydrous Na_2SO_4 and concentrated in vacuo to give almost colorless crystals of the cyclic polyamine, which was used in the subsequent alkylation step without further purification.

***anti*-5,7,9,14,16,18-Hexamethyl-2,11-diaza[3.3]metacyclophane (13):** 85% yield from **11b**; white solid decomposing over 220 °C; ^{1}H NMR δ 1.04 (s, internal CH_3, 6 H), 1.70 [br s, NH (exchangeable with D_2O), 2 H], 2.38 (s, external CH_3, 12 H), 3.83 (AB quartet, J_{AB} = 14.4 Hz, Δν = 32.4 Hz, CH_2, 8 H), and 6.76 (br s, Ar H, 2 H); MS, m/z M$^+$ 322.

5,8,15,18-Tetramethyl-2,11-diaza[3.3]paracyclophane (17a): 90% yield from **16d**; white crystals, mp 200–205 °C; ^{1}H NMR δ 1.80 [s, NH (exchangeable with D_2O), 2 H], 2.22 (s, CH_3, 12 H), 3.78 (AB quartet, J_{AB} = 14.3 Hz, Δν = 30.8 Hz, CH_2, 8 H), and 6.73 (s, Ar H, 4 H); MS, m/z M$^+$ 294.

5,8,14,17,23,26-Hexamethyl-2,11,20-triaza[3.3.3]paracyclophane (17b): 78% yield from **16e**; white powder, mp 150–160 °C; ^{1}H NMR δ 1.74 [br s, NH (exchangeable with D_2O), 3 H], 2.01 (s, CH_3, 18 H), 3.68 (s, CH_2, 12 H), and 6.71 (br s, Ar H, 6 H); MS, m/z M$^+$ 441.

5,6,8,9,14,15,17,18-Octamethyl-2,11-diaza[3.3]paracyclophane (17c): 82% yield from **16f**; white solid decomposing over 230 °C; ^{1}H NMR δ 1.87 [br s, NH (exchangeable with D_2O), 2 H], 2.22 (s, CH_3, 24 H), and 4.14 (s, CH_2, 8 H); MS, m/z M$^+$ 350.

Hydrolytic Detosylation of *N*-Tosylazaheterophanes. A General Procedure. The tosylated aza macrocycle (1 mmol) was dissolved in 90% H_2SO_4 (5 mL) and stirred at 110 °C for 2 h. After cooling, the solution was cautiously diluted with water (5 mL) and poured into an aqueous solution of NaOH (excess). The resulting solid was extracted with $CHCl_3$, dried over anhydrous Na_2SO_4, and concentrated to dryness to give the macrocyclic polyamine, which was not further purified.

2,11-Diaza[3.3](2,6)pyridinophane (24a): 88% yield from **23a**; ^{1}H NMR δ 3.33 [br s, NH (exchangeable with D_2O), 2 H], 4.02 (s, CH_2, 8 H), 6.54 (B_2 part of an AB_2 system, J_{AB} = 7.45 Hz, 3,5-Py H, 4 H), and 7.10 (A part of an AB_2 system, J_{AB} = 7.45 Hz, 4-Py H, 2 H); MS, m/z M$^+$ 240. Anal. Calcd for $C_{14}H_{16}N_4$: C, 69.74; H, 6.71; N, 23.32. Found: C, 69.36; H, 6.94; N, 23.44.

2,11,20-Triaza[3.3.3](2,6)pyridinophane (24b): 81% yield from **23b**; ^{1}H NMR δ 3.23 [s, NH (exchangeable with D_2O), 3 H], 3.94 (s, CH_2, 12 H), 7.09 (B_2 part of an AB_2 system, J_{AB} = 7.58 Hz, 3,5-Py H, 6 H), and 7.55 (A part of an AB_2 system, J_{AB} = 7.58 Hz, 4-Py H, 3 H); MS, m/z M$^+$ 360. Anal. Calcd for $C_{21}H_{24}N_6$: C, 69.97; H, 6.71; N, 23.32. Found: C, 70.06; H, 6.88; N, 23.36.

2,17-Diaza[3.3](6,6')-2,2'-bipyridinophane (24c): 90% yield from **23c**; physical and spectroscopic properties of **24c** are in agreement with those reported.[14,30]

General Procedure for the N-Methylation of Polyamino Macrocycles. A stirred mixture of cyclic polyamine (0.2 mmol), HCO_2H (10 mL), and 40% CH_2O (2 mL) was refluxed under a nitrogen atmosphere for 24 h. After cooling, the reaction mixture was treated with 37% HCl (1 mL) and concentrated in vacuo to dryness. The residue was basified with aqueous NaOH and extracted with CH_2Cl_2. The CH_2Cl_2 extract was dried over anhydrous Na_2SO_4 and evaporated in vacuo to leave crude crystals of the desired derivative, which could be purified by recrystallization from an appropriate solvent.

***anti*-*N,N'*-Dimethyl-5,7,9,14,16,18-hexamethyl-2,11-diaza[3.3]metacyclophane (14):** 77% yield from **13**; mp 160–162 °C (MeOH); ^{1}H NMR δ 1.05 (s, internal CH_3, 6 H), 2.34 (s, external CH_3, 12 H), 2.68 (s, NCH_3, 6 H), 3.54 (AB quartet, J_{AB} = 13.7 Hz, Δν = 26.6 Hz, CH_2, 8 H), and 6.72 (br s, Ar H, 2 H); MS, m/z M$^+$ 350. Anal. Calcd for $C_{24}H_{34}N_2$: C, 82.23; H, 9.78; N, 7.99. Found: C, 82.36; H, 9.73; N, 8.02.

***N,N'*-Dimethyl-5,8,15,18-tetramethyl-2,11-diaza[3.3]paracyclophane (18a):** 85% yield from **17a**; mp 111–113 °C (MeOH); ^{1}H NMR δ 2.20 (s, CH_3, 12 H), 2.51 (s, NCH_3, 6 H), 3.37 (AB quartet, J_{AB} = 13.4 Hz, Δν = 33.2 Hz, CH_2, 8 H), and 6.79 (s, Ar H, 4 H); MS, m/z M$^+$ 322. Anal. Calcd for $C_{22}H_{30}N_2$: C, 81.94; H, 9.38; N, 8.68. Found: C, 81.99; H, 9.33; N, 8.76.

***N,N'*-Dimethyl-5,6,8,9,14,15,17,18-octamethyl-2,11-diaza[3.3]paracyclophane (18b):** 76% yield from **17c**; mp 220–228 °C (acetone); ^{1}H NMR δ 2.22 (s, CH_3, 24 H), 2.55 (s, NCH_3, 6 H), and 3.67 (s, CH_2, 8 H); MS, m/z M$^+$ 378. Anal. Calcd for $C_{26}H_{38}N_2$: C, 82.48; H, 10.12; N, 7.40. Found: C, 82.37; H, 10.15; N, 7.46.

***N,N'*-Dimethyl-2,11-diaza[3.3](2,6)pyridinophane (25a):** 61% from **24a**; mp 120–122 °C (hexane); ^{1}H NMR δ 2.73 (s, NCH_3, 6 H), 3.87 (s, CH_2, 8 H), 6.79 (B_2 part of an AB_2 system, J_{AB} = 7.45 Hz, 3,5-Py H, 4 H), and 7.15 (A part of an AB_2 system, J_{AB} = 7.45 Hz, 4-Py H, 2 H); MS, m/z M$^+$ 268. Anal. Calcd for $C_{16}H_{20}N_4$: C, 71.61; H, 7.51; N, 20.88. Found: C, 71.78; H, 7.44; N, 20.71.

***N,N',N''*-Trimethyl-2,11,20-triaza[3.3.3](2,6)pyridinophane (25b):** 68% yield from **24b**; mp 149–150 °C (petroleum ether); ^{1}H NMR δ 2.45 (s, NCH_3, 9 H), 3.68 (s, CH_2, 12 H), 7.05 (B_2 part of an AB_2 system, J_{AB} = 7.33 Hz, 3,5-Py H, 6 H), and 7.37 (A part of an AB_2 system, J_{AB} = 7.33 Hz, 4-Py H, 3 H); MS, m/z M$^+$ 402. Anal. Calcd for $C_{24}H_{30}N_6$: C, 71.61; H, 7.51; N, 20.88. Found: C, 71.74; H, 7.94; N, 20.98.

***N,N'*-Dimethyl-2,17-diaza[3.3](6,6')-2,2'-bipyridinophane (25c):** 82% yield from **24c**; mp 275 °C dec (DCM/AcOEt); ^{1}H NMR δ 2.78 (s, NCH_3, 6 H), 3.90 (s, CH_2, 8 H), 7.02 (dd, J = 7.7, 1.1 Hz, 5-Py H, 4 H), 7.28 (t, J = 7.7 Hz, 4-Py H, 4 H), and 7.70 (dd, J = 7.7, 1.1 Hz, 3-Py H, 4 H); MS, m/z M$^+$ 422. Anal. Calcd for $C_{26}H_{26}N_6$: C, 73.91; H, 6.20; N, 19.89. Found: C, 73.85; H, 6.20; N, 19.77.

X-ray Structure Determination. X-ray data for **16d** were collected by using a crystal of dimensions 0.24 × 0.28 × 0.56 mm on an Enraf-Nonius CAD4 diffractometer equipped with Mo Kα radiation (λ = 0.71073 Å) and a graphite monochromator. Crystal data are as follows: $C_{34}H_{38}N_2O_4S_2$, fw = 602.8, monoclinic space group $C2/c$, a = 20.534 (3) Å, b = 14.584 (2) Å, c = 10.377 (2) Å, β = 100.57 (2)°, V = 3055 (2) Å^3, Z = 4, D_{calcd} = 1.311 g cm^{-3}, T = 23 °C, μ = 2.1 cm^{-1}. One quadrant of data was collected by ω–2θ scans within 2° < 2θ < 50°. Data reduction included corrections for background, Lorentz, and polarization; absorption was insignificant. Of 2686 unique data, 1846 had $I > 3\sigma(I)$ and were used in the refinement.

The structure was solved by direct methods and refined by full-matrix least squares based on F with $w = \sigma^{-2}(F_o)$, non-hydrogen atoms being refined anisotropically. Hydrogen atoms were located by difference maps and included as fixed contributions with isotropic B = 5.0 Å^2. At convergence, R = 0.044, R_w = 0.057

for 191 variables, and the maximum residual density was 0.25 e Å^{-3}.

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Supplementary Material Available: Tables of coordinates for hydrogen atoms, anisotropic thermal parameters, bond distances and angles, torsion angles, and least-squares planes for macrocycle **16d** (6 pages). Ordering information is given on any current masthead page.

Some Transformations of 2-Methylene-1,3-diselenoles

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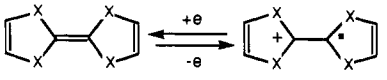
2-Benzylidene-4-phenyl-1,3-diselenole (**5**) was transformed into the green nitroso derivative **7** and the red phenylazo derivative **8** by reaction with NO^+ and PhN_2^+ ions, respectively. Although the parent heterocycle **10** failed to give such substitution and underwent extensive decomposition, it could be transformed into the formyl derivative **13** as well as the novel push–pull-stabilized thioaldehyde **15**. Formyl derivative **13** was further converted into the vinylogous π-donor **20** in ~50% yield. Several other reactions of aldehyde **13** are also reported.

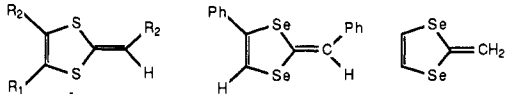
There has been considerable interest in the chemistry of tetrathiafulvalene (**1**, TTF) and its selenium analogue (**2**, TSeF) as a result of the ability of these compounds and many of their derivatives to undergo reversible one-electron oxidation leading to stable cation radicals (**3**), many salts of which show unusual electrical conductivity in the solid state.[1]



1. X = S
2. X = Se

3

Some years ago, we reported a number of novel reactions of several 2-(substituted methylene)-1,3-dithioles (**4**; 1,4-dithiafulvenes),[2] compounds that represent partial structural analogues of tetrathiafulvalenes.[2] In this paper, we present the results of a study of some transformations of the analogous 5-phenyl-2-(phenylmethylene)-1,3-diselenole (**5**)[3] as well as of the parent heterocycle **10**.[4]



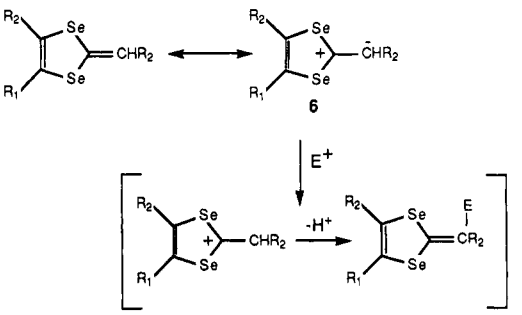
4 5 10

Results and Discussion

Reactions at the Exo Methylene Position. In view of the presumed importance of the dipolar contributor **6** (Scheme I), electrophilic substitution at the exocyclic carbon might at first be expected, although substitution by an electron-transfer process would be more analogous to the behavior of the corresponding dithiafulvene system.[2]

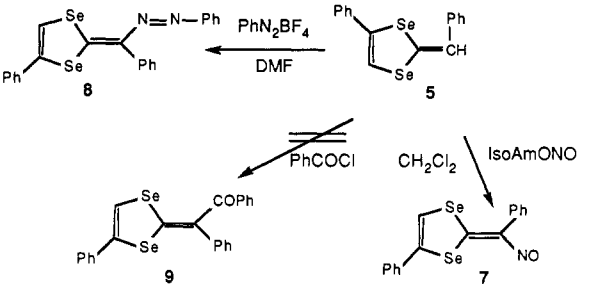
Our initial investigations were carried out with readily available *cis*-5-phenyl-2-(phenylmethylene)-1,3-diselenole (**5**).[3] The corresponding trans isomer afforded the same products.[5] Diselenole **5** was substituted readily by nitrosonium and benzenediazonium ions to yield products **7** and **8**, whereas the use of benzoyl chloride did not lead to **9**, but led to recovery of isomerized starting material

Scheme I



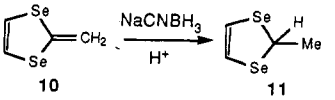
6

Scheme II



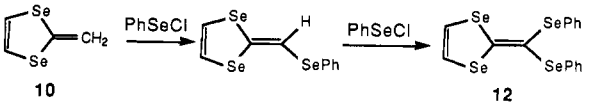
8 5 9 7

Scheme III



10 11

Scheme IV



10 12

(Scheme II). This behavior paralleled that of the corresponding sulfur analogue **4** (R_1 = H, R_2 = Ph), and strengthened our belief that perhaps the reactions were occurring via electron transfer rather than by electrophilic substitution.

In a recent publication, we described the preparation of the parent 2-methylene-1,3-diselenole (**10**) and its oxidative conversion by iodine to TSeF (**2**).[4] In contrast to the behavior of **5**, diselenole **10** did not give characterizable

(1) Bryce, M. R. *Aldrichim. Acta* **1985**, *18*, 73 and references cited therein.
(2) Lakshmikantham, M. V.; Cava, M. P. *J. Org. Chem.* **1981**, *46*, 3246.
(3) Lalezari, I.; Shafiee, A.; Yalpani, M. *J. Org. Chem.* **1973**, *38*, 338.
(4) Jackson, Y. A.; White, C. L.; Lakshmikantham, M. V.; Cava, M. P. *Tetrahedron Lett.* **1987**, *28*, 5635.
(5) This assignment is arbitrary and is based on the known chemistry of **5** isomerizing quantitatively to the *trans*-diphenyl compound in the presence of a trace of acid (see ref 3).

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