dried ($MgSO_4$), and evaporated in vacuo. The residue was subjected to column chromatography (silica gel; eluent, benzene). Recrystallization of the first eluate afforded 3.8 g (54%) of **2**. Recrystallization of the second eluate afforded 160 mg (2.3%) of **3**.

Dimethyl 4,5-dihydro-2′-methylenespiro[benzo[*b*]thiophene-6(7*H*),3′(2′*H*)-thiophene]-2,5′-dicarboxylate (2): colorless plates (EtOH); mp 154.0–155.0 °C; IR (KBr) ν (cm^{-1}) 2950, 2842, 1710, 1622, 1297, 1074, 745; ^1H NMR ($CDCl_3$) δ (ppm) 1.82–1.93 (1 H, m), 2.06–2.13 (1 H, m), 2.69–2.92 (2 H, m), 2.98 and 3.04 (2 H, AB d, J = 17 Hz), 3.79 (3 H, s), 3.86 (3 H, s), 5.14 (1 H, d, J = 2 Hz), 5.24 (1 H, dd, J = 2, 1 Hz), 6.51 (1 H, d, J = 1 Hz), 7.52 (1 H, s); ^{13}C NMR ($CDCl_3$) δ (ppm) 23.0, 33.9, 37.5, 52.1, 52.5, 56.9, 105.4, 130.6, 131.5, 133.6, 134.9, 137.9, 141.2, 153.6, 162.2, 162.7; MS m/e 336 (M^+). Anal. Calcd for $C_{16}H_{16}O_4S_2$: C, 57.12; H, 4.79. Found: C, 56.85; H, 4.89.

Dimethyl [2.2](2,3)(2,3)thiophenophane-5,12-dicarboxylate (dimethyl 2,3,7,8-tetrahydrocycloocta[1,2-*d*:5,6-*b*]dithiophene-5,10-dicarboxylate) (3): colorless needles (EtOH); mp 197.0–198.0 °C; IR (KBr) ν (cm^{-1}) 1707, 1463, 1298, 1262, 1083, 753; ^1H NMR ($CDCl_3$) δ (ppm) 3.06 (4 H, s), 3.30 (4 H, s), 3.81 (6 H, s), 7.37 (2 H, s); MS m/e 336 (M^+). Anal. Calcd for $C_{16}H_{16}O_4S_2$: C, 57.12; H, 4.79. Found: C, 57.30; H, 4.91.

Treatment of 1 with NaI in DMF for 24 h. A solution of 2.0 g (42 mmol) of **1** and 9.0 g (58 mmol) of NaI in 30 mL of dry DMF was stirred for 24 h at 60 °C under N_2. The mixture was poured into water, and the organics were extracted with $CHCl_3$. The extract was washed with aqueous $Na_2S_2O_3$ and brine, dried ($MgSO_4$), and evaporated in vacuo. The residue was subjected to column chromatography (silica gel; eluent, benzene). Recrystallization of the eluate afforded 840 mg (44%) of **4**.

Dimethyl 4,5-dihydro-2′-(iodomethylene)spiro[benzo[*b*]thiophene-6(7*H*),3′(2′*H*)-thiophene]-2,5′-dicarboxylate (4): colorless needles (ethanol); mp 177 °C dec; IR (KBr) ν (cm^{-1}) 2946, 1694, 1612, 1468, 1254, 1076, 739; ^1H NMR ($CDCl_3$) δ (ppm) 1.86–1.96 (1 H, m), 2.06–2.15 (1 H, m), 2.69–2.96 (2 H, m), 2.97 and 3.07 (2 H, AB d, J = 17 Hz), 3.81 (3 H, s), 3.87 (3 H, s), 6.20 (1 H, s), 6.87 (1 H, s), 7.52 (1 H,s); MS m/e 462 (M^+). Anal. Calcd for $C_{16}H_{15}IO_4S_2$: C, 41.57; H, 3.27. Found: C, 41.87; H, 3.38.

Treatment of 2 with Br_2. To a solution of 500 mg (1.3 mmol) of **2** in 25 mL of CH_2Cl_2 was added 480 mg (3.0 mmol) of Br_2 and the mixture was stirred at rt for 17 h. The mixture was poured into water, and the organic phase was separated and washed with $NaHCO_3$(aq) and brine. After drying ($MgSO_4$), the solvent was removed by evaporation. The residue was subjected to column chromatography (silica gel; eluent, benzene). Recrystallization of the first eluate afforded 323 mg (44%) of **6**, and recrystallization of the second eluate afforded 10 mg (1.3%) of **5**.

1,2-Bis(2-(bromomethyl)-5-(methoxycarbonyl)-3-thienyl)ethane (5): colorless plates (hexane/$CHCl_3$); mp 180.0–181.0 °C; IR (KBr) ν (cm^{-1}) 1703, 1257, 756, 590; ^1H NMR ($CDCl_3$) δ (ppm) 2.93 (4 H, s), 3.88 (6 H, s), 4.54 (4 H, s), 7.52 (2 H, s); ^{13}C NMR ($CDCl_3$) δ (ppm) 23.7, 28.6, 52.4, 132.6, 134.8, 140.9, 141.4, 162.2; MS m/e 494, 496, 498 (M^+). Anal. Calcd for $C_{16}H_{16}Br_2O_4S_2$: C, 38.73; H, 3.25. Found: C, 39.10; H, 3.45.

Dimethyl 4,5-dihydro-2′-(dibromomethylene)spiro[benzo[*b*]thiophene-6(7*H*),3′(2′*H*)-thiophene]-2,5′-dicarboxylate (6): colorless needles (ethanol) mp 165.0–168.0 °C; IR (KBr) ν (cm^{-1}) 1711, 1469, 1252, 746; ^1H NMR ($CDCl_3$) δ (ppm) 2.05 (1 H, dd, J = 6, 13 Hz), 2.60–2.78 (1 H, m), 2.82–3.03 (3 H, m), 3.79 (3 H, s), 3.87 (3 H, s), 4.02 (1 H, dd, J = 2, 1 Hz), 6.63 (1 H, s), 7.52 (1 H, s); ^{13}C NMR ($CDCl_3$) δ (ppm) 23.1, 27.7, 31.2, 52.2, 52.7, 58.2, 74.2, 129.2, 130.9, 133.6, 134.5, 138.8, 140.4, 149.0, 161.5, 162.6; MS m/e 492, 494, 496 (M^+). Anal. Calcd for $C_{16}H_{14}Br_2O_4S_2$: C, 38.88; H, 2.86. Found: C, 38.56; H, 3.17.

Treatment of 2 with 1 equiv of $BTMABr_3$. A solution of 500 mg (1.3 mmol) of **2** and 586 mg (1.5 mmol) of $BTMABr_3$[7] in 25 mL of CH_2Cl_2 was stirred at rt for 17 h. The reaction mixture was poured into water, and the organic phase was washed with $NaHCO_3$ and brine. After the organic phase was dried ($MgSO_4$), the solvent was removed by evaporation. The residue was subjected to column chromatography (silica gel; eluent, benzene). Recrystallization of the eluate afforded 363 mg of **7** in 58% yield.

Dimethyl 4,5-dihydro-2′-(bromomethylene)spiro[benzo[*b*]thiophene-6(7*H*),3′(2′*H*)-thiophene]-2,5′-dicarboxylate (7): colorless needles (ethanol); mp 174.0–177.0 °C; IR (KBr) ν (cm^{-1}) 2946, 1693, 1469, 1295, 736; ^1H NMR ($CDCl_3$) δ (ppm) 1.85–1.96 (1 H, m), 2.08–2.17 (1 H, m), 2.70–2.96 (2 H, m), 3.03 (2 H, AB dd, J = 17 Hz), 3.81 (3 H, s), 3.87 (3 H, s), 6.11 (1 H, s), 6.67 (1 H, s), 7.52 (1 H, s); MS m/e 414, 416 (M^+). Anal. Calcd for $C_{16}H_{15}BrO_4S_2$: C, 46.27; H, 3.64. Found: C, 46.56; H, 3.88.

Treatment of 2 with H_3PO_4 in AcOH. A solution of 100 mg (0.30 mmol) of **2** and 1.0 mL of H_3PO_4 in 10 mL of AcOH was stirred at 75 °C for 12 h. The reaction mixture was poured into water, and the precipitate was extracted with CH_2Cl_2. The organic layer was washed with $NaHCO_3$(aq) and brine, dried ($MgSO_4$), and evaporated in vacuo. The residue was subjected to column chromatography (silica gel; eluent, benzene). Recrystallization of the first eluate afforded 1.0 mg (1%) of **9**. Recrystallization of the second eluate afforded 68 mg (57%) of **8**.

1-(2-(Methoxycarbonyl)-5-methyl-4-thienyl)-2-(2-(acetoxymethyl)-5-(methoxycarbonyl)-3-thienyl)ethane (8): colorless needles (hexane/benzene); mp 85.0–87.0 °C; IR (KBr) ν (cm^{-1}) 2954, 1722, 1459, 1251, 1062, 753; ^1H NMR ($CDCl_3$) δ (ppm) 2.07 (3 H, s), 2.22 (3 H, s), 2.74–2.89 (4 H, m), 3.85 (3 H, s), 3.87 (3 H, s), 4.99 (2 H, s), 7.49 (1 H, s), 7.51 (1 H, s); ^{13}C NMR ($CDCl_3$) δ (ppm) 13.3, 20.8, 29.0, 29.2, 52.0, 52.2, 58.1, 128.9, 132.5, 134.7, 135.0, 137.6, 139.7, 140.7, 142.4, 162.4, 162.6, 170.4; MS m/e 396 (M^+). Anal. Caldc for $C_{18}H_{20}O_6S_2$: C, 54.53; H, 5.08. Found: C, 54.81; H, 5.16.

Dimethyl 1-methylcyclohepta[1,2-*c*:4,5-*b*′]dithiophene-3,6-dicarboxylate (9): colorless needles (hexane); mp 171.0–173.0 °C; IR (KBr) ν (cm^{-1}) 2946, 1710, 1462, 1254, 754; ^1H NMR ($CDCl_3$) δ (ppm) 2.41 (3 H, s), 2.87–3.01 (4 H, m), 3.83 (3 H, s), 3.84 (3 H, s), 4.60 (2 H, s), 7.41 (1 H, s); ^{13}C NMR ($CDCl_3$) δ (ppm) 13.4, 24.1, 26.9, 28.9, 51.8, 52.0, 121.9, 128.4, 136.6, 136.8, 139.0, 139.4, 140.7, 146.8, 162.7, 163.0; MS m/e 336 (M^+). Anal. Calcd for $C_{16}H_{16}O_4S_2$: C, 57.12; H, 4.79. Found: C, 56.96; H, 5.10.

Treatment of 2 with H_2SO_4. A solution of 500 mg of **2** and 5.0 mL of H_2SO_4 in 50 mL of dioxane was stirred at rt for 140 h. This mixture was poured into water, and the organic products were extracted with CH_2Cl_2. The extract was washed with aqueous $NaHCO_3$ and brine and dried ($MgSO_4$). The solvent was removed by evaporation, and the residue was subjected to column chromatography (silica gel; eluent, benzene and $CHCl_3$). Recrystallization of the benzene eluate afforded 76 mg (15%) of **8**. Recrystallization of the chloroform eluate afforded 77 mg (14%) of **10**.

1-(2-(Methoxycarbonyl)-5-methyl-4-thienyl)-2-(2-(hydroxymethyl)-5-(methoxycarbonyl)-3-thienyl)ethane (10): colorless prisms (hexane/AcOEt); mp 140.0–141.0 °C; IR(KBr) ν (cm^{-1}) 3426, 1712, 1681, 1452, 1263, 882, 753; ^1H NMR ($CDCl_3$) δ (ppm) 2.22 (3 H, s), 2.42 (1 H, br s), 2.72–2.84 (4 H, m), 3.84 (3 H, s), 3.86 (3 H, s), 7.48 (1 H, s), 7.53 (1 H, s); MS m/e 354 (M^+). Anal. Calcd for $C_{16}H_{18}O_5S_2$: C, 54.22; H, 5.12. Found: C, 54.39; H, 5.24.

Registry No. 1, 7353-89-1; 2, 136629-85-1; 3, 136629-86-2; 4, 136629-87-3; 5, 136629-88-4; 6, 136629-89-5; 7, 136629-90-8; 8, 136629-91-9; 9, 136629-92-0; 10, 136629-93-1; methyl 2-thiophenecarboxylate, 5380-42-7; chloromethyl methyl ether, 107-30-2.

Titration of Organolithiums and Grignards with 1-Pyreneacetic Acid

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Received June 3, 1991

Many of the more convenient alkyllithium titration methods[1] utilize the simple titration technique where the addition of an alkyllithium causes a titration reagent to lose a proton, usually from a hydroxy group, in a stoichiometric reaction. After the first equivalent has reacted,

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0022-3263/91/1956-6950$02.50/0

Table I. Titration of Organometallics

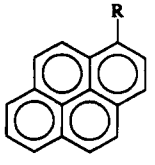
R-metal	reagent	molarity
n-BuLi	1	1.70 ± 0.01[a]
	2	1.60 ± 0.11[b]
	c	1.71 ± 0.03[d]
s-BuLi	1	1.14 ± 0.01[b]
t-BuLi	1	0.99 ± 0.01[b]
MeMgI[e]	1	1.02 ± 0.05[b]
1-Li-hexyne[f]	1	0.68 ± 0.04[b]
LDA[g]	1	0.57 ± 0.01[b]

[a] Five measurements, reagent concentration 30–100 mM (80–280 mg). [b] Two measurements. [c] 4-Biphenylmethanol. [d] Five measurements, reagent concentration 60–140 mM (110–260 mg). [e] Made in situ; nominally 1.37 M (100% yield). [f] Made in situ; nominally 0.82 M (100% yield). [g] Made in situ; nominally 0.64 M (100% yield).

additional alkyllithium will produce a colored dianion species, usually due to proton abstraction from a benzylic site, thus indicating titration end point. Titration reagent/indicators that operate on this principle include *N*-pivaloyl-*o*-toluidine,[2] *N*-pivaloyl-*o*-benzylaniline,[2] 4-biphenylmethanol,[3] 4-biphenylacetic acid,[3] 2,5-dimethoxybenzyl alcohol,[4] diphenylacetic acid,[5] and 1,3-diphenyl-2-propanone tosylhydrazone.[6] In our experience, however, the above titration reagents are not fully satisfactory because the color of the dianion is most often yellow or orange. This will make the end point difficult to observe when aged alkyllithium solutions are estimated, the latter being quite often rather intensely colored themselves. Another problem is that a relatively low concentration of the titration reagent will give a faint or pale yellow dianion color, thus delaying the observed end point.

Quite recently, an entirely different single-titration procedure was introduced,[7] involving the cleavage of red diphenyl ditelluride into pale yellow alkylation and anionic products. This procedure is particularly valuable in that Grignard and alkynyllithium reagents can also be analyzed, which does not seem to be the case with the other reagent/indicators.

As far as the benzylic anion-forming reagents are concerned, it can be expected that the provision of more conjugation into the structure of the titration reagent/indicator will shift the λ_{max} of the dianion toward longer wavelengths so that the appearance of an easily observed red or blue color would then be an unmistakable indication of the titration end point. We have now tested this idea using readily available "pyrenologues" of Juaristi's[3] 4-biphenyl derivatives, i.e., 1-pyreneacetic acid[8] (1) and 1-pyrenemethanol[9] (2), and report that the dianion from the



1 R = CH_2COOH

2 R = CH_2OH

former has an intense red color that makes the titration end point very easy to observe. In a typical titration using 1-pyreneacetic acid in THF, each successive drop of the alkyllithium solution produces a transient red color followed by rapid fadeout to pale green. When the end point is reached the intensive red color stays for hours. With 1-pyrenemethanol (2) the color change is to olive green but the titration end point is somewhat broader (Table I).

For comparison, titration experiments were conducted using 1-pyreneacetic acid and one of the more popular established reagent/indicators, biphenylmethanol, in parallel titrations of a same *n*-butyllithium batch (Table I). When varying concentrations of titration reagents were used the variance in the titration results (BuLi concentration) was ±0.01 mol/L with the pyreneacetic acid and ±0.03 mol/L with 4-biphenylmethanol. It was also found that consistently lower butyllithium concentrations resulted from the use of comparatively smaller amounts of the biphenylmethanol reagent. Thus, a typical butyllithium concentration change was from 1.68 to 1.75 mol/L when 110 and 259 mg, respectively, of the biphenylmethanol was used, whereas the corresponding change was from 1.69 to 1.71 mol/L when 80 and 280 mg, respectively, of the pyreneacetic acid was used. All this means, of course, is that it is important to use constant and relatively large amounts of the reagent when performing titrations with 4-biphenylmethanol while 1-pyreneacetic acid is not very sensitive to variations in the amount of reagent used.

1-Pyreneacetic acid was also tested for the titration of certain other organometallic reagents. Good results were obtained with *sec*- and *tert*-butyllithium, and even with lithium diisopropylamide (LDA) where the end-point color change occurred on a single final drop (Table I). Grignard reagents and alkynyllithiums can also be estimated but the end point is not quite as sharp (Δc is about ±0.05 mol/L).

1-Pyreneacetic acid is readily recovered from acidified titration end mixture. Acidification using DCl/D_2O followed by an H_2O wash gave the Ar–CHD–COOH derivative that showed in its NMR spectrum the remaining benzylic H at δ 4.37 with 50% of its original intensity. This leaves little doubt that the end-point color in fact comes from the benzylic–carboxylic dianion. The good crystallization characteristics of 1-pyreneacetic acid makes the recovery of the reagent very simple, unlike that of some of the other titration reagent/indicators.

In conclusion, we believe that 1-pyreneacetic acid is the reagent/indicator of choice for the titration of organolithiums and Grignard reagents. Presumably, the other pyreneacetic acid isomers would perform just as well but the 1-isomer is probably the easiest to prepare by acetylation of pyrene followed by the Willgerodt–Kindler reaction.[8]

Experimental Section

1-Pyreneacetic acid, made as described,[8] was recrystallized from toluene/methanol (20:1). All titration reagents were dried to standard weight under oil pump vacuum before use. For the actual titration, the alkyllithium solution was added dropwise with a syringe to a stirred solution of 1-pyreneacetic acid (100–200 mg) or 4-biphenylmethanol (200–300 mg) in dry THF (10 mL) under argon at ambient temperature. If the rate of addition is kept sufficiently slow (overall 3–4 min) there is very little heating of the titration mixture.

For regeneration, the final titration mixture was evaporated to get an orange yellow solid which was treated with 2 M aqueous HCl. The mixture was extracted twice with dichloromethane, and the combined organic layers were washed with brine, dried, and evaporated. Recrystallization from toluene/methanol (20:1) gave 1-pyreneacetic acid, mp 221–222 °C (lit.[10] 222.5–223 °C) in 80% yield.

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Note Added in Proof. It has been recently reported (Einhorn, C.; Einhorn, J.; Luche, J.-L. *Tetrahedron Lett.* **1991**, *32*, 2771) that addition will compete with COOH deprotonation when alkyllithiums react with carboxylic acids. The initial addition product undergoes elimination of LiOH to a ketone which can then react with another molecule of the alkyllithium. In such cases the 1:1 stoichiometry required for titrimetry would obviously no longer be maintained, and the compounds along the competing reaction path, or their anions, would be colorless. We have now examined some of our titration end point solutions by HPLC and NMR and find less than 1% of alkylation products in the isolated crude material from pyreneacetic acid/BuLi titration. Therefore, the conclusions drawn in our titration paper remain valid.

Registry No. 1, 64709-55-3; 1 dianion, 136569-20-5; 2, 24463-15-8; *n*-BuLi, 109-72-8; *s*-BuLi, 598-30-1; *t*-BuLi, 594-19-4; LDA, 4111-54-0; MeMgI, 917-64-6; 1-Li-hexyne, 17689-03-1; 4-biphenylmethanol, 3597-91-9.

Bimolecular Cyclization of 2-Fluoro-*N*-(hydroxyalkyl)benzamides. 2. Synthesis and Structural Characterization of 17- and 20-Membered Macrocycles[1]

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Received May 31, 1991

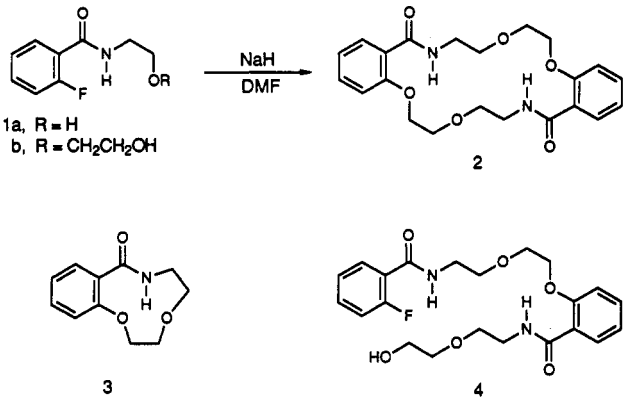
We have described a method for construction of macrocyclic diamides that involves a "one-step" bimolecular cyclization of 2-fluoro-*N*-(2-hydroxyalkyl)benzamides (e.g., **1a**).[1] The process was demonstrated in the context of 14-, 16-, and 18-membered ring synthesis. It is expected that this class of macrocycles will provide access to novel molecular receptors for a wide range of synthetic applications. In this paper we report an extension of the method to preparation of new heterocyclic systems containing 17- and 20-membered rings (e.g., **2** and **5**). It is demonstrated that **2** provides convenient access to novel tetraoxadiaza crown ethers **6a** and **6b**.

Results and Discussion

As shown in Scheme I, treatment of a solution of 2-fluoro-*N*-[2-(2′-hydroxyethyl)ethoxy]benzamide (**1b**) in DMF (2.0 M) with sodium hydride (4 equiv) at 55 °C for 22 h gave 9,10:19,20-dibenzo-1,4,11,14-tetraoxa-7,17-diazacycloeicosane-8,18-dione (**2**) in 39% isolated yield; none of the 9,10-benzo-1,4-dioxa-7-azecin-8-one (**3**) could be detected. At lower starting concentrations of **1b** (0.01 M, 55 °C for 4 days) **2** was still produced (41%), but **3** also was obtained in 7% isolated yield. Utilization of milder reaction conditions (ambient temperature, 20 h) provided alcohol **4** (54% isolated yield) along with recovered starting material. It was shown that **4** gave macrocycle **2** on treatment with NaH in DMF.

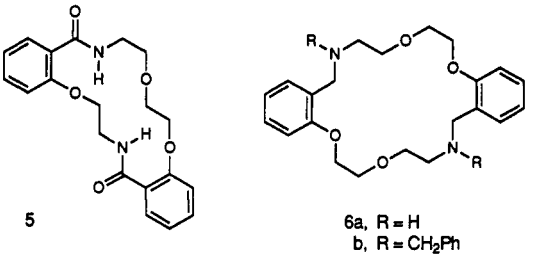
The isolation of **4** is of interest because in the earlier study directed at 14-membered ring formation,[1] no evidence for acyclic reaction intermediates could be obtained. This observation was suggestive of a template effect[3] in

Scheme I



which formation of the second bond was substantially faster than the first. Although the hypothetical template effect is kinetically less effective for the 20-membered ring synthesis, the yield of **2** is reasonable and oligomerization is not a problem, even at high concentrations of **1b** (e.g., 2 M).

Odd-numbered macrocyclic diamides are available in reasonable yield by a simple modification of the protocol for bimolecular cyclization. Thus, treatment of an equimolar mixture of **1a** and **1b** with NaH/DMF at ambient temperature for 4 days gave 9,10:16,17-dibenzo-1,4,11-trioxa-7,14-diazacycloheptadecane-8,15-dione (**5**) in 36% yield, along with **2** (12%), traces of the macrocycle derived from **1a**,[1] and recovered starting materials; macrocycle **5** was easily isolated by flash chromatography on silica gel.



Reduction of **2** with the borane–dimethyl sulfide complex in THF in the presence of boron trifluoride etherate gave the macrocyclic diamine **6a** in 93% yield. Dibenzylation of **6a** with benzyl bromide/NaH in THF gave the *N,N*-dibenzyl derivative **6b** (80%). X-ray crystallographic studies of **2** and **6b** provided the molecular structures shown in Figures 1 and 2.

In contrast to the 14-membered macrocycles[1] that display a butterfly-like conformation in the solid state, **2** assumes a bracket conformation with the aromatic rings in nearly parallel planes; the averaged planes of the aromatic rings in **2** intersect at an angle of 8.2°. The distance from an orthogonal projection from the plane defined by C(1)–C(2)–C(3)–C(4)–C(4a)–C(24a) to C(16a) is 2.37 Å while that to C(14) is 2.76 Å. Both NH groups are within the macrocyclic cavity, and, as a result, two weak intramolecular hydrogen bonds are possible.[4] The unconstrained H(11)–O(17) and H(23)–O(5) distances are 2.01 and 2.05 Å, respectively; N(11)–H(11)–O(17) and N(23)–H(23)–O(5) angles are 131 and 134°.

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(2) Inquiries regarding the X-ray crystallographic analyses should be directed to F.S.T.

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(4) (a) A similar amide orientation is present in the 14-membered analogues; see ref 1. (b) For the observation of "very weak" intramolecular hydrogen bonds in synthetic derivatives of the quinoxaline antibiotic triostin A, see: Hossain, M. B.; van der Helm, D.; Olsen, R. K.; Jones, P. G.; Sheldrick, G. M.; Egert, E.; Kennard, O.; Waring, M. J.; Viswamitra, M. A. *J. Am. Chem. Soc.* **1982**, *104*, 3401.

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