Synthesis of 3,5,12-Triazawurtzitanes (3,5,12-Triazatetracyclo[5.3.1.1^{2,6}.0^{4,9}]dodecanes)[1]

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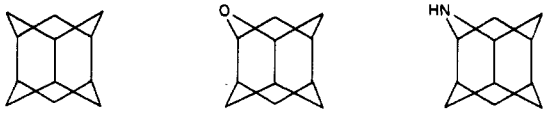
The first examples of 3,5,12-triazawurtzitanes (3,5,12-triazatetracyclo[5.3.1.1^{2,6}.0^{4,9}]dodecanes) are described. *cis,cis*-1,3,5-Triformylcyclohexane (**8**) has been synthesized by Swern oxidation of *cis,cis*-1,3,5-tris(hydroxymethyl)cyclohexane (**7**). Reaction of **8** in ether solvent at 25 °C with selected primary amines, in the absence of added catalyst, leads to good yields of crystalline 3,5,12-trisubstituted-3,5,12-triazawurtzitanes **10a–e** (R = CH_3, C_2H_5, $C_6H_5CH_2$, 4-$CH_3OC_6H_4CH_2$, 4-$(CH_3)_2NC_6H_4CH_2$). The crystal structure of the tribenzyl derivative **10c** has been established by X-ray crystallography. Under the same conditions isopropylamine and *tert*-butylamine react with trial **8** to produce triimines **9f,g**, which do not cyclize to wurtzitanes. In solution in various solvents, all triazawurtzitanes **10a–e** are shown by ^{1}H NMR to exist in equilibrium with their corresponding triimines **9a–e**. A different reaction occurs with trial **8**, in the presence of an acid catalyst, and methylamine or benzylamine in refluxing methanol or toluene, respectively, to yield 3,5-disubstituted-3,5-diaza-2-oxotricyclo[5.3.1.0^{4,9}]decanes **14a,b**.

The hydrocarbon wurtzitane (iceane, tetracyclo[5.3.1.1^{2,6}.0^{4,9}]dodecane, **1**) has been known since 1974.[2-5] Ganter and co-workers prepared the first wurtzitanes incorporating a ring hetero atom--3-oxawurtzitane (**2**)[6] and 3-azawurtzitane (**3**).[7] Working independently, Hamon and co-workers also prepared **2**.[8]



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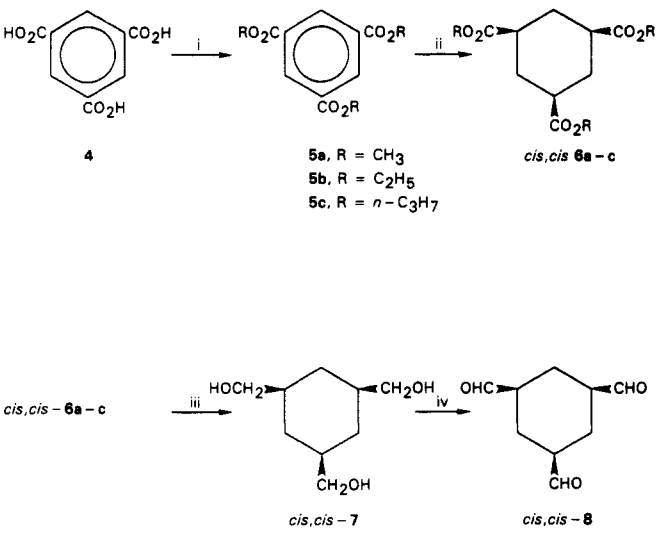
In this report we describe the first synthesis of a wurtzitane incorporating more than one heteroatom within the ring. 3,5,12-Trisubstituted-3,5,12-triazawurtzitanes (3,5,12-triazatetracyclo[5.3.1.1^{2,6}.0^{4,9}]dodecanes, **10a–e**) have been obtained by condensation of 1,3,5-triformylcyclohexane (**8**) with selected amines.

The trialdehyde **8** was obtained in four steps in 60% overall yield from trimesic acid (**4**) (Scheme I). Esterification of **4** with either methanol, ethanol, or 1-propanol in excess, by refluxing with hydrogen chloride catalyst, leads to the triester **5a**, **5b**, or **5c**, respectively, in quantitative yield. Hydrogenation of **5a**, **5b**, or **5c** in acetic acid solvent (Pt catalyst, 50 psi, 25 °C) yields pure *cis,cis*-cyclohexane-1,3,5-tricarboxylate esters (*cis,cis*-**6a**, **6b**, or **6c**, respectively), also in quantitative yield. Reduction of the esters **6a–c** with lithium aluminum hydride in refluxing ether solvent produces *cis,cis*-1,3,5-tris(hydroxymethyl)-cyclohexane (*cis,cis*-**7**) in yields that vary depending on the alcohol R group of the ester reactant (R = CH_3, 57%; C_2H_5, 81%; *n*-Pr, 84%). Use of tetrahydrofuran as reaction solvent in the reduction in place of ether leads to 90–95% yields of **7** from **6c** (see Experimental Section). The lower yield with the methyl ester is believed to result from polymerization of some of the intermediates, more facile with the methyl than with the ethyl or propyl esters. The product derived from the *n*-propyl ester is of very high purity and is formed in higher yield than that derived from the ethyl ester. The preparation of triol **7** herein described provides a significant improvement in yield over the previously reported methods.[10]

Scheme I[a]



[a] (i) ROH, HCl, reflux; (ii) H_2, Pt, CH_3CO_2H, 25 °C, 20–50 psi; (iii) $LiAlH_4$, $(C_2H_5)_2O$, reflux; (iv) $(COCl)_2$, $(CH_3)_2SO$, -55 °C.

Synthesis of *cis,cis*-1,3,5-triformylcyclohexane (**8**) was achieved by a modified Swern oxidation of triol **7**.[11,12] The pure aldehyde, obtained by chromatography on silica gel, is a crystalline solid, mp 60–63 °C (70% yield). The

(1) Presented, in part, at the Pacific Conference on Chemistry and Spectroscopy, Pasadena, CA, Oct 28, 1983.
(2) Cupas, C. A.; Hodakowski, L. *J. Am. Chem. Soc.* **1974**, *96*, 4668.
(3) Tobler, H.; Klaus, R. O.; Ganter, C. *Helv. Chim. Acta* **1975**, *58*, 1455.
(4) (a) Hamon, D. P. G.; Taylor, G. F. *Tetrahedron Lett.* **1975**, *155*. (b) Hamon, D. P. G.; Taylor, G. F. *Aust. J. Chem.* **1976**, *29*, 1721. (c) Hamon, D. P. G.; Raston, C. L.; Taylor, G. F.; Varghese, J. N.; White, A. H. *Aust. J. Chem.* **1977**, *30*, 1837.
(5) Fieser, L. F. *J. Chem. Ed.* **1965**, *42*, 408.
(6) Klaus, R. O.; Tobler, H.; Ganter, C. *Helv. Chim. Acta* **1974**, *57*, 2517.
(7) Klaus, R. O.; Ganter, C. *Helv. Chim. Acta* **1980**, *63*, 2559.
(8) Hamon, D. P. G.; Taylor, G. F.; Young, R. N. *Aust. J. Chem.* **1977**, *30*, 589.
(9) Lukes, R.; Galik, V. *Collect. Czech. Chem. Commun.* **1954**, *19*, 712.
(10) Galik, V.; Kafka, Z.; Safar, M.; Landa, S. *Collect. Czech. Chem. Commun.* **1974**, *39*, 895.
(11) Manusco, A. J.; Huang, S. L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.
(12) Manusco, A. J.; Brownfain, D. S.; Swern, D. *J. Org. Chem.* **1979**, *44*, 4148.

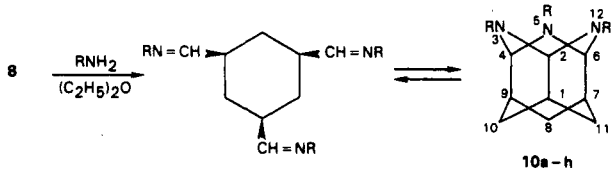
Table I. Synthesis of 3,5,12-Trisubstituted-3,5,12-triazawurtzitanes

compd	R	yield,[a] %	mp,[b] °C	mol form[c]
10a	CH_3	99	64–75[d]	$C_{12}H_{21}N_3$
10b	C_2H_5	88	50–60[d]	$C_{15}H_{27}N_3$
10c	$C_6H_5CH_2$	83	92–97[e]	$C_{30}H_{33}N_3$
10d	$4\text{-}CH_3OC_6H_4CH_2$	71	91–100[e]	$C_{33}H_{39}N_3O_3$
10e	$4\text{-}(CH_3)_2NC_6H_4CH_2$	100	115–129[e]	$C_{36}H_{48}N_6$

[a] Crude product. [b] The wide melting point range is attributed to triimine formation on heating. [c] Elemental analyses obtained for C, H, and N were in agreement with the theoretical values within ±0.3%. Mass spectra show the molecular ion for each substance. [d] Melting point of crude product; attempted recrystallization caused decomposition. [e] melting point after recrystallization from pentane or hexane (ca. 50% recovery). Melting points of the crude products were approximately 10 deg lower.

stereochemistry of 8, as well as that of precursors **6a–c** and **7a–c**, was established as cis,cis in each case by high resolution ^1H NMR; trans isomers could not be detected (only one signal for the exocyclic protons is observed).

The reaction of *cis,cis*-1,3,5-triformylcyclohexane (8) with primary amines in ether solvent at 25 °C leads to triimines **9** and in some cases to 3,5,12-trisubstituted-3,5,12-triazawurtzitanes **10**. Crystalline triazawurtzitanes



cis,cis-**9a**, R = CH_3
9b, R = C_2H_5
9c, R = $C_6H_5CH_2$
9d, R = $4\text{-}CH_3OC_6H_4CH_2$
9e, R = $4\text{-}(CH_3)_2NC_6H_4CH_2$
9f, R = $(CH_3)_2CH$
9g, R = $(CH_3)_3C$
9h, R = H

10a–e were obtained with methylamine, ethylamine, benzylamine, 4-methoxybenzylamine, and 4-(dimethylamino)benzylamine in high yields (Table I). The reaction is analogous to the trimerization of acyclic aldimines (CH_2=NR or RCH=NH) leading to 1,3,5- or 2,4,6-trisubstituted-1,3,5-hexahydrotriazines.[13-15] Structures **10a–e** are supported by their NMR and mass spectra and infrared spectra (see Table II and Experimental Section). The wurtzitane stability decreases in the order of N-substitution: benzyl > 4-methoxybenzyl > 4-(dimethylamino)benzyl > methyl > ethyl (vide infra). With isopropylamine and *tert*-butylamine, no evidence of the wurtzitane structure is seen in the infrared or ^1H NMR spectra (a 10-Hz doublet near δ 3.9) and the products isolated are crystalline triimines (**9f,g**; see Table II and Experimental Section). Reaction of 8 with a large excess of methylamine over KOH gave triimine **9a**.

The structure of the benzyl derivative **10c** was established by X-ray crystallography. The chair-shaped triazacyclohexane ring, at the top of the triazawurtzitane cage in Figure 1, is asymmetrically substituted in the crystal; the benzyl methylene carbons linked to N(3) and N(12)

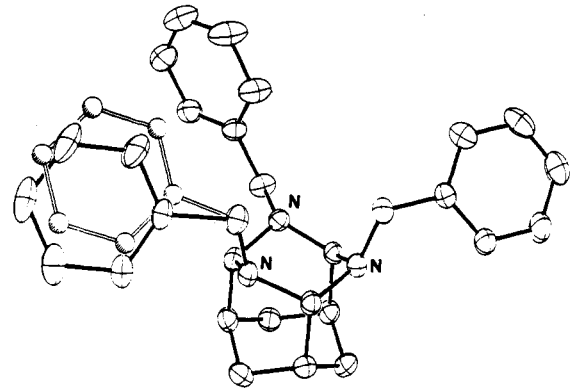


Figure 1. Computer-generated perspective drawing of the final X-ray model of 3,5,12-tribenzyl-3,5,12-triazawurtzitane (**10c**). Two locations were found for benzyl ring C; the major and minor forms are shown with filled and empty bonds, respectively. Hydrogen atoms are omitted for clarity.

are axial with respect to this ring, while the methylene on N(5) is equatorial. This asymmetric conformer apparently packs with minimum free energy and is the only one found in the crystal. On the other hand, the solution ^1H NMR spectrum shows no detectable departure from threefold symmetry (see Table II); this could be caused by rapid dynamic axial–equatorial transitions occurring at each nitrogen. In the cage, the average distance for the methine–methine bonds is 1.566 Å (range: 0.005 Å) and for the methine–methylene bonds, 1.523 Å (range, 0.015 Å); this difference is indicative of the strain in the cage. Corresponding distances observed in an X-ray study of wurtzitane[4c] are 1.553 Å (CH–CH) and 1.523 Å ($CH–CH_2$). No other X-ray studies of wurtzitane derivatives or analogues have been reported. The strain in wurtzitane cages is primarily torsional, caused by the eclipsed conformation of the methine substituents. The average cage C–N bond length in **10c** is 1.466 Å (range, 0.012 Å) and the cage nitrogens are pyramidal, with an average angle between the N-methylene bond and the C–N–C ring plane of 40.8°; for pure tetrahedral (sp^3) geometry, this angle would be 54.8°.

In solution in various solvents, all of the wurtzitanes are observed to be in equilibrium with the corresponding triimines. With the benzylamines **10c–e** in $CDCl_3$, the equilibrium concentration of the favored wurtzitane forms (reached in approximately 4 h at 25 °C) is approximately 80%, 80%, and 70%, respectively. With the methyl and ethylwurtzitane derivatives (**10a,b**), conversion to the triimine forms **9a,b** is much more rapid and complete. With the ethyl compound **10b** in $CDCl_3$, the half-life is approximately 10 min; within 1 h, conversion to the triimine **9b** is virtually complete; in pyridine-d_6 the conversion to the triimine is slower but practically complete within 18 h. The methyl derivative **10a** behaves like **10b**, completely converting to the triimine **9a** in $CDCl_3$ within 18 h. Removal of the $CDCl_3$ solvent from solutions of **10a,b** after 18 h produces an oily mixture of triimine and wurtzitane (approximately 1:1) as seen in the rapidly determined ^1H NMR spectra. The solvent effect on the **9** ⇄ **10** equilibrium was examined for the 4-dimethylamino derivative **10e** in three solvents. The equilibrium concentration of **10e** was found to be approximately 85% in CD_2Cl_2, 70% in $CDCl_3$, and only 55% in CD_3CN.

The reaction of ammonia with *cis,cis*-1,3,5-triformylcyclohexane (8) under various conditions leads to a polymeric substance, believed to be a polymer of the triimine **9h** (R = H). At very high pH (>12), the rate of polymerization is slower and some of the parent 3,5,12-triaza-

(13) (a) Nielsen, A. T.; Atkins, R. L.; Moore, D. W.; Scott, R.; Mallory, D.; LaBerge, J. M. *J. Org. Chem.* **1973**, *38*, 3288. (b) Nielsen, A. T.; Atkins, R. L.; DiPol, J.; Moore, D. W. *J. Org. Chem.* **1974**, *39*, 1349.
(14) Smolin, E. M.; Rapoport, L. In *The Chemistry of Heterocyclic Compounds*; Weissberger, A., Ed.: Interscience: New York, 1959; Vol. 13, Chapter 9.
(15) Katritzky, A. R.; Patel, R. C.; Riddell, F. G. *Angew, Chem., Int. Ed. Engl.* 1981, *20*, 521.

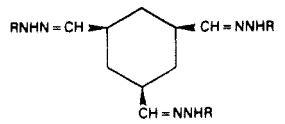
Table II. Proton NMR Spectral Data of 3,5,12-Trisubstituted-3,5,12-triazawurtzitanes 10 and 1,3,5-Tris[(substituted-imino)methyl]cyclohexanes 9 ($CDCl_3$ solvent, 30 °C)

		^{1}H NMR chemical shifts, ppm			
		wurtzitane 10		triimine 9	
compd	R	NCHN	R	CH=N	R
10a, 9a	CH_3	3.87 d; J = 10 Hz	CH_3 s 2.84	7.75 d; J = 4 Hz	CH_3 s 3.30
10b, 9b	C_2H_5	3.98 d; J = 10 Hz	CH_3 t 1.00, CH_2 q 2.82; J = 7 Hz	7.70 d; J = 4 Hz	CH_3 t 1.17, CH_2 q 3.47; J = 7 Hz
10c, 9c	$C_6H_5CH_2$	3.88 d; J = 9.8 Hz	C_6H_5 7.29, 7.21, CH_2 s 4.10	7.70 d; J = 4 Hz	C_6H_5 7.3, 7.2, CH_2 s 4.6
10d, 9d	4-$CH_3OC_6H_4CH_2$	[a]	C_6H_4 7.13, 6.93, CH_2 s 4.03, CH_3 s 3.98	7.68 s[b]	CH_2 s 4.58
10e, 9e	4-$(CH_3)_2NC_6H_4CH_2$	4.00 d; J = 10 Hz	C_6H_4 7.10, 6.65, CH_2 s 4.05, CH_3 s 3.00	7.65 s[b]	CH_2 s 4.55
9f	i-C_3H_7			7.22 d; J = 5 Hz	CH_3 d 1.12; J = 6 Hz CH m 3.32
9g	t-C_4H_9			7.62 d; J = 5.5 Hz	CH_3 s 1.15

[a] Signal obscured by the R group signals. [b] Broad signal.

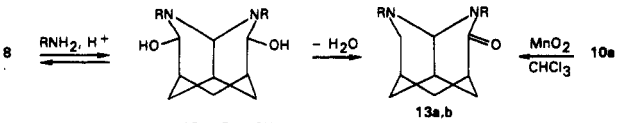
wurtzitane **10h** is believed to be present. High pH also favors stabilization of the related 1,3,5-hexahydrotriazine.[16] Evidence for the formation of **10h** in solution is seen in the ^{1}H NMR spectrum of the reaction mixture obtained from trial 8 and ND_4OD in D_2O. A singlet at δ 5.0 is assigned to the 2,4,6-hydrogens since the 1,7,9-hydrogens presumably were exchanged by deuterium to produce **10h**-*1,3,5,7,9,12-d*$_6$. In solutions containing NH_4OH as well as ND_4OD, this signal is seen as a doublet at δ 4.7 (J = 10 Hz) in **10h** due to coupling between the 2,4,6- and 1,7,9-hydrogens. Attempts to trap **10h** as the 3,5,12-triacetyl derivative (**10**, R = $COCH_3$) by reaction with acetic anhydride or ketene in strongly basic solution met with only partial success because of the low equilibrium concentration of **10h** under the reaction conditions.

Reaction of trial 8 with phenylhydrazine or hydrazine leads to trishydrazones **11a,b**. These products polymerize with great ease and could not be cyclized to 3,5,12-triamino-3,5,12-triazawurtzitane derivatives (**10**, R = C_6H_5-NH or NH_2).



cis,cis-**11a**, R = C_6H_5
11b, R = H

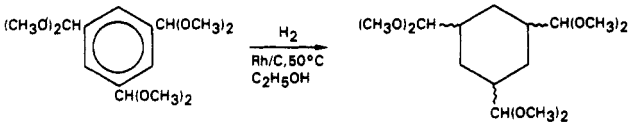
The reaction of 1,3,5-triformylcyclohexane (**8**) with primary amines in refluxing ethanolic acetic acid takes a different course. The equilibrium mixture in this reaction includes significant amounts of carbinolamine intermediates, including partially cyclized tricyclics such as **12**. From methylamine the final product is a crystalline amide (3,5-dimethyl-2-oxo-3,5-diazatricyclo[5.3.1.0^{4,9}]decane, **13a**, 41% yield) having two ^{1}H NMR methyl signals and a distinctive doublet (^{1}H, δ 4.56, J = 10 Hz; protons at C-4, C-9). Elemental analysis, infrared, ^{13}C NMR, and mass spectra also support the structure assignment. An isomeric 3,5-diaza-12-oxawurtzitane structure does not agree with the spectral data. The same type of reaction occurred between trial 8 and excess benzylamine in the presence of an acidic ion exchange resin catalyst in refluxing toluene, leading to the dibenzyl derivative **13b** (36% yield). The more vigorous acid-catalyzed reaction conditions may favor a hydride transfer in **12**, possibly with an iminium ion intermediate. The product **13a** was also obtained, with loss of methylamine, by oxidation of wurtzitane **10a** (R = CH_3) with manganese dioxide at 25 °C in chloroform solvent. Oxidation occurs at the bridgehead methine, ultimately leading to **13a**.



12a, R = CH_3
12b, R = $C_6H_5CH_2$

13a,b

Our initial efforts to synthesize *cis,cis*-1,3,5-triformylcyclohexane (**8**) involved synthesis of a precursor, hexamethyl acetal **15**. 1,3,5-Triformylbenzene[17] was converted into its hexamethyl acetal **14** by reaction with trimethyl orthoformate in refluxing methanol (ammonium chloride catalyst). Hydrogenation of **14** with rhodium on charcoal catalyst in ethanol (50 °C, 50 psi) gave a mixture of isomeric acetals (*cis,cis*-**15**, 8.5% and *cis,trans*-**15**, 37%).



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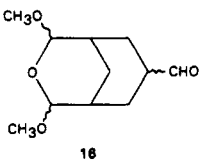
15

(*cis,trans*/*cis,cis* = 4/1)

Attempts to hydrolyze or cleave the isomers of **15** to form trial 8 were unsuccessful; this was not surprising in retrospect since **8** undergoes very facile polymerization in the presence of acids. Mild hydrolysis of either isomer in 1 N hydrochloric acid at 25 °C was incomplete; an oil was produced, revealing a strong ^{1}H NMR aldehyde signal at δ 9.98 in addition to a methoxy signal at δ 3.4 in $CDCl_3$ solvent. The hydrolysis was also incomplete in 12 N HCl at 25 °C and in 1 N HCl at 100 °C or by treatment with trimethyliodosilane. The products always contained methoxy and aldehyde ^{1}H NMR signals. The relative peak intensities of the product suggest the formation of bicyclic aldehyde acetal **16** (stereochemistry unknown).



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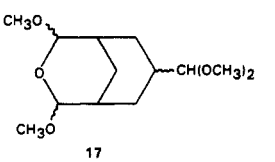

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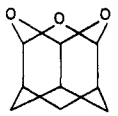
Reaction of trial 8 with methanol at 25 °C in the presence of acidic Amberlite-G120 ion exchange resin and

(16) Nielsen, A. T.; Moore, D. W.; Ogan, M. C.; Atkins, R. L. *J. Org. Chem.* **1979**, *44*, 1678.

(17) Lonshchakova, T. I.; Buzykin, B. I.; Liakumovich, A. G.; Tsivunin, V. S. *Zh. Org. Khim.* **1978**, *14*, 593.

Drierite led to a crystalline product having an ^1H NMR spectrum different from the expected hexamethyl acetal **15**. The observed methyl to acetal signal intensity ratio was 12:1, rather than the expected 18:1, and the signals in the ring CH_2/CH region of the two substances were different. This product is believed to be the bicyclic acetal **17** (stereochemistry unknown). The bicyclic endocyclic acetal ring structure in **16** and **17** is evidently somewhat resistant to reaction with water or methanol in the presence of weakly acidic catalyst. More vigorous reaction conditions result in polymerization. On the other hand, mild acid hydrolysis does effect cleavage of the exocyclic acetal group in **17** to produce **16**.

The cyclization of trial **8** to 3,5,12-trioxawurtzitane **18** was investigated. Solutions of **8** in various solvents (acetonitrile, diethyl ether, pentane) containing acid catalysts such as acetic acid and Amberlite-G120 ion exchange resin gave either recovered **8** or polymers. The ^1H NMR spectra of crude reaction products reveal no signals attributable to **18** (absence of the characteristic doublet of the wurtzitane ring methines).



18

Experimental Section

Melting points were determined on a Kofler hot stage. NMR spectra were recorded on a Nicolet WB200, Varian XL-100, or Varian EM360 spectrometer (tetramethylsilane internal standard in organic solvents, 3-(trimethylsilyl)propanesulfonic acid in D_2O), mass spectra on a Hewlett-Packard 5985 GC/MS system (70 eV), and infrared spectra on a Perkin-Elmer 137 or Nicolet 7199 FT instrument. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, TN.

Triethyl Benzene-1,3,5-tricarboxylate (5b). Hydrogen chloride was bubbled into a solution of trimesic acid (50.0 g, 0.237 mol) in 1 L of absolute ethanol until saturated (temperature maintained at 25–30 °C by ice-bath cooling; 1 h was required to saturate the solution with HCl). The solution was heated under reflux for 1 h, then cooled to 25 °C overnight. Volatiles were removed under reduced pressure at 30–40 °C, and the residue was chilled in an ice bath and treated with 50 mL of ice water. The product was filtered, washed with cold water, and dried to yield 67.6 g (96.5%) of **5b**: mp 132–136 °C; lit.[10] mp 135 °C, 73.6% yield; mp 133 °C.[18]

Trimethyl benzene-1,3,5-tricarboxylate (5a) was prepared in the same manner as **5b**, leading to an 88% yield of the triester, mp 141–145 °C; lit.[18] mp 144 °C.

Tri-*n*-propyl benzene-1,3,5-tricarboxylate (5c) was prepared from 1-propanol in the same manner as **5b**, leading to a 97% yield of the triester: bp 197–200 °C (0.1 mm), mp 24–26 °C; lit.[19] mp 23–24 °C; ^1H NMR ($CDCl_3$), δ 8.88 (s, 3 H, CH), 4.54 (t, 6 H, CH_2O), 1.94 (m, 6 H, CH_2), 1.11 (t, 9 H, CH_3).

***cis,cis*-Triethyl 1,3,5-Cyclohexanetricarboxylate (*cis,cis*-6b).** Triethyl trimesate (33.4 g, 0.114 mol), acetic acid (180 mL), and platinum oxide catalyst (2.0 g) were shaken with hydrogen in a Parr apparatus (25 °C, 20–50 psi, 3.5 h). Filtration of the catalyst followed by concentration to remove volatiles gave 33.9 g (99.5%) of *cis,cis*-**6b** as chunky prisms (mp 28–29 °C; lit.[10,11] mp 36–37 °C, 91.8% yield); ^1H NMR ($CDCl_3$) reveals absence of reactant aryl CH and acetic acid protons and presence of pure *cis,cis* isomer: δ 4.16 (q, CH_2 of CH_3CH_2, 6 H), 2.2–2.5 (m, CH, CH_2, 9 H), 1.27 (t, CH_3, 9 H), 1.2–1.7.

***cis,cis*-Trimethyl 1,3,5-cyclohexanetricarboxylate (*cis,cis*-6a)** was prepared in the same manner as **6b**, leading to a 95% yield of the triester: mp 39–43 °C; lit.[10] mp 46 °C, 95% yield.

***cis,cis*-Tri-*n*-propyl cyclohexane-1,3,5-tricarboxylate (*cis,cis*-6c)** was prepared in the same manner as **6b**, leading to a 98% yield of the triester: bp 180–185 °C (0.1 mm); ^1H NMR ($CDCl_3$) δ 4.20 (t, 6 H, CH_2O), 2.0–3.0 (m, 9 H, CH, CH_2), 1.7 (m, 6 H, CH_2), 0.9 (t, 9 H, CH_3). Anal. Calcd for $C_{18}H_{30}O_6$: C, 63.13; H, 8.83. Found: C, 63.06; H, 8.42.

***cis,cis*-1,3,5-Tris(hydroxymethyl)cyclohexane (*cis,cis*-7).** A solution of *cis,cis*-tri-*n*-propyl cyclohexane-1,3,5-tricarboxylate (**6c**, 32.18 g, 0.094 mol) in ether (125 mL) was added dropwise, with stirring, during a 2-h period to a solution of lithium aluminum hydride (11.93 g, 0.3144 mol) in ether (500 mL), keeping the temperature at 25–30 °C. After addition was complete, the mixture was heated under reflux with stirring for 16 h. The mixture was cooled to 5 °C and water (25 mL) was added dropwise, with stirring, during a 30-min period, keeping the temperature at 5–10 °C. After stirring at 10 °C for 15 min, ethanol (50 mL of 95%) was added dropwise with stirring during a 30-min period, keeping the temperature at 10 °C. After being stirred at 20–25 °C for 3 h, the mixture was filtered through a medium-porosity, sintered-glass filter, and the solid was washed with 95% ethanol. The collected solid was extracted twice with 250-mL portions of boiling ethanol. The filtrate and the combined extracts were concentrated under reduced pressure to remove volatiles, leaving a white solid (16.36 g) that was extracted three times with boiling dioxane (300 mL and 2 × 200 mL). The combined extracts were concentrated to a volume of 50 mL and cooled to yield 13.52 g of *cis,cis*-**7**, mp 115–118 °C; a second crop (0.18 g, mp 108–114 °C) was isolated from the filtrate (total yield 13.7 g, 83.7%); concentration of the filtrate to dryness gave 2.6 g of yellow oil from which no additional crystalline material could be isolated. Use of tetrahydrofuran solvent in the above reaction procedure in place of ether leads to ca. 90–95% yields of *cis,cis*-**7**.[20]

Use of the triethyl ester **6b** in the above procedure gave an 81% yield of *cis,cis*-**7**: mp 114–117 °C; lit.[10,11] mp 102–103 °C, 111–112 °C; 69% and 77% yields. Reduction of the trimethyl ester **6a** gave *cis,cis*-**7** in 57% yield with a mp of 95–99 °C, as well as more insoluble polymeric material; lit.[11] 55% yield. The ^1H NMR spectrum of pure *cis,cis*-**7** (D_2O) indicated pure cis,cis isomer: δ 3.52 (d, J = 5 Hz, CH_2O, 6 H), 0.3–1.0, 1.2–2.0 (m, ring CH, CH_2, 9 H); additional signals for CH_2O were absent, indicating absence of the cis,trans isomer (high resolution spectra).

***cis,cis*-1,3,5-Triformylcyclohexane (*cis,cis*-8) (*All operations are to be conducted in a good hood.*).** A solution of dry dimethyl sulfoxide (10 mL, freshly vacuum distilled from CaH_2) in 30 mL of dry methylene chloride was added, with stirring, to a solution of oxalyl chloride (10.0 g, 78.8 mmol) in 150 mL of dry methylene chloride during a 10-min period while keeping the temperature at −55 to −60 °C (dry ice/acetone bath; $CaCl_2$ tube protected outlet). After being stirred for 15 min, a solution of 3.48 g (20 mmol) of *cis,cis*-1,3,5-tris(hydroxymethyl)cyclohexane (**7**) in 80 mL of dry dimethyl sulfoxide was added during a 15-min period (temperature −55 °C). The clear solution was allowed to stand without stirring at −55 °C for 2.25 h. Triethylamine (42 mL) was then added over a 5-min period (−55 °C); the cold bath was removed and the reaction mixture was allowed to warm to −30 °C during the next 20 min and (by employing a water bath) to warm to 20 °C during the next 15 min. After standing at 22 °C for 30 min, water (100 mL) was added, with stirring, over a 5-min period. The mixture was immediately poured into a separatory funnel and the methylene chloride layer was separated. Concentrated hydrochloric acid (about 2.5 mL) was added to the aqueous part to adjust the pH to about 1.5–2.0, followed by extraction with two 50-mL portions of methylene chloride. The combined methylene chloride solutions were washed once with 50 mL of 1 N hydrochloric acid and once with 50 mL of water. After drying by stirring with $MgSO_4$ for 30 min, followed by filtration, the filtrate was concentrated to remove volatiles leaving 5.38 g of a mobile orange oil containing *cis,cis*-**8** and dimethyl sulfoxide (^1H NMR assay). (The crude product may be kept in a dry ice chest prior to purification by chromatography, but should not be stored at higher temperatures.) The entire crude product

(18) von Pechmann, H. *Liebigs Ann. Chem.* **1891**, *264*, 261.
(19) Breusch, F. L.; Ulusoy, E. *Instanbul Univ. Fen Fak. Mecmuasi. Ser. C* **1961**, *26*, 1; *Chem. Abstr.* **1961**, *55*, 27204i.
(20) Communication from R. L. Willer, Morton Thiokol Inc., Elkton Division, Elkton, MD 21921.

was placed on a silica gel column (2.5 × 40 cm) and eluted with methylene chloride to yield three fractions in order: (1) 0.06 g of an unidentified yellow oil of unpleasant odor, (2) 2.35 g (70%) of *cis,cis*-**8** which crystallized on chilling, mp 58–60 °C, and (3) 0.29 g of dimethyl sulfoxide (most remains on the column). The trial was purified by trituration with 20 mL of carbon tetrachloride at 25 °C to yield small chunky prisms, mp 60–63 °C (91% recovery). (Attempts to recrystallize the material from boiling carbon tetrachloride led to complete conversion to an amorphous polymer of **8**, mp 135–150 °C.) IR of **8**: 2680, 2780, 2960, 1700, 1440, 1420, 1060 cm^{-1}. ^1H NMR of **8**: ($CDCl_3$) δ 9.70 (s, CHO, 3 H), 2.0–3.0, 0.8–1.7 (m, CH, CH_2, 9 H). The pure crystalline **8** may be stored indefinitely at 0 C without decomposition. Anal. Calcd for $C_9H_{12}O_3$: C, 64.27; H, 7.19. Found: C, 63.96; H, 7.19.

Attempts to prepare **8** by oxidation of triol **7** with other oxidants (activated MnO_2, pyridinium chlorochromate, 2,2′-bipyridinium chlorochromate) gave unreacted triol and/or polymerized trial **8**.

A solution of *cis,cis*-1,3,5-triformylcyclohexane (**8**, 0.336 g, 2 mmol) in 30 mL (40 mmol) of 1.5 M ammonium hydroxide was stored at 0 °C for 20 h. The resulting turbid mixture was extracted with four 25-mL portions of methylene chloride. The combined extracts were dried with $MgSO_4$, filtered, and concentrated to yield 0.01 g of oil, unidentified. A white precipitate remaining in the aqueous part was removed by filtration (0.09 g, amorphous, mp >280 °C). Concentration of the aqueous part to dryness gave 0.20 g of an amorphous glassy white solid, with a mp of >295 °C, which was insoluble in chloroform and would not redissolve in water; the ^1H NMR spectrum (Me_2SO-d_6) reveals broad signals near δ 9.8 (weak singlet), 5.4, 1–3, and 7–8 (exchange with D_2O); the IR spectrum (KBr) shows broad bands at 3100 (strong NH/OH), 2900 (CH), 1700 (weak C=O/C=N) cm^{-1}.

The reaction of trial **8** (10 mg) with ammonium hydroxide-d_5 in D_2O (0.5 mL of 15 M) was examined by ^1H NMR spectroscopy. When mixed at 25 °C, a clear solution resulted producing a singlet at δ 5.0 and multiplets at δ 2.7–3.1, 1.6–2.3, 0.7–1.4 (CH, CH_2). After 16 h, the NMR spectrum was unchanged. In solutions containing a mixture of NH_4OH and ND_4OD the singlet at δ 5.0 appears partly as a doublet at δ 4.7 (J = 10 Hz).

cis,cis-1,3,5-Triformylcyclohexane (**8**, 100 mg, 0.6 mmol) was added at 0 °C to concentrated ammonium hydroxide (2 mL, 50 mmol) that contained 3 drops of 50% aqueous sodium hydroxide (pH 13.5). To the resulting clear solution was added a solution of potassium carbonate (6.9 g, 50 mmol) in 25 mL of water, with stirring, followed by the addition (at 0–10 °C) of acetic anhydride (7 mL, 70 mmol) over a period of 10 min; carbon dioxide evolved vigorously during the addition. Stirring was continued at 5–10 °C for 2 h. The clear solution was extracted with methylene chloride (6 × 25 mL). The dried extracts were concentrated to remove solvent and the residue was sublimed at 55–70 °C (0.1 mm) for 30 min to remove acetamide and to leave a residue (80 mg) of white crystals, mp 185–192 °C, mixed with gum. The residue was dissolved in boiling 2-propanol (4 mL), and the solution was concentrated to a volume of 1 mL and chilled to 0 °C. A white amorphous solid which separated was filtered off and washed with cold 2-propanol; the filtrate was concentrated to dryness to yield an oil mixed with small crystals (50 mg): mp 165–180 °C; ^1H NMR ($CDCl_3$) δ 6.60 (d, J = 10 Hz, CH), 2.3 (s, strong CH_3C=O signal); mass spectrum, m/e (relative intensity) M^+ 291 (9.4), 249 (10.2), 248 (9.3), 206 (16.4), 164 (12.2), 163 (8.2), 43 (100). Chromatography of the product on silica gel (CH_2Cl_2) gave only traces of gum.

3,5,12-Trimethyl-3,5,12-triazawurtzitane (3,5,12-Trimethyl-3,5,12-triazatetracyclo[5.3.1.1^{2,6}.0^{4,9}]decane (10a)). A solution of methylamine (0.30 g, 10 mmol) in 100 mL of anhydrous ether was added to *cis,cis*-1,3,5-triformylcyclohexane (**8**, 0.336 g, 2 mmol) which had been dissolved in 10 mL of tetrahydrofuran. After standing at 25 °C for 4 days, the solvents and excess amine were removed under reduced pressure to leave 0.41 g (99%) of **10a** as long needles, mp 64–75 °C. On standing at ambient temperature, the crystals slowly became oily: ^1H NMR spectra data are in Table II. Anal. Calcd for $C_{12}H_{21}N_3$: C, 69.52; H, 10.21; N, 20.27; M_r, 207.31. Found: C, 69.33; H, 10.40; N, 20.02; M_r, 207 (mass spectrum).

The same procedure that was employed in the preparation of **10a** was used with ethylamine (5 molar equiv) to prepare **10b**. Employing a reaction time of 17 h, 0.22 g (88%) of crude, crystalline **10b**, mp 50–60 °C, was obtained from 1 mmol of trial **8**. The mass spectrum (CI, CH_4) of the crude **10b** shows a strong M^+ at 249. The infrared spectrum of crude **10b** (KBr) reveals an imine **9b** C=N band of moderate intensity at 1640 cm^{-1}.

Attempts to purify the crude products **10a** and **10b** by crystallization from various solvents or by sublimation led to oily mixtures of **10a**, **9a** and **10b**, **9b**, respectively.

Preparation of the 3,5,12-tribenzyl-substituted wurtzitanes **10c–e** followed the procedure used to obtain **10a**, except that only a slight excess of amine was employed (3.2–3.3 molar equiv of amine for 1 molar equiv of trial **8**). Reaction times were varied arbitrarily (times in hours in parentheses) for **10c** (16), **10d** (42), and **10e** (24). The products could be recrystallized from pentane or hexane; melting points are not sharp owing to much retrogression to the triimines which occurs on heating. The infrared spectra of recrystallized samples (KBr) revealed the absence of OH, NH, C=N, or C=O bands. ^1H NMR data are in Table II; molecular ions are seen in the mass spectra (CI, CH_4). Synthesis data for **10a–e** are summarized in Table I.

X-ray Diffraction Analysis of 10c: $C_{30}H_{33}N_3$; M_r, 435.615, monoclinic space group $P2_1/c$, a = 10.968 (1), b = 11.965 (1), and c = 18.857 (2) Å, β = 95.77 (1)°, vol = 2461.5 (4) Å^3, Z = 4, ρ_{calc} = 1.18 g/cm^3, μ(Cu Kα) = 4.94 cm^{-1}, F(000) = 936.

A clear colorless crystal (0.35 × 0.40 × 0.60 mm) was used for data collection on a Nicolet R3M automated diffractometer with an incident beam monochromator at 295 K. Lattice parameters were determined from 25 centered reflections with $60 \le 2\theta < 80°$. The data collection range was $-12 \le h \le 12$, $0 \le k \le 14$, and $-20 \le l < 22$, $\sin\theta/\lambda_{max}$ = 0.59 Å^{-1}. Three standards were monitored every 60 reflections and exhibited a 2.5% maximum random variation. A total of 6256 reflections were measured in the $\theta/2\theta$ mode with a scan width from [2θ(Kα_1) − 1.0°] to [2θ(Kα_2) + 1.0°]; scan rate was a function of count rate (4°/min minimum, 30°/min maximum). There were 4190 unique reflections, R_{int} = 0.012 from merging equivalent reflections, 3393 observed with $F_o > 3\sigma(F_o)$. Lorentz and polarization corrections applied.

The structure was solved by direct methods[21] as implemented in the SHELXTL system[22] of computer programs. In the block-cascade least-squares refinement, the function minimized was $\Sigma w(|F_o| - |F_c|)^2$ where $w = 1/[\sigma^2(|F_o| + g(F_o)^2)$. In this work g = 0.0004. There were 353 parameters refined, including the atom coordinates and anisotropic temperature parameters for all non-H atoms, and isotropic temperature factors for the tertiary hydrogens. Other hydrogens were included at calculated positions with C–H = 0.96 Å, H–C–H = 109.5°, C–C–H = 109.5 or 120.0°, and U(H) = 1.2U_{eq}(C), and were shifted along with the neighboring carbon in the least-squares refinement.

Benzyl ring C is disordered (i.e., displays two overlapping images in the electron density map), and the refinement indicates that it occupies alternate positions C and C′ with respective occupancies of 70 and 30 (1)%. For benzyl rings C and C′, the C–C distances were fixed at 1.395 Å and the C–C–C angles at 120°. The final residuals were R = 0.055 and wR = 0.066 with an error for observations of unit weight of 1.90. The largest shift to error ratio in the final cycle was 0.06 and final difference Fourier excursions were 0.14 and −0.19 e Å^{-3}. Atomic scattering factors are from the International Tables for Crystallography.[23]

***cis,cis*-1,3,5-Tris[(isopropylimino)methyl]cyclohexane (*cis,cis*-9f).** A solution of *cis,cis*-1,3,5-triformylcyclohexane (**8**, 0.17 g, 1.0 mmol) in 10 mL of tetrahydrofuran was added to a solution of isopropylamine (0.30 g, 5 mmol), in 50 mL of ether. After standing at 25 °C for 16 h, the clear solution was concentrated to dryness to yield 0.29 g (100%) of **9f** as clusters of fine white needles: mp 55–58 °C; ^1H NMR data are in Table II; IR (Nujol) 1640 cm^{-1} (C=N, strong, sharp peak). Anal. Calcd for $C_{18}H_{33}N_3$: C, 74.17; H, 11.41; N, 14.42. Found: C, 73.99; H, 11.29; N, 14.34.

(21) Karle, J.; Karle, I. L. *Acta Cryst.* **1966**, *21*, 849.
(22) Sheldrick, G. M. SHELXTL 1980: Minicomputer Programs for Structure Determination; University of Göttingen; Federal Republic of Germany.
(23) *International Tables for X-Ray Crystallography*; Birmingham: Kynoch Press (Present distributor: D. Reidel, Dordrecht, Netherlands), 1974; Vol. IV.

A sample of **9f** dissolved in D_2SO_4 (99%) revealed a ^1H NMR spectrum nearly identical with that found in $CDCl_3$ solvent (= CHN signal shifted to δ 8.2, CH_3 doublet to δ 1.3). In Me_2SO-d_6 containing BF_3 etherate, a sample of **9f** also revealed a virtually unchanged spectrum from that of **9f** in Me_2SO-d_6 alone.

The same procedure employed in the preparation of **9f** was used with *tert*-butylamine (1.0 mmol scale) to yield 0.32 g (96%) of crude **9g**: oil mixed with crystals, mp 60–70 °C; ^1H NMR data are in Table II; IR (KBr) 1640 cm^{-1} (C=N, strong sharp peak). An aliquot portion of the crude sample was heated in an oil bath at 50 °C; no appreciable changes in the spectra (IR, NMR) were discerned after 4 h of heating. After 12 h of heating at 70 °C, a dark red, viscous residue was obtained which retains the C=N infrared signal at 1640 cm^{-1}.

cis,cis-1,3,5-Triformylcyclohexane (8, 0.18 g, 0.11 mmol) was dissolved in methylamine (1.5 mL, about 32 mmol) and stored for 1 h at −80 °C (acetone/dry ice bath) over KOH, followed by storage for 17 h at −5 °C. The unreacted methylamine was allowed to boil off at room temperature and the residue extracted with ether and methylene chloride leaving a concentrated aqueous KOH solution. The extracts were concentrated to dryness leaving a viscous oil (0.18 g, 82%) containing principally 1,3,5-tris[1-(2-aza-1-propenyl)]cyclohexane (**9a**): ^1H NMR ($CDCl_3$) δ 7.69, 7.57 (two singlets with 1 Hz splittings, CH=NCH_3, 3 H, mixture of *Z* and *E* isomers 85:15) 3.30, 3.27 (d, *J* = 1 Hz, CH_3, 9 H), 1.0–3.0 (m, CH_2/CH, 9 H); IR 1650 cm^{-1} (C=N).

1,3,5-Triformylcyclohexane Tris(phenylhydrazone) (11a). Hydrochloric acid (12 N, 2 drops) was added to a solution of *cis,cis*-1,3,5-triformylcyclohexane (8, 0.168 g, 1 mmol) and phenylhydrazine (0.43 g, 4 mmol) in 10 mL of ethanol. The mixture was heated on the steam bath for a few minutes, cooled, and concentrated to dryness under reduced pressure. The residue was crystallized from boiling 2-propanol to yield 0.36 g (82%) of small prisms, mp 87–90 °C. Recrystallization from 2-propanol gave a much less soluble product, mp 176–182 °C, as clusters of small prisms: IR (KBr) 3300 (NH), 1600 (C=N) cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.7–7.6 (m, C_6H_5, CH=, 18 H), 1.0–2.7 (m, CH_2, CH, 9 H). (Attempts at further recrystallization of the compound gave an amorphous brown solid having no C=N band in its infrared spectrum.) Analysis of crystalline, high-melting **11a**, calcd for $C_{27}H_{30}N_6$: C, 73.94; H, 6.90; N, 19.16. Found: C, 73.74; H, 7.03; N, 18.97.

cis,cis-1,3,5-Triformylcyclohexane (8, 0.168 g, 1.0 mmol) dissolved in tetrahydrofuran (5 mL) was added to hydrazine (0.163 g of 98%, 5.0 mmol), dissolved in ether (100 mL). A white precipitate formed immediately; after standing at 25 °C for 19 h, the product was filtered to yield 0.16 g of white crystalline product believed to be trishydrazone **11b**: mp 75–100 °C; ^1H NMR (Me_2SO-d_6) δ 7.10 (d, *J* = 5 Hz, CH=N), 1.0–2.7 (m, ring CH_2, CH). Attempted recrystallization from aqueous ethanol produced a polymer.

3,5-Dimethyl-2-oxo-3,5-diazatricyclo[5.3.1.0^{4,9}]decane (13a). Procedure A (from 1,3,5-Triformylcyclohexane (8) and Methylamine). Methylamine (1.24 g of 50% aqueous solution, 20 mmol) and acetic acid (1.2 g, 20 mmol) were added to a solution of *cis,cis*-1,3,5-triformylcyclohexane (8, 336 mg, 2 mmol) in 15 mL of 95% ethanol; the mixture was heated under reflux for 18.5 h. The clear solution was concentrated under reduced pressure to a volume of 2–3 mL (pH ≃ 6). Aqueous sodium hydroxide (10%) was added to adjust the pH to about 10.5. The slightly turbid solution was extracted with ether (8 × 20 mL) and the combined extracts were dried over $MgSO_4$. Concentration of the extracts to dryness gave 160 mg (41%) of crude **13a**, mp 90–110 °C. Recrystallization from benzene/hexane gave 75 mg: mp 115–118 °C; sublimation (0.1 mm, 130 °C) gave prisms, mp 117–118 °C; IR (KBr) 1650 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 4.56 (d, *J* = 10 Hz, 1 H, NCHN), 3.07 (s, 3 H, CH_3), 2.54 (s, 3 H, CH_3), 1.1–2.0 (m, 11 H, CH_2, CH); ^{13}C NMR ($CDCl_3$) δ 177.87 (C=O), 78.39 (NCN), 52.70 (CH_3NC=O), 43.46 (CH_3NC), 38.42, 37.91 (*C*C=O or CN), 34.39, 32.26, 29.51, 29.15, 26.80 (endocyclic CH_2, CH); mass spectrum, *m/e* (relative intensity) 194 (M^+, 24), 137 (100), 122 (35), 94 (80). Anal. Calcd for $C_{11}H_{18}N_2O$: C, 68.00; H, 9.34; N, 14.41. Found: C, 67.92; H, 9.17; N, 14.19.

3,5-Dimethyl-2-oxo-3,5-diazatricyclo[5.3.1.0^{4,9}]decane (13a). Procedure B (Manganese Dioxide Oxidation of 3,5,12-Trimethyl-3,5,12-triazawurtzitane (10a)). A mixture of 3,5,12-trimethyl-3,5,12-triazawurtzitane (**10a**, 0.28 g, 1.35 mmol), activated manganese dioxide (5.0 g), and chloroform (50 mL) was stirred magnetically at 25 °C for 11.5 h. Filtration, followed by concentration of the filtrate to dryness gave 90 mg of crude **13a**, as prisms, mp 85–110 °C. The MnO_2 was extracted with 50 mL of boiling chloroform to yield an additional 20 mg of **13a**, mp 100–116 °C; total yield 110 mg (42%). Recrystallization from benzene/hexane gave 60 mg of chunky prisms of **13a**, mp 108–116 °C; its spectral properties (IR, NMR) were identical with the material prepared by procedure A.

3,5-Dibenzyl-2-oxo-3,5-diazatricyclo[5.3.1.0^{4,9}]decane (13b). A mixture of *cis,cis*-1,3,5-triformylcyclohexane (8, 0.44 g, 2.6 mmol), benzylamine (5.56 g, 52 mmol), powdered Drierite (2.0 g), Bio-Rad polystyrenesulfonic acid ion exchange resin AG 50W-X8 (0.35 g, 200–400 mesh containing 5.1 mequiv of H^+/g, 44–50% water), and toluene (50 mL) was heated under reflux, with stirring, for 4.5 h. The cooled mixture was filtered, and the filtrate was concentrated at 100 °C (0.1 mm) to yield a viscous yellow oil (1.09 g). Elution chromatography on a silica gel column (2.5 × 42 cm) with methylene chloride/ether (2:1 by volume) gave 0.32 g (36%) of crude crystalline **13b**, mp 121–134 °C. Recrystallization from carbon tetrachloride (DARCO G-60 decolorizing charcoal) gave 0.06 g of **13b** as prisms, mp 141–142 °C, and a second crop, 0.085 g, mp 135–140 °C: IR (KBr) 1650 cm^{-1} (C=O), OH and/or NH absent; ^1H NMR ($CDCl_3$) δ 7.32 (s, C_6H_5, 10 H), 5.80 (AB q, *J* = 15 Hz, 2 H, benzyl CH_2), 4.68 (d, *J* = 10 Hz, 1 H, C*H*N), 3.92 (AB q, *J* = 15 Hz, 2 H, benzyl CH_2), 1–3 (m, CH_2 and CH, 11 H); ^{13}C NMR ($CDCl_3$) δ 177.64 (C=O), 139.34, 138.04 (C-1, phenyl), 128.39, 128.55 (meta C, phenyl), 128.14, 127.90 (ortho C, phenyl), 127.16 (para C, phenyl), 73.42 (NCN), 59.97 (O=C-$NCH_2C_6H_5$), 49.83 ($NCH_2C_6H_5$), 49.01 (endo CH_2N), 38.55 (*C*H-O=O), 34.34, 32.16, 29.52, 29.52, 28.79 (endocyclic CH_2, CH); mass spectrum, *m/e* (relative intensity) M^+ 346 (2.0), 91 (100). Anal. Calcd for $C_{23}H_{26}N_2O$: C, 79.73; H, 7.56; N, 8.09. Found C, 78.71; H, 7.52; N, 7.99.

1,3,5-Tris(dimethoxymethyl)benzene (14). A mixture of 1,3,5-triformylbenzene[17] (16.2 g, 0.1 mol, mp 161–164 °C), trimethyl orthoformate (57.4 g, 0.54 mol), ammonium chloride (0.46 g), and absolute methanol (34.4 g, 1.07 mol) was heated under reflux for 1.5 h. After cooling to 25 °C, diethyl ether (80 mL) was added, and the mixture was filtered to remove ammonium chloride. The filtrate was treated with 4% aqueous sodium hydroxide solution (25 mL) and extracted with three 25-mL portions of water. The water extracts were extracted with two 100-mL portions of ether. The original solution and the ether extracts were combined and dried over K_2CO_3. Concentration under reduced pressure to remove solvents gave an oil (28.5 g), which was dissolved in boiling absolute methanol (57 mL), treated with decolorizing charcoal (DARCO G-60), and filtered while hot. The cooled filtrate was diluted with water (340 mL) to precipitate 18.1 g (60%) of the crystalline tris acetal **14**, mp 41–47 °C; recrystallization from aqueous methanol gave prisms, mp 45–47 °C: ^1H NMR ($CDCl_3$) δ 7.65 (s, aryl CH, 3 H), 5.50 (s, CH, 3 H), 3.32 (s, CH_3O, 18 H). On standing, the filtrate slowly deposited 1,3,5-triformylbenzene: 1.35 g, mp 155–157 °C. Anal. Calcd for $C_{15}H_{24}O_6$ (**14**): C, 59.98; H, 8.05. Found: C, 60.01; H, 7.99.

***cis,cis*- and *cis,trans*-1,3,5-Tris(dimethoxymethyl)cyclohexane (15a, 15b).** A solution of 1,3,5-tris(dimethoxymethyl)benzene (**14**, 1.62 g, 5.4 mmol) in absolute ethanol (60 mL) and 5% rhodium on charcoal catalyst (3.2 g) was shaken with hydrogen in a Parr apparatus (50 psi, 50 °C, 21 h). After cooling and filtration of the catalyst, the filtrate was concentrated to remove solvents and yield 0.70 g of colorless oil mixed with crystals. Dilution with hexane and cooling at 0 °C deposited 0.14 g (8.5%) of *cis,cis*-**15a**: mp 78–80 °C; ^1H NMR ($CDCl_3$) δ 4.13 (d, *J* = 6 Hz, OC*H*O, 3 H), 3.42 (s, CH_3O, 18 H), 0.3–2.3 (m, ring CH and CH_2, 9 H). Anal. Calcd for $C_{15}H_{30}O_6$: C, 58.80; H, 9.87. Found: C, 58.54; H, 9.98.

The filtrate from crystallization of the cis isomer was concentrated to yield *cis,trans*-**15b** (0.45 g, 37%): bp 165–170 °C (0.1 mm); ^1H NMR ($CDCl_3$) δ 4.13 (d, *J* = 6 Hz, *cis*-OC*H*O, 2 H), 4.10 (d, *J* = 6 Hz, *trans*-OC*H*O, 1 H), 3.42 (s, *cis*-CH_3O, 12 H), 3.40 (s, *trans*-CH_3O, 6 H), 0.3–2.3 (m, ring CH and CH_2, 9 H).

Reaction of *cis,cis*-1,3,5-Triformylcyclohexane (8) with Methanol. A mixture of *cis,cis*-1,3,5-triformylcyclohexane (8, 0.168 g, 1 mmol) in methanol (5 mL), Amberlite-CG120 Type 1

(0.02 g), and powdered Drierite (0.3 g) was stirred magnetically for 16 h at 25 °C (flask protected by $CaCl_2$ tube). Filtration and concentration to dryness gave 0.25 g (96%) of white prisms of crude acetal **17** with mp 70–80 °C: ^1H NMR (CD_3CN/Me_2SO-d_6) δ 4.14 (d, J = 6 Hz, 3 CH), 3.30 (s, CH_3O, 12 H), [2.85 (d, J = 12 Hz), 0.8–1.2 (m), 0.65 (q, J = 12 Hz), CH_2 + CH, 9 H]; aldehyde signal absent. On standing in ambient air, the compound produced a gummy white solid, partly soluble in $CDCl_3$ (^1H NMR of the $CDCl_3$ soluble portion revealed an aldehyde signal at δ 9.7).

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Supplementary Material Available: One figure showing full numbering used in X-ray analysis and the hydrogen atom locations; tables of (1) atom coordinates and equivalent isotropic thermal parameters for the non-hydrogen atoms, (2) anisotropic thermal parameters for non-hydrogen atoms, (3) hydrogen atom coordinates and thermal parameters, and (4) bond distances and valence angles (5 pages). Ordering information is given on any current masthead page.

Synthesis of Mono- and Difunctionalized Ditopic [24]N_6O_2 Macrocyclic Receptor Molecules

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The 24-membered macrocycle 1,13-dioxa-4,7,10,16,19,22-hexaazacyclotetracosane ([24]N_6O_2, **1**) as the free amine forms complexes with transition-metal cations, and in aqueous solution the polyprotonated form binds anions. Compound **1** also is an efficient catalyst in the transformation reactions of adenosine triphosphate and acetyl phosphate. A selective procedure for the preparation of derivatives of **1** containing pendant functionality is described in an effort to incorporate additional nucleophilic groups and potential general-acid–general-base catalytic sites. A convergent approach to these molecules employs 9-benzoyl-6,12-bis(*p*-tolylsulfonyl)-1,17-bis(methylsulfonyl)-6,9,12-triaza-3,15-dioxaheptadecane (**13**) in cyclization reactions with either *N'*-benzoyl-*N,N''*-bis(*p*-tolylsulfonyl)diethylenetriamine (**11**) or *N,N',N''*-tris(*p*-tolylsulfonyl)diethylenetriamine (**18**). Selective debenzoylation of these macrocycles gives respectively the protected 7,19-diamine **15** or the 7-monoamine **20**. The former was used in the preparation of the 7,19-bis(2-aminoethyl) (**2**), -(2-hydroxyethyl) (**3**), and -(2-mercaptoethyl) (**4**) derivatives of **1**. Compound **4** was isolated as the macrobicyclic disulfide **17**. The monoamine **20** was used in the preparation of the corresponding 7-monosubstituted derivatives of **1**, compounds **5**, **6**, and **7**.

The complexation of anions in chemical as well as biochemical processes has recently been explored by the use of macrocyclic and macropolycyclic polyammonium molecules.[1-3] These organic receptor molecules form stable and selective complexes with a variety of inorganic as well as organic anions.[4-12] Recently, it has been shown that macrocyclic polyammonium cations also can act as catalysts in the transformation of bound substrates such as ATP[13] and acetyl phosphate.[14] Among the various macrocyclic polyamines studied, the 24-membered dioxo hexaaza macrocycle **1**[15] presents a particularly interesting set of properties. In addition to catalyzing the hydrolysis of ATP and acetyl phosphate, pyrophosphate formation via a phosphorylated macrocyclic intermediate demonstrates the role of nucleophilic catalysis. Compound **1** acting as a supramolecular catalyst[3,16] thus performs the overall reactions catalyzed by ATPases and kinases. Recently, it was demonstrated that a third component, calcium ion, added to the complex of ATP and **1** regulates the hydrolytic reaction of ATP and allows for the formation of pyrophosphate.[17] Thus, with compound **1** three principal features of enzymatic reactions, specificity, catalysis, and regulation, have been demonstrated.

In order to gain an understanding of the catalytic behavior of the receptor–catalyst **1** and increase its efficiency, a series of new macrocycles containing additional functionality was designed. The intention was to provide

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(1) Pierre, J.-L.; Baret, D. *Bull. Soc. Chim. Fr.* **1983**, 367–380.
(2) (a) Vogtle, F. *Top. Curr. Chem.* **1981**, 143–161. (b) Kimura, E. *Top. Curr. Chem.* **1985**, *128*, 113–141. (c) Schmidtchen, F. P. *Top. Curr. Chem.* **1986**, *132*, 101–133.
(3) Lehn, J. M. *Science (Washington, D.C.)* **1985**, *227*, 849–856.
(4) Simmons, H. E.; Park, C. H. *J. Am. Chem. Soc.* **1968**, *90*, 2428–2429.
(5) Graf, E.; Lehn, J. M. *J. Am. Chem. Soc.* **1976**, *98*, 6403–6405.
(6) (a) Lehn, J. M.; Souveaux, E.; Willard, A. K. *J. Am. Chem. Soc.* **1978**, *100*, 4914–4916. (b) Dietrich, B.; Guilhem, J.; Lehn, J. M.; Pascard, C.; Souveaux, E. *Helv. Chim. Acta* **1984**, *67*, 91–104.
(7) Dietrich, B.; Hosseini, M. W.; Lehn, J. M.; Sessions, R. B. *J. Am. Chem. Soc.* **1981**, *103*, 1282–1283.
(8) Cullinam, J.; Gelb, R. I.; Margulis, T. N.; Zompa, L. J. *J. Am. Chem. Soc.* **1982**, *104*, 3048–3053.
(9) Hosseini, M. W.; Lehn, J. M. *J. Am. Chem. Soc.* **1982**, *104*, 3525–3527; *Helv. Chim. Acta* **1986**, *69*, 587–603.
(10) (a) Kimura, E.; Sakonaka, A.; Yatsunami, T.; Kodama, M. *J. Am. Chem. Soc.* **1981**, *103*, 3041–3045. (b) Kimura, E.; Kodama, M.; Yatsunami, T. *J. Am. Chem. Soc.* **1982**, *104*, 3182–3187.
(11) (a) Peter, F.; Gross, M.; Hosseini, M. W.; Lehn, J. M.; Sessions, R. B. *J. Chem. Soc., Chem. Commun.* **1981**, 1067–1069. (b) Peter, F.; Gross, M.; Hosseini, M. W.; Lehn, J. M. *J. Electroanal. Chem. Interfacial Electrochem.* **1983**, *144*, 279–292. (c) Garcia-Espana, E.; Micheloni, M.; Paoletti, P.; Bianchi, A. *Inorg. Chim. Acta* **1985**, *102*, L9–L9.
(12) (a) Manfrin, M. E.; Sabbatini, N.; Moggi, L.; Balzani, V.; Hosseini, M. W.; Lehn, J. M. *J. Chem. Soc., Chem. Commun.* **1984**, 555–556. (b) Manfrin, M. F.; Moggi, L.; Castelvetro, V.; Balzani, V.; Hosseini, M. W.; Lehn, J. M. *J. Am. Chem. Soc.* **1985**, *107*, 6888–6892.
(13) Hosseini, M. W.; Lehn, J. M.; Mertes, M. P. *Helv. Chim. Acta* **1983**, *66*, 2454–2466; **1985**, *68*, 818.
(14) Hosseini, M. W.; Lehn, J. M. *J. Chem. Soc., Chem. Commun.* **1985**, 1155–1157.
(15) Comarmond, J.; Plumere, P.; Lehn, J. M.; Agnus, Y.; Louis, R.; Weiss, R.; Kahn, O.; Morgenstern-Badarau, I. *J. Am. Chem. Soc.* **1982**, *104*, 6330–6340.

0022-3263/87/1952-1662$01.50/0