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Synthesis, Characterization, and Solid-State Structure of a New Hexachelating Ligand and Its Complex with Gallium(III)

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The ligand *N,N′,N″*-tris(3,5-dimethyl-2-hydroxybenzyl)-1,4,7-triazacyclononane, TX-TACNH$_3$ (**1**), was synthesized from the parent amine, TACN, by reaction with formaldehyde and 2,4-dimethylphenol. This compound crystallizes from diethyl ether in the triclinic system, space group $P\bar{1}$, with a = 10.384 (2) Å, b = 11.174 (1) Å, c = 15.067 (2) Å, α = 105.38 (1)°, β = 109.41 (1)°, γ = 91.68 (1)°, and two molecules per unit cell. TX-TACNH$_3$ undergoes reaction with Ga(ClO$_4$)$_3$·6H$_2$O in ethanol to give the monoprotonated complex [Ga(TX-TACN)H]$^+$[ClO$_4$]$^-$ (**2a**). The complex crystallizes from methanol as the monosolvate in the monoclinic system, space group $P2_1/c$, with a = 8.833 (1) Å, b = 27.408 (4) Å, c = 14.485 (2) Å, β = 96.68 (1)°, and four formula units per unit cell. Gallium is fully chelated by the ligand in an octahedral environment. The molecule of solvation, methanol, is within hydrogen-bonding distance of two of the three phenolic oxygens (interatomic distances: O1–O100 = 2.57 Å, O2–O100 = 2.75 Å, and O3–O100 = 3.41 Å).

The development of metal-chelating agents for medical applications is an actively growing area of research.[1] While much effort has been put into the synthesis of ethylenediamine derivatives, these ligands yield a potential coordination sphere consisting of an $N_2O_4^{4-}$ core, which produces an anionic complex when bound to gallium(III) or indium(III).[2] Accordingly, these complexes are not very lipophilic. Hydrophilicity may be the principal reason radiolabeled complexes of $^{111}In^{3+}$ and $^{68}Ga^{3+}$ are unable to cross the blood–brain barrier.[3] Current research in our group is directed toward the development of hexachelating ligands that possess a potential coordination sphere consisting of an $N_3O_3^{3-}$ core, thereby producing neutral, highly lipophilic complexes of Ga^{3+} or In^{3+}. We now report the synthesis and characterization of a new hexachelating ligand, *N,N′,N″*-tris(3,5-dimethyl-2-hydroxybenzyl)-1,4,7-triazacyclononane (TX-TACNH$_3$) (Figure 1), and its complex with gallium(III).

Experimental Section

Caution! Perchlorate salts of metal complexes are potentially explosive and should be handled with care and only in small amounts.

(A) General Comments. Ga(ClO$_4$)$_3$·6H$_2$O was obtained from Ventron Alfa Products. Formaldehyde (37% w/w solution in water) and 2,4-dimethylphenol were purchased from Fisher. 1,4,7-Triazacyclononane (TACN) was prepared as reported in the literature.[4] All solvents were of reagent grade. All materials were used without further purification. All NMR experiments were performed on a 7.05-T Varian XL-300 spectrometer (Varian Instruments Group, Palo Alto, CA). ^{1}H (300 MHz) and ^{13}C (75 MHz) spectra were internally referenced to tetramethylsilane. ^{13}C NMR peak assignments were made from gated decoupled spectra. Melting points were determined by using an Electrothermal melting point apparatus. Mass spectral data were obtained from a VG-ZAB-3F mass spectrometer and processed by using an associated VG-11-250 data system. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, TN.

(B) Synthesis of *N,N′,N″*-Tris(3,5-dimethyl-2-hydroxybenzyl)-1,4,7-triazacyclononane (TX-TACNH$_3$) (1). To a round-bottom flask containing 0.30 g (0.0023 mol) of TACN in 15 mL of CH$_3$OH and fitted with a water-cooled condenser was added 0.70 g (0.0085 mol) of a 37% w/w formaldehyde solution in H$_2$O. The mixture was heated to gentle reflux with stirring for 3 h, during which time the color of the solution changed from colorless to light yellow. At this time, a solution containing 0.95 g (0.0078 mol) of 2,4-dimethylphenol, dissolved in 10 mL of CH$_3$OH, was added to the hot reaction mixture in 1-mL portions. After the mixture was heated overnight, a white crystalline solid separated from the reaction mixture. This crude product was collected by filtration and washed with cold (0 °C) methanol. Crude yield: 0.35 g. The filtrate was heated to reflux and the reaction allowed to continue for 1 day, yielding an additional 0.10 g of crude product. The combined yields were dissolved in benzene, and the mixture was dried by distillation of the water–benzene azeotrope. Pure product was obtained by rotoevaporation of the remaining benzene solvent and recrystallization of the dry crude material from diethyl ether. Total yield of **1**: 0.32 g (25.9% based on TACN).

^{1}H NMR (20 °C, CDCl$_3$): δ 2.19 (H$_a$, s, 3 H), 2.22 (H$_b$, s, 3 H), 2.84 (H$_c$, s, 4 H), 3.70 (H$_d$, s, 2 H), 6.59 (phenyl H, s, 1 H), 6.90 (phenyl H, s, 1 H); the phenolic protons were not observed. ^{13}C{^{1}H} NMR (20 °C, CDCl$_3$): δ 15.75 (Me$_a$), 20.48 (Me$_b$), 55.15 (TACN ring CH$_2$), 62.44 (benzylic CH$_2$), 120.97, 124.61, 127.09, 127.79, 130.86, 152.92 (phenyl C's). MS-FAB: M + H, *m/z* 532. Melting point: 163.5–165.0 °C. Anal. Calcd for $C_{33}H_{45}N_3O_3$: C, 74.54; H, 8.35. Found: C, 74.56; H, 8.31.

(C) Synthesis of [Ga(TX-TACN)H]$^+$[ClO$_4$]$^-$·CH$_3$OH (2a). A solution containing 270 mg of **1** (0.000 51 mol) and 230 mg of Ga(ClO$_4$)$_3$·6H$_2$O (0.000 49 mol) in 100 mL of CH$_3$CH$_2$OH was heated to reflux for 2 days. When the solution was cooled to room temperature, an off-white microcrystalline material was deposited in the flask. The crude product was collected by filtration, washed with cold (0 °C) ethanol, and redissolved in 10 mL of warm methanol. Pale amber crystals were obtained after cooling to −10 °C. Yield of the monosolvated product (**2a**): 186 mg (51.9%, based on Ga).[5]

^{1}H NMR (20 °C, CD$_3$OD): δ 2.16 (Me$_a$, s, 3 H), 2.20 (Me$_b$, s, 3 H), 2.42 (TACN ring CH$_2$, m, 1 H), 2.54 (TACN ring CH$_2$, m, 1 H), 2.92 (TACN ring CH$_2$, m, 1 H), 3.14 (TACN ring CH$_2$, m, 1 H), 3.43 (benzylic CH$_{2a}$, d, $J_{CH_{2a}-CH_{2b}}$ = 11.9 Hz, 1 H), 4.67 (benzylic CH$_{2b}$, d, $J_{CH_{2b}-CH_{2a}}$ = 11.9 Hz, 1 H), 6.65 (phenyl H, s, 1 H), 6.95 (phenyl H, s, 1 H). Note: the acidic proton was not observed (due to exchange with solvent deuteriums). ^{13}C {^{1}H} NMR (20 °C, CD$_3$OD): δ 17.12 (Me$_a$), 20.52 (Me$_b$), 56.72 (TACN ring CH$_2$), 63.26 (benzylic CH$_2$), 121.24, 126.73, 127.86, 129.81, 132.97, 159.08 (phenyl C's). Melting point: 315 °C dec. MS-FAB: M + H, m/*z* 598/600. Anal. Calcd for $GaC_{34}H_{47}ClO_8N_3$: C, 55.87; H, 6.48; N, 5.75; Ga, 9.54. Found: C, 55.68; H, 6.77; N, 5.83; Ga, 9.56.

(D) X-ray Diffraction Studies of TX-TACNH$_3$ (1) and [Ga(TX-TACN)H]$^+$[ClO$_4$]$^-$·CH$_3$OH (2a). Single crystals of **1** were grown from a saturated diethyl ether solution at room temperature. Suitable crystals of the gallium complex were obtained from saturated methanol at −10 °C. Data for both structures were collected at room temperature on an Enraf-Nonius CAD4 diffractometer using Mo Kα radiation. An absorption correction was not applied to TX-TACNH$_3$. An empirical[6] absorption correction was applied to the gallium complex (**2a**). Positions for hydrogen atoms were calculated by assuming idealized geometry and

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(1) Bulman, R. A. *Structure and Bonding*; Springer-Verlag: Berlin, 1987; Vol. 67.

(2) Mathias, C. J.; Sun, Y.; Welch, M. J.; Green, M. A.; Thomas, J. A.; Wade, K. R.; Martell, A. E. *Nucl. Med. Biol.* **1988**, *15*, 69.

(3) Metal complexes that cross the blood–brain barrier (e.g. Tc-PnAO) are typically neutral and very lipophilic: Holm, S.; Andersen, A. R.; Vorstrup, S.; Lassen, N. A.; Paulson, O. B.; Holmes, R. A. *J. Nucl. Med.* **1985**, *26*, 1129.

(4) White, D. W.; Karcher, B. A.; Jacobson, R. A.; Verkade, J. G. *J. Am. Chem. Soc.* **1979**, *101*, 4921.

(5) Evaporation of mother liquor followed by extraction with CH$_2$Cl$_2$ gave 80 mg of pink-lavender crystals. While mass spectroscopy, as well as ^{13}C and ^{1}H NMR spectroscopy, of this material was indistinguishable from that of **2a**, its melting point was significantly lower than that of **2a**: 258 °C dec. Elemental analysis suggests the material to be the hemisolvate of the neutral complex Ga(TX-TACN)·$^1/_2$CH$_2$Cl$_2$ (**2b**). Anal. Calc for $GaC_{33}H_{43}N_3O_3 \cdot {}^1/_2CH_2Cl_2$: C, 62.78; H, 6.76; N, 6.56; Ga, 10.88. Found: C, 62.23; H, 7.27; N, 6.39; Ga, 10.28.

(6) Walker, N.; Stuart, D. *Acta Crystallogr., Sect. A* **1983**, *A39*, 158.

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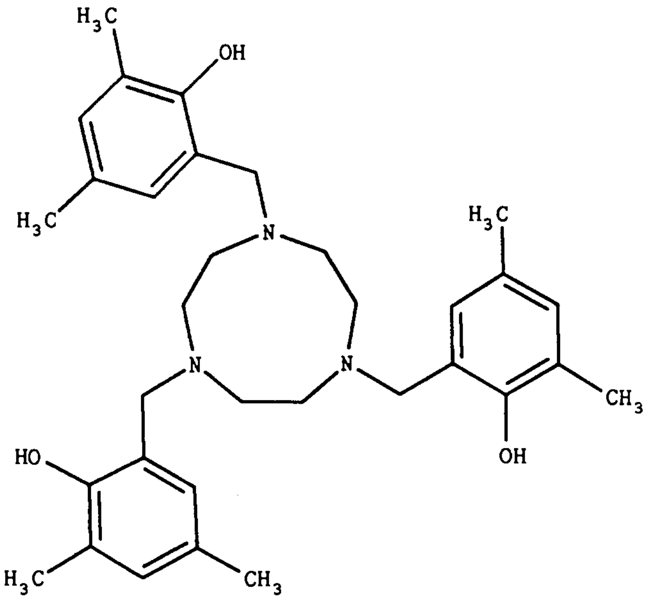

Figure 1. *N,N′,N″*-Tris(3,5-dimethyl-2-hydroxybenzyl)-1,4,7-triazacyclononane.

Table I. Crystallographic Data for TX-TACNH$_3$ (**1**) and [Ga(TX-TACN)H]$^+$[ClO$_4$]$^-$·CH$_3$OH (**2a**)

	1	2a
formula	$C_{33}H_{45}N_3O_3$	$GaClO_8N_3C_{34}H_{47}$
fw	531.74	730.94
space group	$P\bar{1}$ (No. 2)	$P2_1/c$ (No. 14)
a, Å	10.384 (2)	8.833 (1)
b, Å	11.174 (1)	27.408 (4)
c, Å	15.067 (2)	14.485 (2)
α, deg	105.38 (1)	
β, deg	109.41 (1)	96.68 (1)
γ, deg	91.68 (1)	
V, Å^3	1576.5 (9)	3482 (1)
Z	2	4
T, °C	20	20
λ(Mo Kα), Å	0.71073	0.71073
ρ_{calc}, g cm^{-3}	1.120	1.394
μ, cm^{-1}	0.67	9.15
transmission coeff		1.000–0.601
$R(F_o)$	0.054	0.061
$R_w(F_o)$	0.069	0.079

a bond distance of 0.95 Å. Phenolic protons of TX-TACNH$_3$ (**1**) were located and refined isotropically. For methyl groups, one hydrogen was located in a difference Fourier map, its position was idealized, and the remaining positions were calculated. We were unable to observe the location of the acidic hydrogen in [Ga(TX-TACN)H]$^+$[ClO$_4^-$]. All data reduction and structure refinement was carried out by using the Enraf-Nonius structure determination package. Crystallographic data and details of data collection, for **1** and **2a**, are presented in Table I.

Results and Discussion

(A) Synthesis of *N,N′,N″*-Tris(3,5-dimethyl-2-hydroxybenzyl)-1,4,7-triazacyclononane (1). TX-TACNH$_3$ (**1**) is produced in good yield by the reaction of the Mannich base[7] of formaldehyde and 1,4,7-triazacyclononane[4] (TACN) with 2,4-dimethylphenol. This procedure is similar to that used to produce HBED-type (*N,N′*-bis(2-hydroxybenzyl)ethylenediamine-*N,N′*-diacetic acid) ligands.[2] Small amounts of incomplete N-alkylation products may be removed by simple recrystallization from diethyl ether. However, the crude product obtained from the reaction mixture is pure enough for most applications.[8]

(B) Structure of TX-TACNH$_3$ (1). An ORTEP drawing of **1** based on its X-ray crystal structure is shown in Figure 2. Selected bond distances and angles are listed in Table II.

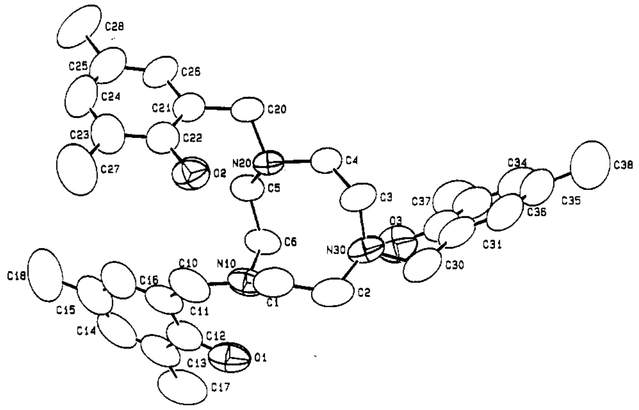

Figure 2. ORTEP drawing of TX-TACNH$_3$ (**1**). Ellipsoids are drawn at 50% probability.

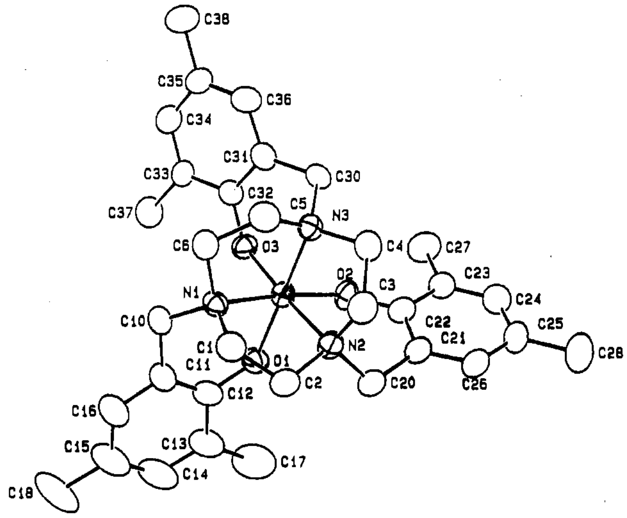

Figure 3. ORTEP drawing of [Ga(TX-TACN)]H$^+$ (cation of **2a**). Ellipsoids are drawn at 50% probability.

The molecule exhibits intramolecular hydrogen bonding between the phenolic protons and the amine nitrogens, with bond lengths of 1.81, 1.83, and 1.84 Å for N1–H1, N2–H2, and N3–H3, respectively.

(C) Synthesis of [Ga(TX-TACN)H]$^+$[ClO$_4$]$^-$·CH$_3$OH (2a). The ligand TX-TACNH$_3$ (**1**) forms a stable complex with Ga^{3+} in alcoholic media. Chelation of the metal is able to proceed even in the acidic reaction environment (HClO$_4$ is formed during the course of the reaction), giving the complex in its protonated form.[5] The Ga complex is readily soluble in polar solvents, such as dichloromethane and methanol,[9] and is not sensitive toward air or moisture.[10]

(D) Structure of [Ga(TX-TACN)H]$^+$[ClO$_4$]$^-$·CH$_3$OH (2a). An ORTEP drawing of the gallium complex, **2a**, is shown in Figure 3. Important bond distances and angles are shown in Table III. Present in the unit cell are the cationic metal complex, its associated perchlorate anion, and methanol as a molecule of solvation. The gallium center is bound in a slightly distorted octahedral coordination sphere by the three amine nitrogens and the three phenoxy oxygens of the fully chelating ligand. The distortion of the coordination sphere is most evident as a compression of N–Ga–N angles from 90° (see Table III).

The presence of hydrogen bonding between the methanol and the gallium complex may be inferred from Ga–O bond lengths as well as oxygen–oxygen distances. The methanol oxygen, O100, is relatively close to phenoxy oxygens O1 (2.57 Å) and O2 (2.75

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(7) Julia, M. *Bull. Soc. Chim. Fr.* **1955**, 850.

(8) We have observed no difference in any in vitro test between crude and recrystallized TX-TACNH$_3$ when complexed with ^{68}Ga^{3+}.

(9) The solubility properties of this complex are in stark contrast with those of a similar complex, Ga[(5-MeOsal)$_3$tame]: Green, M. A.; Welch, M. J. *J. Am. Chem. Soc.* **1984**, *106*, 3689.

(10) In vitro experiments, where the radiolabeled ^{68}Ga complex is mixed with whole rat blood, indicate no exchange with transferrin occurs.

Table II. Selected Bond Distances (Å) and Bond Angles (deg) with Estimated Standard Deviations for TX-TACNH$_3$ (**1**)

		Bond Distances			
O1–C12	1.370 (4)	O1–H1	0.963 (2)	N1–H1	1.805 (3)
O2–C22	1.381 (3)	O2–H2	1.00 (3)	N2–H2	1.83 (3)
O3–C32	1.368 (4)	O3–H3	0.99 (4)	N3–H3	1.85 (4)
N1–C1	1.473 (4)	N1–C6	1.478 (3)	N1–C10	1.489 (4)
N2–C4	1.475 (3)	N2–C5	1.467 (3)	N2–C20	1.492 (3)
N3–C2	1.479 (4)	N3–C3	1.478 (4)	N3–C30	1.478 (4)
C1–C2	1.505 (4)	C3–C4	1.527 (4)	C5–C6	1.521 (4)
C10–C11	1.498 (4)	C20–C21	1.501 (4)	C30–C31	1.519 (5)
C11–C12	1.399 (4)	C21–C22	1.384 (4)	C31–C32	1.393 (5)
		Bond Angles			
C12–O1–H1	100.5 (3)	C22–O2–H2	107 (2)	C33–O3–H3	107 (2)
O1–H1–N1	150.5 (2)	O2–H2–N2	146 (3)	O3–H3–N3	148 (3)
O1–C12–C11	120.4 (4)	O2–C22–C21	120.3 (3)	O3–C32–C31	120.1 (3)
C1–N1–C6	115.8 (2)	C4–N2–C5	112.3 (2)	C2–N3–C3	114.5 (2)
C1–N1–C10	111.8 (2)	C4–N2–C20	109.4 (2)	C2–N3–C30	108.1 (2)
C6–N1–C10	112.5 (2)	C5–N2–C20	107.5 (2)	C3–N3–C30	109.7 (2)
N1–C1–C2	115.6 (2)	N2–C5–C6	117.0 (2)	N3–C3–C4	115.2 (2)

Table III. Selected Bond Distances (Å) and Bond Angles (deg) with Estimated Standard Deviations for [Ga(TX-TACN)H]$^+$[ClO$_4$]$^-$·CH$_3$OH (**2a**)

		Bond Distances			
Ga–O1	1.996 (3)	Ga–O2	1.937 (3)	Ga–O3	1.900 (3)
Ga–N1	2.097 (4)	Ga–N2	2.119 (4)	Ga–N3	2.112 (4)
O1–C12	1.391 (6)	O2–C22	1.378 (6)	O3–C32	1.359 (6)
N1–C1	1.500 (6)	N2–C2	1.496 (6)	N3–C4	1.484 (6)
N1–C6	1.489 (6)	N2–C3	1.485 (7)	N3–C5	1.506 (6)
N1–C10	1.525 (6)	N2–C20	1.505 (7)	N3–C30	1.502 (6)
C1–C2	1.530 (7)	C3–C4	1.526 (7)	C5–C6	1.532 (7)
C10–C11	1.507 (7)	C20–C21	1.520 (7)	C30–C31	1.497 (7)
C11–C12	1.382 (7)	C21C22	1.397 (7)	C31–C32	1.393 (7)
O1–O100	2.57 (2)	O2–O100	2.75 (2)	O3–O100	3.41 (2)
		O100–C101	1.40 (2)		
		Bond Angles			
O1–Ga–O2	87.0 (1)	O1–Ga–O3	91.8 (1)	O1–Ga–N1	89.9 (1)
O1–Ga–N2	92.6 (1)	O1–Ga–N3	172.3 (1)	O2–Ga–O3	90.0 (1)
O2–Ga–N1	173.0 (1)	O2–Ga–N2	90.6 (1)	O2–Ga–N3	99.0 (1)
O3–Ga–N1	96.3 (1)	O3–Ga–N2	175.6 (1)	O3–Ga–N3	93.0 (1)
N1–Ga–N2	83.4 (1)	N1–Ga–N3	83.7 (1)	N2–Ga–N3	82.5 (1)
Ga–O1–C12	130.6 (3)	Ga–O2–C22	130.4 (3)	Ga–O3–C32	128.1 (3)
Ga–N1–C1	110.5 (3)	Ga–N2–C2	104.6 (3)	Ga–N3–C4	104.9 (3)
O1–C12–C11	121.0 (4)	O2–C22–C21	120.7 (4)	O3–C32–C31	121.5 (4)

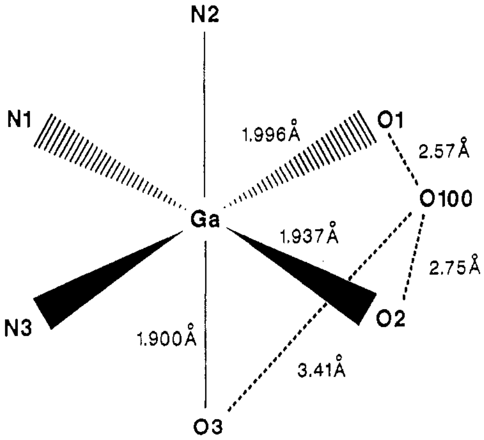

Figure 4. Coordination sphere of **2a**.

Å).[11] Consequently, there is an observable increase in the bond lengths Ga–O1 (1.996 Å) and Ga–O2 (1.937 Å), while O3, the most distant of the phenoxy oxygens from O100, is involved in the shortest Ga–O bond (1.900 Å)[12] (Figure 4). We were unable to determine the exact location of the acidic hydrogen present in the molecule.

Presently, we are investigating the synthesis of triazacyclononane derivatives as ligands for radioactive metals, ^{68}Ga^{3+} and ^{111}In^{3+}. We are most interested in the effect various substituents on TACN will have on the stability and biodistribution of the radiolabeled complexes produced.

Acknowledgment. We thank the National Institutes of Health (Grant CA-42925) and Department of Energy (Grant FG02-87ER60512) for financial support. NMR spectra were obtained with the assistance of Dr. Andre d'Avington, Director of the Washington University High-Resolution NMR Service Facility. This facility is funded in part by Biomedical Research Support Instrument Grant 1 S10 RR02004 and by a gift from the Monsanto Co. We thank Dr. Andrew Tyler of Washington University Medical School for obtaining mass spectra of **1** and **2a**. The Washington University Mass Spectrometry Resource is supported by a grant from the National Institutes of Health (RR00954). The MICROVAX Computer and Enraf-Nonius CAD4 diffractometer used in the structure determinations were purchased with National Science Foundation Grant CHE-8615556.

Registry No. **1**, 119480-60-3; **2a**, 119480-62-5; **2b**, 119480-61-4; TACN, 4730-54-5; formaldehyde, 50-00-0; 2,4-dimethylphenol, 105-67-9.

Supplementary Material Available: For both **1** and **2a**, listings of positional parameters, thermal parameters, and crystallographic data, and for **2a**, stereoscopic views of the unit cell (19 pages); for **1** and **2a**, tables of F_o and F_c (41 pages). Ordering information is given on any current masthead page.

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[11] Schuster, P.; Zundel, G.; Sandorfy, C. *Hydrogen Bonding*; North-Holland Publishing Co.: Amsterdam, 1976; distributed in the U.S.A. by Elsevier Publishing Co., Inc., 52 Vanderbilt Ave., New York 10017.

[12] A normal Ga–O bond length is 1.941 Å; see ref 9.