

**CISTULYNES: PROTON NMR AND SINGLE-CRYSTAL X-RAY
EVIDENCE FOR STRUCTURE AND CATION ENCAPSULATION
IN A RIGID, MOLECULAR CHANNEL MODEL SYSTEM**

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Abstract: A novel, tetra-acetylenic, macrotricyclic molecular receptor is shown by X-ray crystallography to have a channel-like structure and by NMR techniques to selectively accommodate both metallic and organic cations within its compartment.

In his Nobel prize address, Lehn noted that "cylindrical macrotricycles...represent the basic unit of a cation channel based on stacks of linked macrocycles."¹ Cation-conducting channels are of interest because of their biological importance and simply from the mechanistic point of view. We report here the synthesis and X-ray crystal structure of a molecular channel subunit based on the diaza-18-crown-6 system and demonstrate its ability to interact with encapsulated cations by direct NMR observation. We suggest the name "cistulyne," from the Latin *cistula* meaning "little box," for these molecular boxes or receptors having alkynyl linkages. The saturated analog would be a cistulane and complexes would be cistulates.

N,N'-bis(Propargyl)-4,13-diaza-18-crown-6 can be prepared either by treatment of propargylamine with $\text{ICH}_2(\text{CH}_2\text{OCH}_2)_2\text{CH}_2\text{I}$ and Na_2CO_3 in acetonitrile² or by alkylation of 4,13-diaza-18-crown-6 using propargyl bromide.³ We have prepared this compound by both methods and recently reported the crystal structure of its hydrate.⁴ The latter is especially interesting since the macrocycles are stacked and linked by four water molecules in such a way that a channel exists in the crystal. *N,N'*-bis(Propargyl)-4,13-diaza-18-crown-6, **1**, was heated with cuprous chloride and TMEDA in the presence of oxygen and isopropyl alcohol, an approach used by a number of previous workers.⁵ Crude product, having melting point 114-118 °C, was isolated in 80-100% yield depending on conditions. Although this material had a 60 MHz NMR spectrum consistent with the assigned structure, it proved to be a mixture of several, related compounds, including trimeric and tetrameric materials. Chromatography over both alumina and sephadex permitted the separation of at least three distinct fractions.⁶ The dimer product, **2**, was obtained in 12% yield after extensive purification as a white solid having mp 132-133 °C, and a molecular weight of 660 daltons (three trials, theory = 672) determined by vapor pressure osmometry.⁷

The NMR spectra (in CDCl_3 , PPM δ) were determined at 400 MHz (^1H) or 100 MHz (^{13}C) and the positions in the structure are assigned as shown in the figure. Dimer, ^1H : 2.90 (1,t, 16H, $J=5.60$ Hz) 3.56 (2,s,8H), 3.65 (3,s,16H), 3.68 (4,t,16H, $J=5.60$ Hz). ^{13}C -NMR (100 MHz, proton decoupled): 44.91 (2,4C), 53.22 (1,8C), 69.64 (6,4C), 70.07 (4,8C), 70.57 (3,8C), 73.90 (5,4C).

The dimer structure for **2** was confirmed by single-crystal X-ray analysis.⁸ Two views of this compound are shown in Figure 1. A side view is shown at the left and the unit cell is illustrated on the right. The top and bottom macrorings are perfectly aligned and the molecule constitutes a molecular channel subunit.

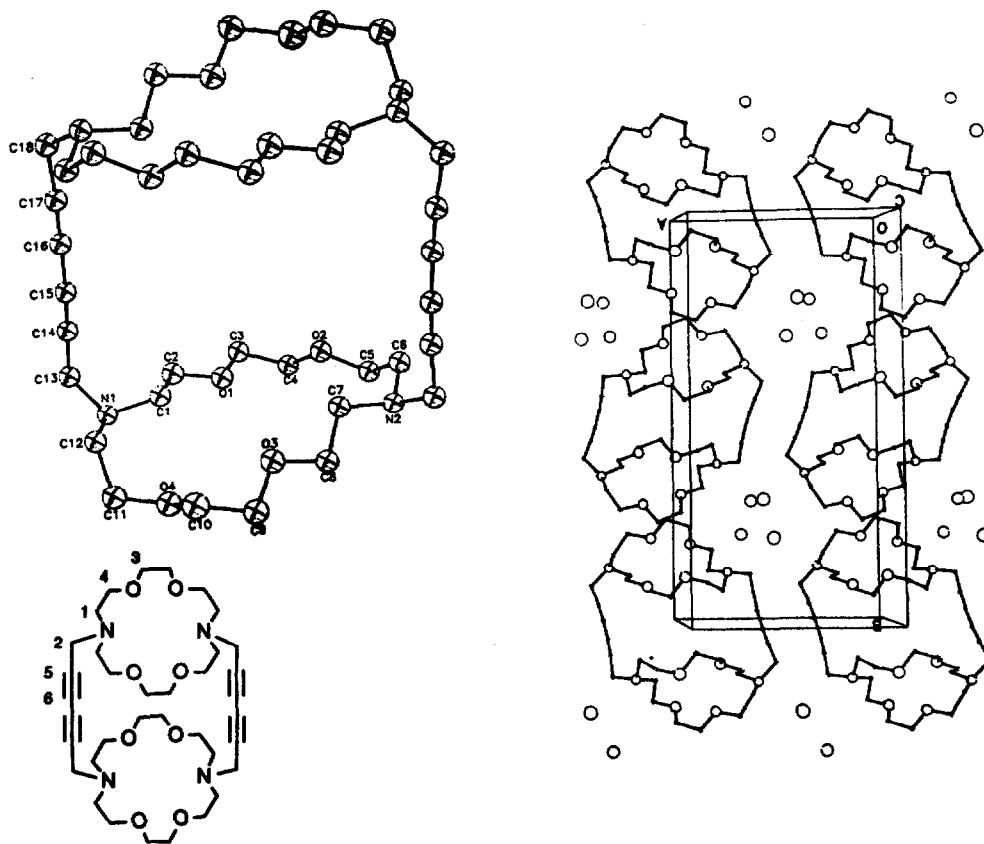


Figure 1. Structure of **2** and ORTEP plots of the molecule and its unit cell.

After early, repeated attempts to obtain crystals suitable for X-ray analysis failed, an alternate approach to the synthesis of **2** was developed in which **1** was added to a vigorously stirred solution of TMEDA, CuCl, and O₂ in THF. This procedure afforded only 6% of **2** but nearly 23% of a material believed to be trimer. Further, heating of *N,N'*-4,13-diaza-18-crown-6 for 16h in MeCN with Na₂CO₃ and Ts-O-CH₂-C≡C-C≡C-CH₂-O-Ts⁹ afforded, after chromatography (alumina, 2-propanol/hexane), a 15% yield of dimer, **2**, and a trace of the presumed trimer or higher oligomer.

The interaction of **2** (mp 132-133 °C) with Na⁺ cation was studied using ²³Na NMR at 105.8 MHz. In tetrahydrofuran solution, NaBF₄ has a linewidth of 38 Hz. Addition of *N,N'*-bis(Propargyl)-4,13-diaza-18-crown-6 in a 1:1 molar ratio leads to an observed ²³Na linewidth of 119 Hz. When the Na:Ligand ratio is altered either to 1:2 or 2:1, the linewidth likewise alters to 115 Hz or 283 Hz,

respectively. When an equimolar ratio of molecular box **2** is added to the solution, however, the ^{23}Na linewidth becomes 572 Hz. This remarkable linewidth reflects both rigidity in the molecular box and solvent exclusion.

It was of obvious interest to see if this molecular box was capable of including simple organic substrates. Of course, Lehn,¹ Sutherland,¹⁰ and others have demonstrated this phenomenon using bicyclic cryptands with ammonium salts. Although **2** was freely soluble in 0.1M DCl in D_2O solution, no adamantane could be extracted either as a solid (sonicated for 3h) or from a cyclohexane solution of this hydrocarbon. Similarly, no evidence for complexation was observed for the dihydrochloride salt of 1,3-diaminopropane. In contrast, solid *p*-phenylenediammonium dihydrochloride (**3**) was extracted stoichiometrically (as judged by NMR integration) by **2** into either $\text{DMSO}-d_6$ or CDCl_3 .

Table 1. ^1H -NMR chemical shifts (in Hz at 400 MHz) for complexes of **2** in CDCl_3 and $\text{DMSO}-d_6$

Compound/Solvent	Proton Position, Host				Guest	
	1	2	3	4	Arom.	NH_3^+
2 in CDCl_3	1160.9	1423.6	1458.7	1469.9	----	----
2 in DMSO	1079.7	1435.9	1398.5	1404.1	----	----
2 + 3 in CDCl_3	1179.8	1457.7	1457.7	1480.9	2638.0	819.2
2 + 3 in DMSO	1151.4	1346.9	1410.6	1435.3	2719.5	1528.0
3 in DMSO	----	----	----	----	2829.1	1383.6

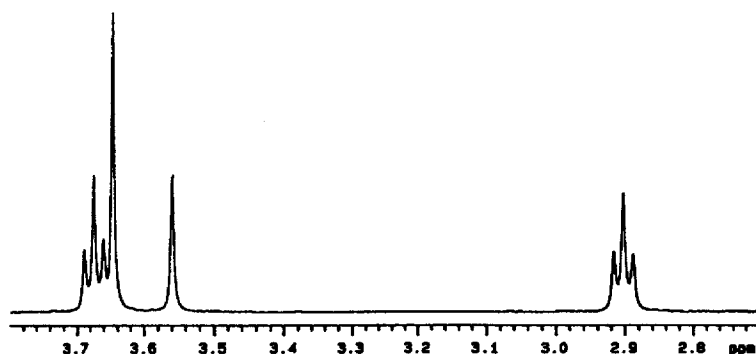


Figure 2. 400 MHz ^1H NMR Spectrum of Cistulyne **2** in CDCl_3

The chemical shift data shown in Table 1 were confirmed by the appropriate decoupling experiments and are recorded in Hz at 400 MHz. Shifts for **3** are not reported for CDCl_3 because the salt is insoluble in this solvent. The data for $\text{DMSO}-d_6$ are complete, however. Upon formation of the 1:1 complex in DMSO solution, pronounced upfield shifts are observed for the hydrogens in position 2 of the host and for the aromatic protons of the guest. The respective shifts for positions 1-4 of host **2** were 72, -89 (upfield), 12, and 31 Hz. The aromatic protons of guest **3** shifted by -109.6 Hz. Host shifts upon complexation were much less dramatic in CDCl_3 . The corresponding shifts for positions 1-4 of **2** were 18.9, 34.0, -1.1, and 11.0 Hz.

To the best of our knowledge, this is the first example of two macrocyclic polyether rings held in rigid opposition by acetylenic linkages. The crystal structure suggests a compartment suitable for complexation of a rigid diammonium salt and the solution NMR clearly confirm such an interaction.

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Notes and References

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6. Among the compounds thus far isolated are materials believed to be trimer and tetramer. In the latter case, we are uncertain if the tetrameric material is actually cyclized and will discuss the overall reaction in detail in the full report of this effort.
7. Compound **2**, white needles, mp 132-133 °C, $C_{36}H_{56}O_8N_4$ requires C, 64.26%; H, 8.39%. Found: C, 64.32%; H, 8.40%. *Crystal structure data for the tetrahydrate: $C_{36}H_{64}O_{12}N_4$* FW 744.93, space group $P2_1/C$, $a = 11.956(2)$, $b = 23.364(2)$, $c = 7.6815(7) \text{ \AA}$, $b = 104.47(1)^\circ$, $d_c = 1.19 \text{ g-cm}^{-3}$, Cu $K\alpha$ radiation, ($\mu = 7.43 \text{ cm}^{-1}$) $R = 0.058$ for 1833 unique reflections with $I > 3\sigma(I)$ measured on an Enraf-Nonius CAD-4 X-ray spectrometer using ω - 2θ scans, $2^\circ < \theta < 58^\circ$.
8. Vapor pressure osmometry was performed using a Wescor Model 5100C device; the solvent was 1,2-dichloroethane and a calibration curve was obtained for 18-crown-6.
9. Oxidative dimerization of propargyl alcohol was accomplished using CuCl in 2-propanol. Care was required during purification since intense heating during distillation of one sample caused explosive decomposition.
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