

A Cyclic Tetramer that Exists Solely in the 1,3-Alternate Conformation in Water

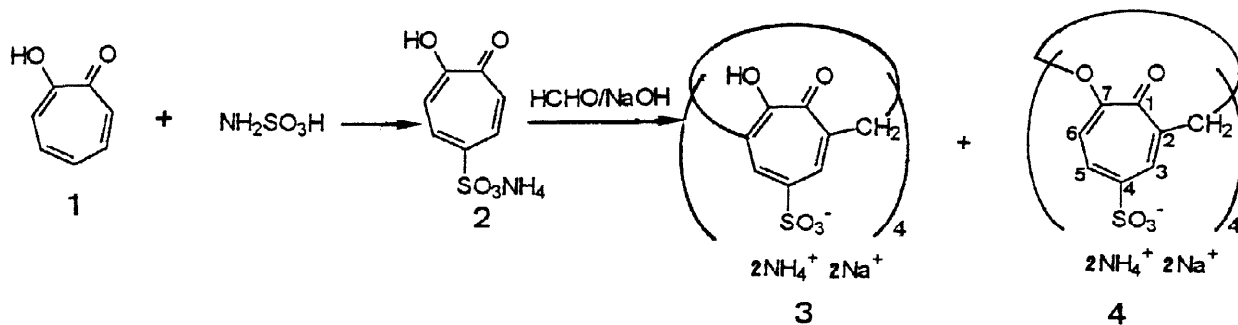
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Received 21 December 1998; revised 11 February 1999; accepted 25 February 1999

Abstract: A yellow water-soluble cyclic tetramer **4** has been isolated as a minor product (5%) from the reaction between 5-sulfonatotropolone and formaldehyde. It exists solely in the 1,3-alternate conformation in D₂O at 25 °C. © 1999 Elsevier Science Ltd. All rights reserved.

Water-soluble synthetic macrocycles containing a hydrophobic cavity are of great interest¹⁻⁵. Their hydrophobic cavities are a good model for the hydrophobic pockets of enzymes. Their solubility in water also enables them to be studied in the biological medium. Recently we reported the water-soluble cyclic tetramer **3** as the major product of the reaction between 5-sulfonatotropolone **2** and formaldehyde under alkaline conditions⁶. This paper reports the isolation of another water-soluble cyclic tetramer **4** as a minor product of the same reaction.



RESULTS AND DISCUSSION

The reaction between 5-sulfonatotropolone **2** and formaldehyde under alkaline conditions produced two macrocycles, namely the light brown solid tetramer **3** in 48% yield (reported earlier⁶) and a yellow solid tetramer **4** in 5% yield. The latter product was overlooked in our earlier work⁶.

The identity of **4** was supported by its mass spectrum, proton and carbon-13 nmr spectra. The relatively broad peak in the *m/z* 933 to 937 region in the negative MALDI-TOF mass spectrum of **4** in dihydroxybenzoic acid as matrix (Figure 1) supports its tetrameric structure of molecular mass 934. The *m/z* peaks at 680 and 466 indicate the breakdown of the tetramer to trimer and dimer respectively.

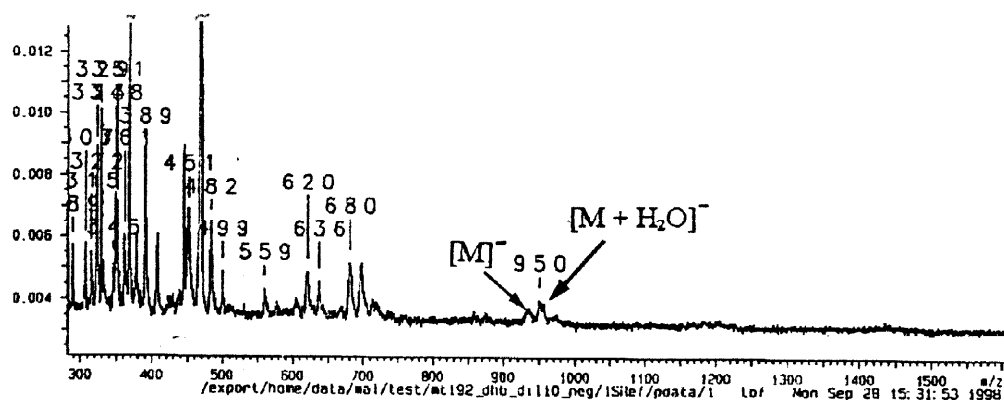


Figure 1. Negative MALDI-TOF mass spectrum of **4** (dihydroxybenzoic acid as matrix).

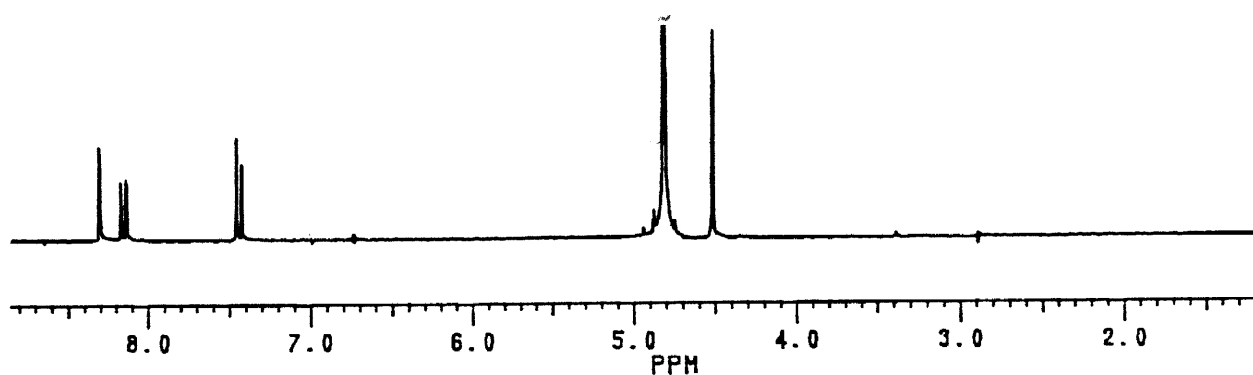


Figure 2. 300 MHz proton nmr spectrum of **4** in D₂O at 25 °C (solvent peak at 4.80 ppm as internal reference).

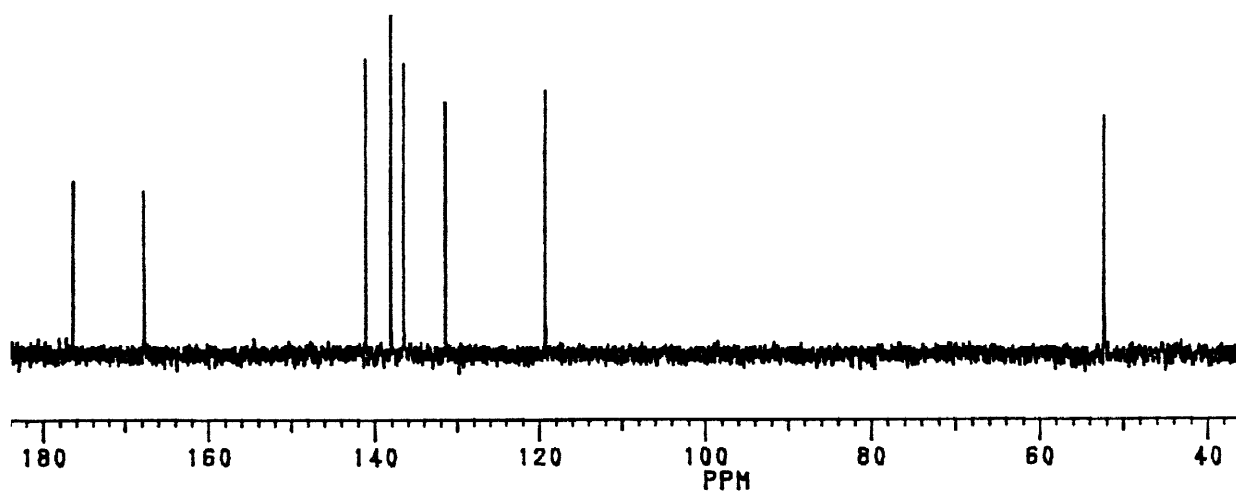


Figure 3. 75 MHz carbon-13 nmr spectrum of **4** in D₂O at 25 °C (TMS as external reference).

The proton nmr spectrum in D₂O at 25 °C (Figure 2, the spectrum remains unchanged at 5 °C) shows the presence of methylene (δ 4.50 s; solvent peak at 4.80 ppm as internal reference) and aromatic protons (δ 7.42, d, J = 10.8 Hz, H₆; 8.13, ddd, J = 11.1, 1.8 and 1.8 Hz, H₅; 8.29, d, J = 1.5 Hz, H₃) in the ratio of 2:3, consistent with 4. The number of carbon peaks (one aliphatic at 52.1 ppm, and seven aromatic at 119.2, 131.4, 136.5, 138.1, 141.1, 167.7 and 176.4 ppm, the last two due to C₇ and C₁) in the carbon-13 nmr spectrum (Figure 3) is also in agreement with 4.

Macrocycle 4 is analogous to calix[4]arenes and has four possible conformations namely cone, partial cone, 1,2-alternate and 1,3-alternate as shown schematically in Figure 4. Each conformer has a distinct peak pattern in its methylene proton nmr spectrum (two doublets for cone, four doublets or two doublets and a singlet for partial cone, one singlet and two doublets for 1,2-alternate and a singlet for 1,3-alternate)⁷. The proton nmr spectrum of 4 in Figure 2 shows that it exists solely in the 1,3-alternate conformation since only a singlet is observed for the methylene protons at δ 4.50 ppm. The analogous water-soluble calix[4]arenes 5 and 6 (without OH groups for intramolecular hydrogen-bonding interactions and carrying charged substituents) were also reported by Shinkai and coworkers⁸, based on their proton nmr studies, to exist predominantly in the 1,3-alternate conformation in D₂O (55% and 83% respectively at 5 °C). The stability of the 1,3-alternate conformation is attributed to the result of a balance of hydrophobic interactions and electrostatic repulsions⁹. The macrocycle 4 is the first example, as far as we are aware, of a cyclic tetramer that exists solely in the 1,3-alternate conformation in water. This conformation, as indicated by its proton nmr spectra, was still maintained even when the polarity of the solvent was reduced by addition of CD₃OD to D₂O until 87.5 % CD₃OD (higher % of CD₃OD not used because of solubility problem). In DMSO-*d*₆ 4 also was found solely in the 1,3-alternate conformation.

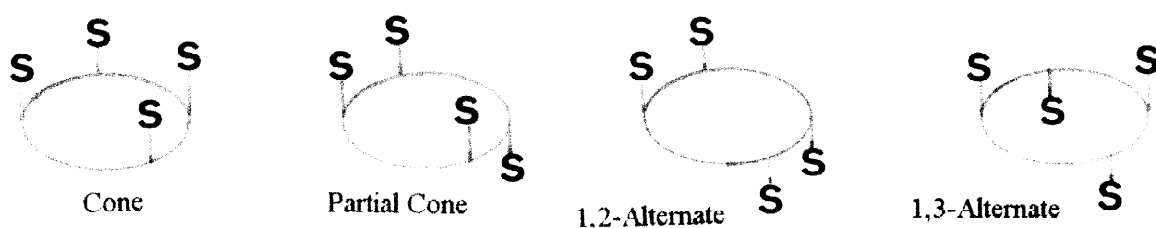
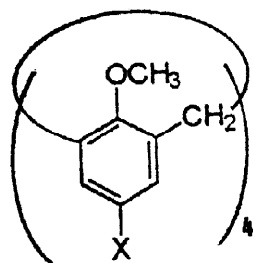


Figure 4. Four possible conformations of cyclic tetramer 4 (S refers to the SO₃⁻ end of the tropolone ring).



5 X = SO₃Na

6 X = CH₂N⁺(CH₃)₃Cl

EXPERIMENTAL

Materials

Tropolone (**1**) was purchased commercially. It was purified by vacuum sublimation.

Macrocycle **4**

To **2** (1.46 g, 6.66 mmol, prepared according to the method of Nozoe and coworkers¹⁰) in a solution made up of 14 mL of distilled water and 20 mL of 0.5 M NaOH was added 1 mL of 3.7% stock formaldehyde solution and the mixture was refluxed for an hour. Then a further 1 mL of the 3.7% stock formaldehyde was added and the mixture continued to be refluxed. This was repeated every hour until a total of 5 mL of the stock formaldehyde solution (6.72 mmole) was added. After the addition of the last portion of formaldehyde, the reaction mixture was refluxed for another hour (total reflux time six hours). The reaction mixture was then evaporated to dryness, followed by recrystallization from water/methanol to remove the major light brown solid **3**. The mother liquor was concentrated to remove any residue **3** (48% yield of **3**)⁶. The volume of the mother liquor was further reduced and it was left to stand overnight to precipitate the yellow solid **4** in 5% yield (70 mg), mp > 230 °C (d).

Anal. Found: C 37.20; H 3.39; N 2.69; Na 4.20; Calc. for (C₃₂H₂₈N₂Na₂O₂₀S₄)·5H₂O: C 37.48; H 3.71; N 2.73; Na 4.49). ¹H nmr (D₂O, 25 °C, solvent peak at 4.80 ppm as internal reference) δ 4.50 (8H, s, CH₂), 7.42 (4H, d, *J* 10.8 Hz, H₆), 8.13 (4H, ddd, *J* 11.1, 1.8, 1.8 Hz, H₅), 8.29 (4H, d, *J* 1.5 Hz, H₃). ¹³C nmr (D₂O, 25 °C, TMS as external reference) δ 52.1, 119.2, 131.4, 136.5, 138.1, 141.1, 167.7 and 176.4.

75 MHz ¹³C and 300 MHz ¹H nmr spectra were recorded with a Bruker AC300 Superconducting nmr spectrometer.

ACKNOWLEDGEMENT

Financial support in the form of a R & D grant from the Malaysian government is gratefully acknowledged. We also thank Dr G.K. Eigendorf of the University of British Columbia in Canada for recording the mass spectrum.

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