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Synthesis and Conformations of a Water-soluble Cyclic Tetramer Obtained from Reacting 5-Sulfonatotropolone with Formaldehyde

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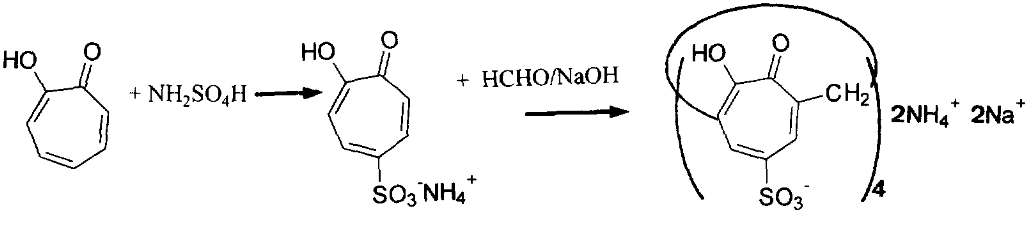
Abstract: A water-soluble cyclic tetramer **3** has been synthesized from reacting 5-sulfonatotropolone with formaldehyde. In D_2O at 25^0C it existed in three major conformations (cone, 1,2-alternate and 1,3-alternate) with a trace amount of partial cone conformation. The latter increased with temperature. All the four conformers were observed in DMSO-d_6 at 25^0C. © 1997 Elsevier Science Ltd.

Water-soluble synthetic macrocycles containing a hydrophobic cavity are of great interest. 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. Not many such macrocycles have been synthesized. Most of them have benzene units as the hydrophobic cavity walls[1,2]. We have synthesized two of them with naphthalene units forming the hydrophobic cavity walls[3,4]. This paper reports the synthesis and conformations of a new water-soluble macrocycle whose hydrophobic cavity walls are formed from four tropolone units.

RESULTS AND DISCUSSION

The commercially available tropolone **1** was converted to ammonium 5-sulfonatotropolone **2** in 74% yield according to the method reported by Nozoe and coworkers[5]. The cyclic tetramer **3** was then synthesized in 48% yield by refluxing an aqueous solution of **2** with formaldehyde. The synthetic scheme is as follows:



1 **2** **3**

The identity of **3** was supported by its mass spectrum, proton nmr spectrum and elemental analysis. The MALDI mass spectrum of the acidic form of **3** (Na^+ replaced by H^+ from Dowex 50W-X8 hydrogen ion exchange resin; the N analysis indicated that the NH_4^+ ions were not exchanged, see **Experimental**) in α-cyano-4-hydroxycinnamic acid as matrix shows the [M+H] ion peak at m/z 891 (Figure 1). Its proton nmr spectrum in D_2O shows equal number of methylene (δ around 4 ppm) and aromatic protons (around 8 ppm).

Macrocycle **3** is analogous to calix[4]arenes and has four possible conformations, cone, partial cone, 1,2-alternate and 1,3-alternate, as shown in Figure 2. Nmr spectroscopy is most useful in conformation analysis of calix[4]arenes because each conformer has a distinct ^1H and ^{13}C nmr spectral pattern. We apply these expected nmr spectral patterns[7] for calix[4]arenes to macrocycle **3** (Table 1).

Table 1. ^1H and ^{13}C nmr spectral patterns for the conformers of **3**

Conformation	**^1H nmr[a]**		**^{13}C nmr**		
	Aromatic H	**CH_2**	**C=O**	**Aromatic C**	**CH_2**
Cone	1s	1 pair d	1 peak	3 peaks	1 peak
Partial cone	2s + 2d or 4s (ratio 1:1:1:1)	2 pairs d (ratio 1:1) or 1 pair d + 1s (ratio 1:1)	3 peaks	9 peaks	2 peaks
1,2-Alternate	2s (ratio 1:1)	1s + 2d (ratio 1:1)	1 peak	3 peaks	2 peaks
1,3-Alternate	1s	1s	1 peak	3 peaks	1 peak

[a] s = singlet; d = doublet

The ^1H nmr spectra of **3** in D_2O at various temperatures are broad (Figure 3), indicating the presence of a mixture of conformers. Its ^{13}C nmr spectra are also broad (Figure 4, compared with that of the monomer **2**) but more informative. The number of peaks in the ^{13}C nmr spectrum at 25^{0}C is in agreement with the presence of a mixture of three conformers, namely cone, 1,2-alternate and 1,3-alternate (compare with the expected number of peaks given in Table 1). It has three carbonyl carbons (167, 172, 175 ppm), nine aromatic ring carbons (120, 125, 130, 133, 135, 137, 139, 141, 142 ppm) and four methylene carbons (44, 49, 56 ppm; the last one is an overlap of two peaks[8]). The three carbonyl carbon peaks indicate roughly equal populations of the three conformers. Only a trace of the fourth conformer, partial cone, was detected in the ^1H nmr spectrum (Figure 3, the small broad peak around 7.2 ppm). At 85^{0}C, this peak became more prominent.

In DMSO-d_6 all four conformers are present. The ^1H nmr spectrum at 92^{0}C (Figure 5) shows the predicted number of peaks in the aromatic proton region. The ^{13}C nmr spectrum at 25^{0}C (Figure 6) also shows the six predicted carbonyl carbon peaks.

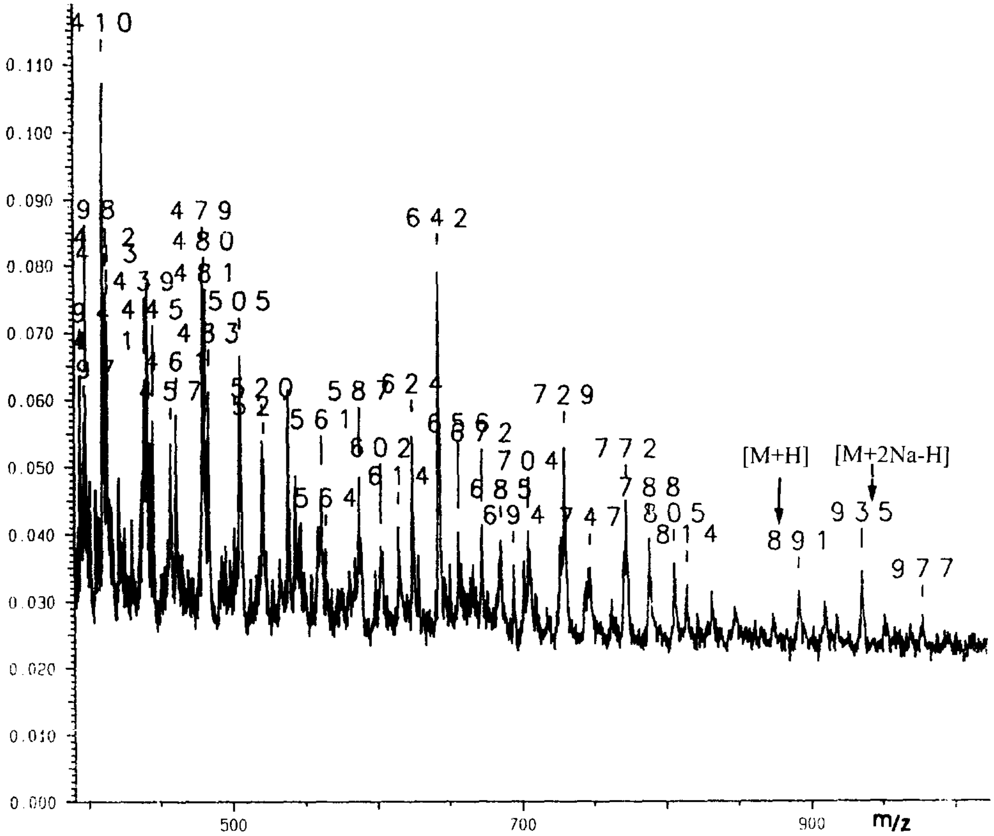
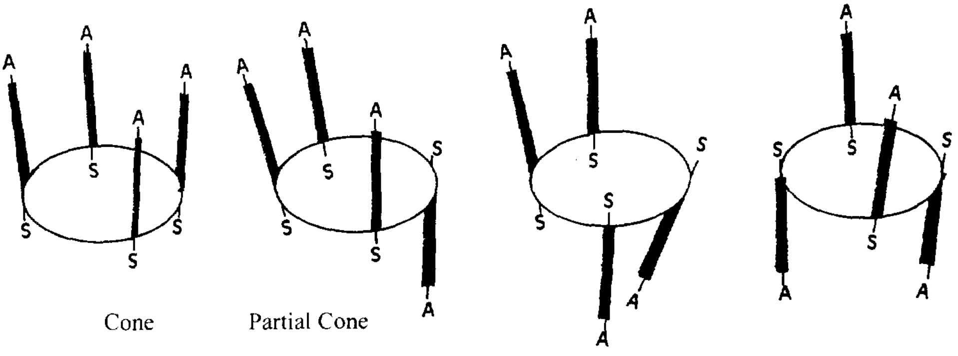


Figure 1. MALDI mass spectrum of the acidic form of **3** (α-cyano-4-hydroxycinnamic acid as matrix, only m/z above 400 shown).



Cone Partial Cone 1,2-Alternate 1,3-Alternate

Figure 2. Four possible conformations of cyclic tetramer **3** (**A** consists of the OH and C=O groups and **S** the SO_3^- group).

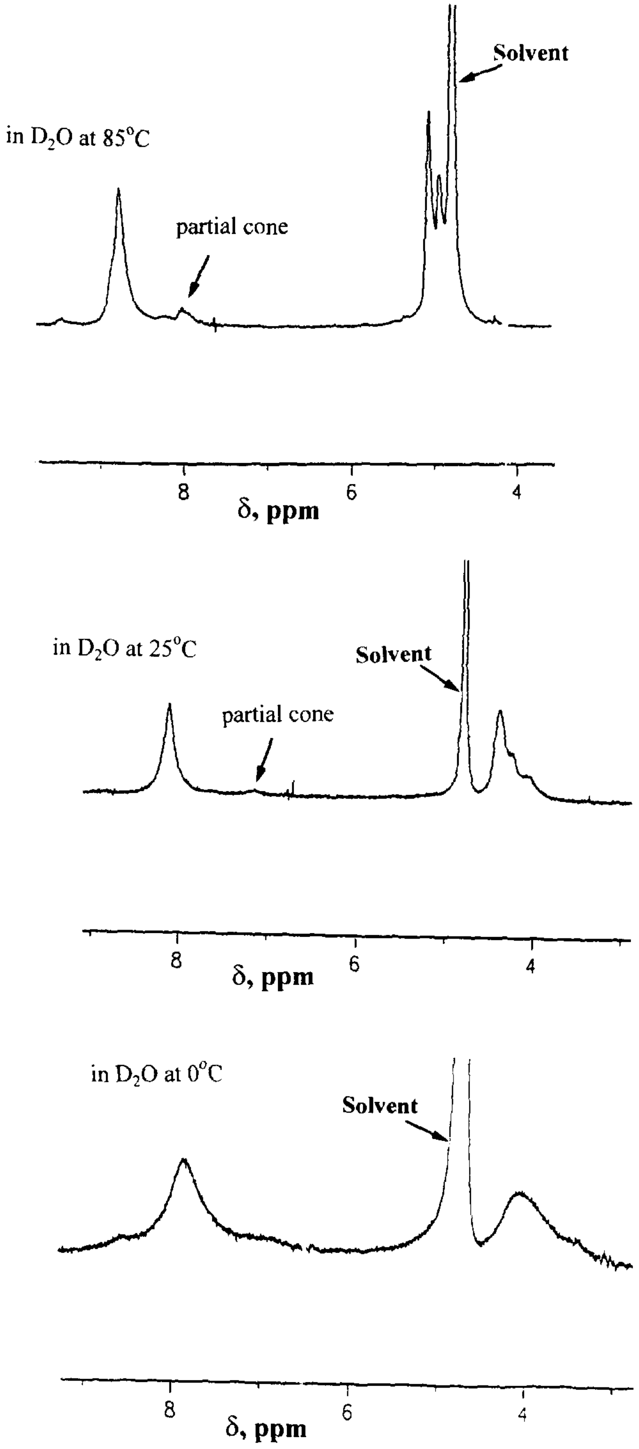


Figure 3. 300 MHz proton nmr spectra of cyclic tetramer **3** in D_2O at various temperatures (solvent peak at 4.80 ppm as internal reference).

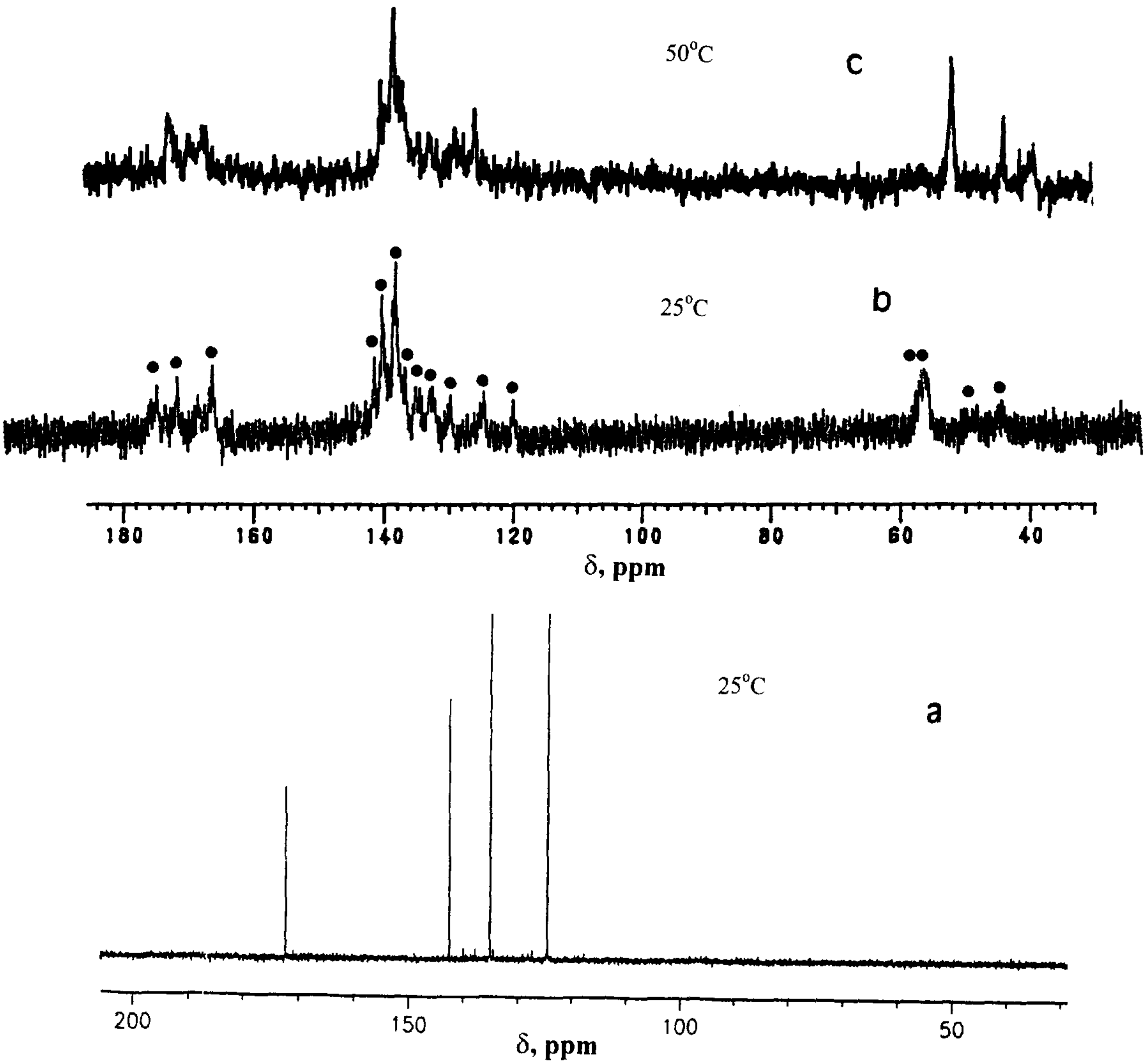


Figure 4. ^{13}C nmr spectra in D_2O of (a) 5-sulfonatotropolone **2**; (b) and (c) cyclic tetramer **3**.

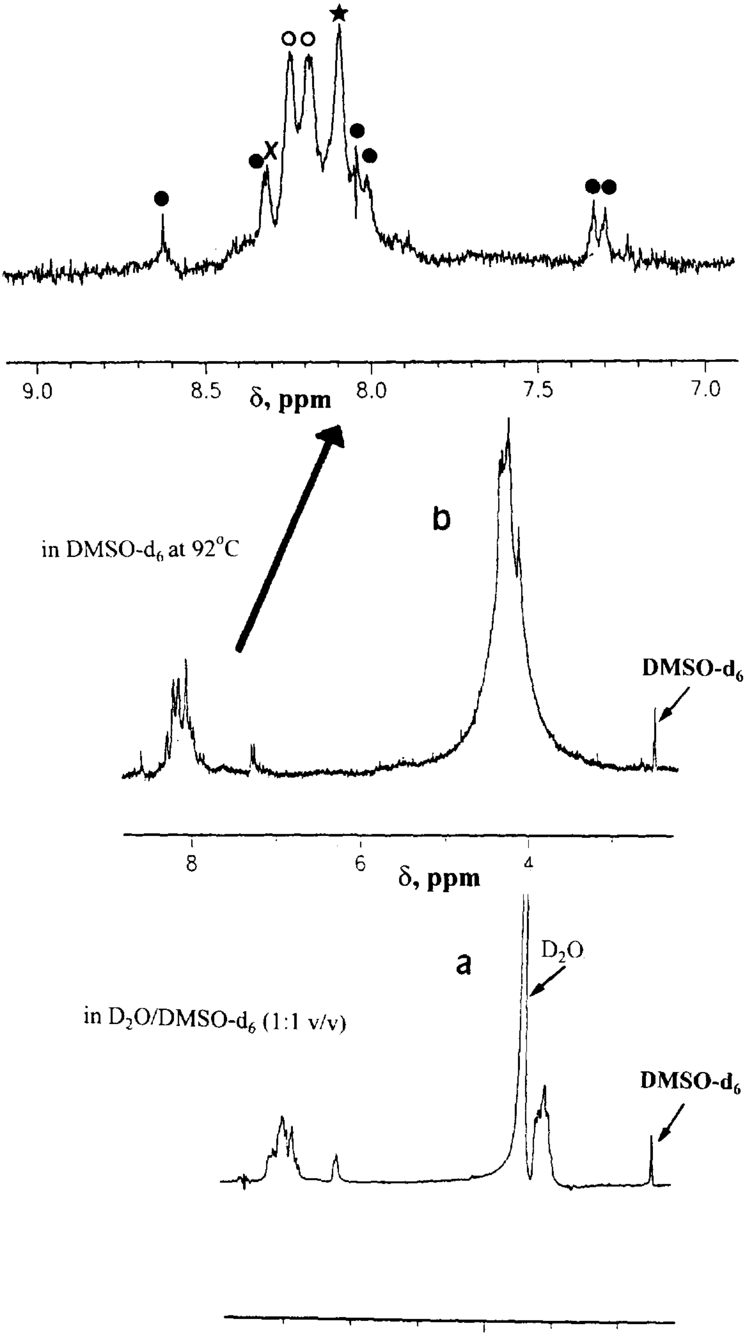


Figure 5. 300 MHz proton nmr spectra of cyclic tetramer **3**: (a) in D_2O/DMSO-d_6 (1:1, v/v) at 25°C and (b) in DMSO-d_6 at 92 °C (solvent peak at 2.50 ppm as internal reference); ★ cone, ● partial cone, o 1,2-alternate, × 1,3-alternate.

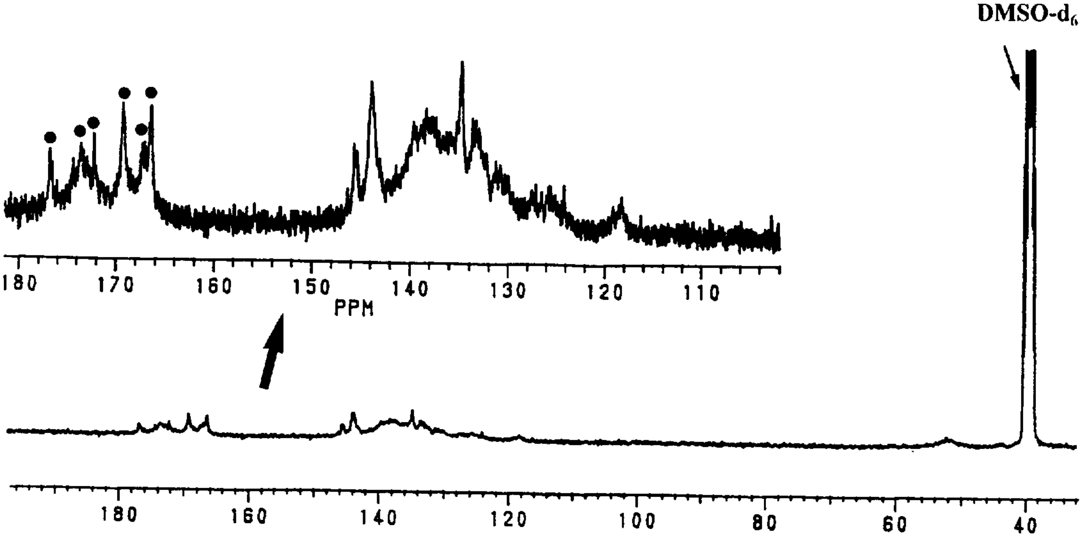
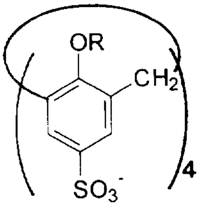


Figure 6. ^{13}C nmr spectra of cyclic tetramer **3** in DMSO-d$_6$ at 25°C.

In contrast, the analogous 4-sulfonatocalix[4]arene (**4**) and its methylated derivative (**5**) do not adopt all the four conformations in the aqueous medium. The former adopts only the cone conformation[9] while the latter exists in the partial cone and 1,3-alternate conformations[10].



4 R = H
5 R = Me

EXPERIMENTAL

Materials.

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

Ammonium 5-sulfonatotropolone (**2**) was synthesized according to the method of Nozoe and coworkers[6]. The compound, light brown colour, was obtained in 74% yield. R_f value 0.73 (tlc on silica gel with n-BuOH/EtOH/H2O in 1:1:1 v/v ratio as eluant); ^{1}H nmr in D_2O (solvent peak at 4.80 ppm as internal reference) δ 7.32(d, 2H) and 7.99(d, 2H); ^{13}C nmr in D_2O δ 124.5, 135.1, 142.5 and 172.4 ppm.

Compound **3** was synthesized as follows. 1.46 g (6.66 mmol) of **2** was dissolved in a solution made up of 14 mL of distilled water and 20 mL of 0.5 M NaOH. To it 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 solution was added and the mixture continued to be refluxed. This was repeated every hour until a total of 5 mL of the 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 to give light brown solid in 48% yield. Compound **3** was isolated as the diammonium disodium salt; mp > 350^0C.

Anal. Found: C 35.87; H 3.97; N 2.74; Na 4.37. Cald. for $(C_{32}H_{28}N_2Na_2O_{20}S_4).8H_2O$: C 35.62; H 4.11; N 2.60; Na 4.26. For **3** after treatment with Dowex 50W-X8 hydrogen ion exchange resin: Found: C 35.82; H 4.25; N 2.74. Cald. for $(C_{32}H_{30}N_2O_{20}S_4).10H_2O$: C 35.89; H 4.67; N 2.61. ^{1}H nmr (D_2O, 25^0C, solvent peak at 4.80 ppm as internal reference) δ 4.36 (CH_2, b), 8.12 (aromatic H, b). ^{13}C nmr (D_2O, 25^0C) δ 44, 49, 56 (CH_2), 120, 125, 130, 133, 135, 137, 139, 141, 142 (aromatic C), 167, 172, 175 (carbonyl C). The MALDI mass spectrum in α-cyano-4-hydroxycinnamic acid matrix of **3** (after treatment with Dowex 50W-X8 hydrogen ion exchange resin) showed the [M+H] ion peak at m/z 891. The peaks at 642, 410 and 212 respectively are probably from the breakdown to the trimer, dimer and monomer.

75 MHz ^{13}C and 300 MHz ^{1}H nmr spectra were recorded with a Bruker AC300 Superconducting nmr spectrometer. The ^{13}C nmr spectra were recorded after sixteen hours of scanning.

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