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# Large Cyclic Oligomers of Furan and Acetone. X-Ray Crystal Structure of the Hexamer and First Synthesis of the Nonamer.

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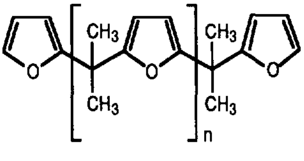
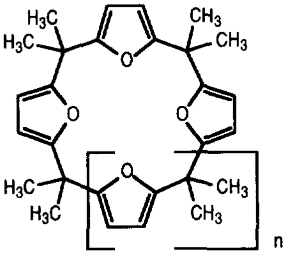
***Abstract:*** *The synthesis of several cyclic oligomers of furan and acetone containing four or more furan units has been re-examined. The structure of the [1.$_6$](2,5)furanophane C6 has been investigated by X-ray crystallography. The first and efficient synthesis of the [1.$_9$](2,5)furanophane C9 is also described.* Copyright © 1996 Elsevier Science Ltd

The synthesis of furan macrocycles by the acid promoted condensation with carbonyl compounds has been known for many years, and [1.$_n$](2,5)furanophanes containing four to eight furan units have been described.[1-5] The octamethyl tetraoxaquaterene **C4** is the most well-known and accessible member of the series.[1-3] As part of our research on furanophanes as naphthalenophane precursors,[6] we undertook the synthesis of **C4** and the larger homologues following the literature procedures.[1-3] However, we realised that data in the literature are rarely comparable because different conditions were used for the synthesis of the same compound. Thus, we decided to investigate possible improvements of these preparations.

The effects of reaction conditions in the condensation of furan with various carbonyl compounds were studied by Rest,[2] but his work focused on the yield of cyclic tetramers although a synthesis of **C6** and **C8** was also described.



**Ln+2**



**Cn+3**

The preparation of **C4** proposed by Chastrette[3b] involves treatment of furan and acetone in EtOH/HCl in the presence of $LiClO_4$ dimethoxyethane (DME) complex. Although the use of lithium salts has been recognised to improve the yield of **C4** we could not find any explanation or additional literature reference accounting for the use of the $LiClO_4 \cdot (DME)_2$ complex. When we compared crude mixtures from preparations in which the $LiClO_4$ was used either as such or as its DME complex we found that the yields were very similar, although in the latter case the mixture contained less resinous materials and the work-up and isolation of **C4** was marginally easier. This does not - in our opinion - compensate for the relatively high cost and hazard[7] of preparing the $LiClO_4{\cdot}(DME)_2$ complex.

An analysis of different crude mixtures obtained varying the ratio of furan to acetone confirmed the observation made by Ackman,[1] that an excess of acetone favours the formation of **C4** over **L2** and **L3**, but it also revealed that **C4** is always the major cyclic component with respect to the larger macrocycles **C5** and **C6**. The ratios **C4**:**C5**:**C6** could be determined by integration of the distinctive resonances of their aromatic protons at $\delta$ 5.88, 5.75, and 5.74 ppm respectively in the $^1$H NMR spectra of the crude mixtures. Under conditions similar to those described by Chastrette,[3b] but without $LiClO_4{\cdot}(DME)_2$ and with a furan to acetone ratio 1:6, the ratio **C4**:**C5**:**C6** was *ca.* 12.5:1:1.2. When we reacted equimolecular mixtures of **L2** and **L3** (under the above-described conditions) with and without the $LiClO_4{\cdot}(DME)_2$ complex, the ratios of **C4**:**C5**:**C6** were 2.8:1:1.8 and 4.2:1:1.4 respectively. The lithium complex is known to accelerate the reaction rate, and the proportions of **C4**, **C5**, and **C6** tend to level out when it is present.[8] This observation provides additional support for the already recognised absence of any template effect of the metal.[2] These results also indicate that the efficient synthesis of the larger cyclic oligomers directly from furan and acetone is hampered by the fact that **C4** constitutes a sink for the growing oligomeric chain. The macrocycle **C5** is always the least favoured product and we did not investigate the optimization of its synthesis any further. In order to obtain good yields of **C6**, the formation of **C4** must be made impossible. This can be easily achieved by using either **L3** or **L6** as the starting materials. The oligomer **L3** can be prepared in a pure form and on a large scale much more easily than **L6**.[9] Ackman[1] used **L3** and the yield of **C6** was 8.8%. Kobuke[3a] cyclised **L6** to **C6** in 52% yield, however **L6** was obtained from **L3**, thus the overall yield of **C6** based on **L3** was 19%. Rest[2] cyclised **L6** to **C6** with a similar yield (50%) to Kobuke.[10] These three preparations differ substantially in terms of concentration, proportion of reactants, presence of $LiClO_4$ (used only by Rest), and solvent.

In this study we subjected **L3** to oligomerization/cyclization in one step. The reaction of **L3** at a concentration 0.4 M in a mixture of EtOH:$HCl_{conc.}$ (85:15, v:v) with 6 moles of acetone and 1.2 moles of $LiClO_4{\cdot}(DME)_2$ complex gave **C6**[11] (15%) and **L9**[12] (36%) along with minor quantities of the higher linear oligomers **L12**, **L15** and **L18**, which were identified in the EIMS of the mixture. Identical yields of **C6** and **L9** were obtained - within experimental error - without the lithium complex. When a vast excess of acetone (50 moles) was present we obtained a complex resinous mixture, while a moderate excess (2 moles) produced a lower yield of **C6**. However, the yield of **C6** was considerably dependent upon the concentration. When the reaction mixture was diluted 10 times, or the reactants were slowly added to the EtOH/HCl mixture over 8h, the yield of **C6** was 25-28%. In all cases only trace quantities of **C9** could be detected in the EIMS of the crude mixtures.

Single crystals of **C6** were obtained from ethyl acetate/methanol, thus we could investigate its structure in the solid state. The X-ray analysis[13] shows (Figure) **C6** to have crystallographic $C_2$ symmetry about an axis passing through two of the furan rings [those containing O(1) and O(24)]. The macrocycle is self-filling, four of the furan rings being oriented approximately orthogonally with respect to the mean plane of the macrocycle, whilst the other two lie almost within this plane. These latter two furan rings are twisted by 14° with respect to each other about the crystallographic $C_2$ axis. The structure is polar with respect to this two-fold axis. In common with the closely related cyclic tetramer,[14] there is, within the macrocycle, a coplanar relationship between one or both of the isopropylidene C-Me bonds and their adjacent furan rings.[15] Only one of the furan rings does not have a methyl group coincident with its ring-plane - that lying on the $C_2$ axis with its oxygen atom directed away from the macrocyclic centre. There are no significant intra- or inter-molecular close contacts to any of the six furan oxygen atoms, nor are there any C-H···π interactions.

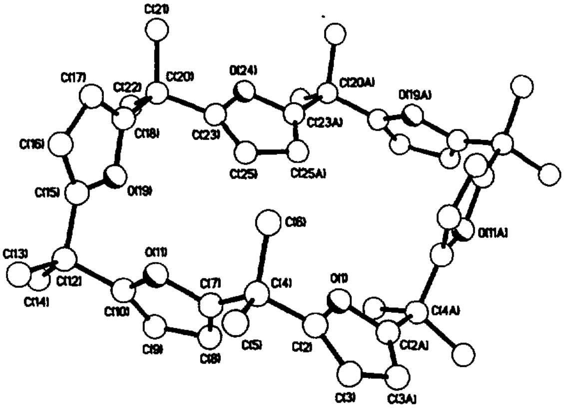


Figure. The X-ray crystal structure of the dodecamethyl[1.$_6$](2,5)furanophane **C6**.

The linear oligomer **L9** is almost insoluble in EtOH/HCl and the absence of any relevant amount of **C9** in the crude mixtures of the various macrocyclization/oligomerization reactions of **L3** could be ascribed either to lack of solubility or to the fact that the macrocyclization leading to **C9** is unfavoured for entropic and/or steric reasons. However, when **L9** was treated with 6 moles of acetone in benzene saturated with anhydrous HCl, where it is soluble, it readily cyclised to give **C9** in 45% isolated yield.[16] When **L3** was subjected to macrocyclization/oligomerization under these reaction conditions, the isolated yields[17] of **C6** and **C9** were 18% and 6.5% respectively.

The [1.$_9$](2,5)furanophane **C9** is the largest cyclic oligomer of furan and acetone synthesised to date. Its preparation, involving three simple steps from acetone and furan is cheap and efficient, thus **C9** can be exploited for further chemical tranformation and for studies in the field of large heterocalixarenes.

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6. Kohnke, F. H.; Parisi, M. F.; Raymo, F. M.; Oneil, P. A.; Williams, D. J. *Tetrahedron* **1994**; *50*, 9113-9124 and references therein.
7. CAUTION! A violent explosion has been reported from contact of cyclooctatetraene with $LiClO_4$ in refluxing ether. See: Silva, R. A. *Chem. Eng. News* **1992**, *70*, 2-2.
8. The oligomerization of furan with acetone is an irreversible reaction, and pure samples of **L3**, **L6**, **C4**, and **C6**, (as well as **L9** and **C9**, *v. infra*) did not show any significan retro-oligomerization under the reaction conditions. Thus, the product distribution should be kinetically controlled. However, a mathematical analysis of the system is made impossible by the fact that a solid material is soon formed from the reaction mixtures. See: a) Mandolini, L. *Adv. Phys. Org. Chem.* **1986**, *22*, 1-111; b) Ercolani, G.; Mencarelli, P. *J. Chem Soc., Perkin Trans. II* **1989**, 187-191; c) Ercolani, G.; Mandolini, L.; Mencarelli, P. *J. Chem Soc., Perkin Trans. II* **1990**, 747-752.
9. **L3** can be distilled, **L6** is purified by column chromatography, see refs. 1 and 3a respectively.
10. In this case the details and the yield for the preparation of **L6** were not reported; see ref. 3a.
11. Column chromatography of the crude mixture on $SiO_2$ (toluene:hexane, 1:4) gave, in order of elution, **C6** and **L9**. Physical and spectroscopic characteristics of **C6** were identical to those reported previously: ref. 3a.
12. **L9**: m. p. 117 °C (from acetone), $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 7.29 (2H, dd, $J$ = 1.8, 0.8 Hz), 6.24 (2H, dd, $J$ = 3.2, 1.8 Hz), 5.93 (2H, dd, $J$ = 3.2, 0.8 Hz), 5.85 and 5.82 (4H, 2 x AB systems, $J$ = 3.2 Hz), 5.78 (10H, s); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 158.7, 158.5, 158.4, 158.2, 140.9, 109.9, 104.2, 104.0, 103.8, 37.5, 37.4, 26.3; EIMS: 932 $M^{+\cdot}$.
13. Crystal data for **C6**: $C_{42}H_{48}O_6$, $M$ = 648.8, orthorhombic, $a$ = 16.679(2), $b$ = 12.136(2), $c$ = 18.926(2) Å, $V$ = 3831 Å$^3$, space group $Aba2$, $Z$ = 4 (the molecule has crystallographic $C_2$ symmetry), $\rho_{calcd}$ = 1.125 g cm$^{-3}$, $\mu(Cu_{K\alpha})$ = 11.3 cm$^{-1}$. 1641 independent measured reflections [$2\theta \leq 128°$] of which 1583 were considered to be observed [$|Fo| > 4\sigma(|Fo|)$]. Data were measured on a Siemens P4/PC diffractometer, $\omega$ scans, $Cu_{K\alpha}$ radiation (graphite monochromator). The structure was solved by direct methods and the non-hydrogen atoms refined anisotropically (based on $F^2$) to give $R_1$ = 0.031, $wR_2$ = 0.086. Computations were carried out using the SHELXTL program system, version 5.03. Further details of the crystal structure investigation can be obtained from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ (UK) on quoting the full journal citation.
14. Hazell, A. *Acta Cryst*, **1989**, *C45*, 137-140.
15. This observation is consistent with the known conformational preference of furan derivatives with substituents at the 2-position. For a brief review on this topic see: Dean, F. M.; Sargent, M. V. in *Comprehensive Heterocyclic Chemistry, Vol. 4*, pp. 542-546; Bird, C. W.; Cheeseman, G. W. H. (Ed.), Pergamon Press, Oxford 1984.
16. The furanophane **C9** was isolated by column chromatography ($SiO_2$; toluene:hexane, 3:7) and recrystallised from acetone: m.p. 94-96 °C, $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 5.76 (18H, s), 1.54 (54H, s); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 158.5, 104.1, 37.5, 26.3; EIMS: 972 $M^{+\cdot}$.
17. The furanophanes **C6** and **C9** were separated from the crude mixture by column chromatography ($SiO_2$; toluene:hexane, 1:3).

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