Syntheses of Tetraoxaquaterene Derivatives

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Several new dimethyl and tetramethyl tetraoxaquaterenes, **3d** and **3e**, have been prepared in order to synthesize the oxygen analogues of porphyrin. The reaction between furan and a ketone using an acidic catalyst gave the cyclic tetramer, tetraquaterene, and oligomers. On the other hand, in the case of furan and an aldehyde, only linear oligomers were isolated. The condensation of furan-containing dimers with carbonyl compounds, both ketone and aldehyde, except formaldehyde, gave the tetraoxaquaterene. In the case of formaldehyde, the yield of cyclic tetramer was negligible.

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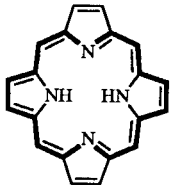
Macrocyclic polyethers containing furan nuclei are attractive compounds for the following two reasons. First, they have the function of crown ethers which complex with special metal cations and certain neutral organic compounds. These macrocycles are characterized by a hydrophilic cavity in their centers in which metal cations and certain neutral organic compounds are selectively bound depending on their ionic diameter. Those compounds containing the furan ring are expected to have a different "Molecular Recognition" function, because the furan oxygen atom has less donating ability than the soft $(CH_2OCH_2)n$ oxygens. Second, the furanomacrocycles are oxygen analogues of porphyrinogen, the mother nucleus of porphyrin, which performs important biochemical reactions such as hemin and chlorophyll. Cram and co-workers [1] and Kobuke and co-workers [2] have already reported about the complexing ability of the furano-crowns. Vogel and co-workers [3,4,5] have recently synthesized tetraoxaporphyrin dication, **2** (R = H), as the oxygen-containing substitute of porphyrin **1**. Porphyrin (**1**) and tetraoxaporphyrin decation (**2**) have a bridged annulene system in which the 18 π-electron system is included.



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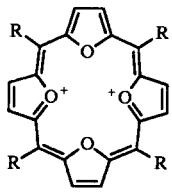

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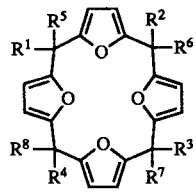


3

a) $R^1 = R^2 = R^3 = R^4 = R^5 = R^6 = R^7 = R^8 = H$
b) $R^1 = R^2 = R^3 = R^4 = R^5 = R^6 = R^7 = R^8 = CH_3$
c) $R^1 = R^2 = R^3 = R^4 = CH_3$, $R^5 = R^6 = R^7 = R^8 = H$
d) $R^1 = R^3 = R^5 = R^6 = R^7 = R^8 = H$, $R^2 = R^4 = CH_3$
e) $R^1 = R^3 = R^5 = R^7 = H$, $R^2 = R^4 = R^6 = R^8 = CH_3$

Vogel and co-workers synthesized dication **2** (R = H) by the dehydrogenation of tetraoxaporphyrinogen, (tetraoxaquaterene TOQA). TOQA **3a** was synthesized by three routes: (1) condensation of 5,5'-methylene-di-2-furaldehyde with 2,2'-difurylmethane [3]; (2) condensation of 2 moles of 2,2'-difurylmethane with 2 moles of formaldehyde [4]; and (3) condensation of 4 moles of furfurylalcohol by zinc chloride [5]. However, the yields were very low (0.5-1%), and therefore, it is not suitable to expand these methods for the preparation of TOQA.

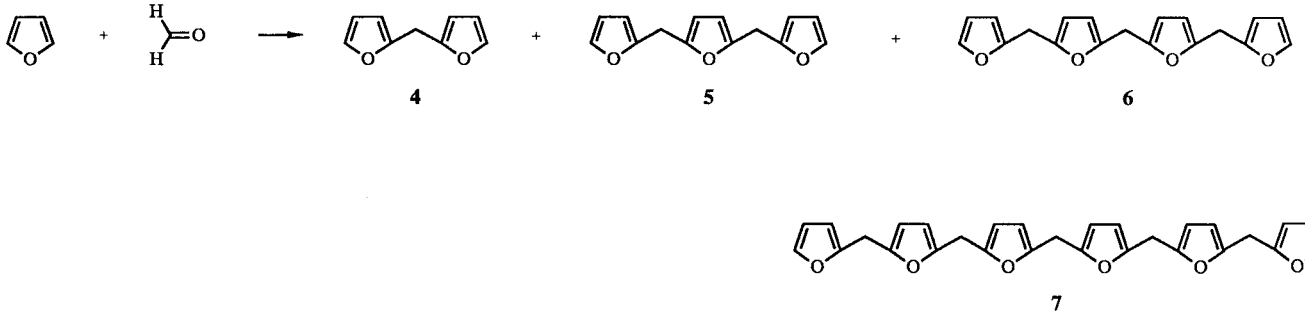
On the other hand, condensation of furan with methyl ketones [6,7,8], diethyl ketone [9], cyclohexanone [10] and keto acids [11] gave the cyclic tetramers **3** (with all R = alkyl) in rather good yields. The synthesis of **3** is further divided into two routes. One is condensation of furan with carbonyl compounds at a mole ratio of more than 1:2, giving TOQA. This is the "direct method" and also produces linear oligomers. The other method is the reaction of linear oligomers, which are produced by the condensation of furan and carbonyl compounds where the mole ratio is less than 1:2, with carbonyl compounds. This is the "indirect method" to prepare TOQA.

The TOQA produced by the condensation of ketones cannot be used to prepare compound **2** dications, because one hydrogen atom must be at positions 5, 10, 15 and 20 in order to obtain compound **2**. For this purpose it is necessary to condense furan with aldehydes. Kobuke and coworkers [2] reported that the condensation of furan and acetaldehyde gave **3c** in an 18% yield.

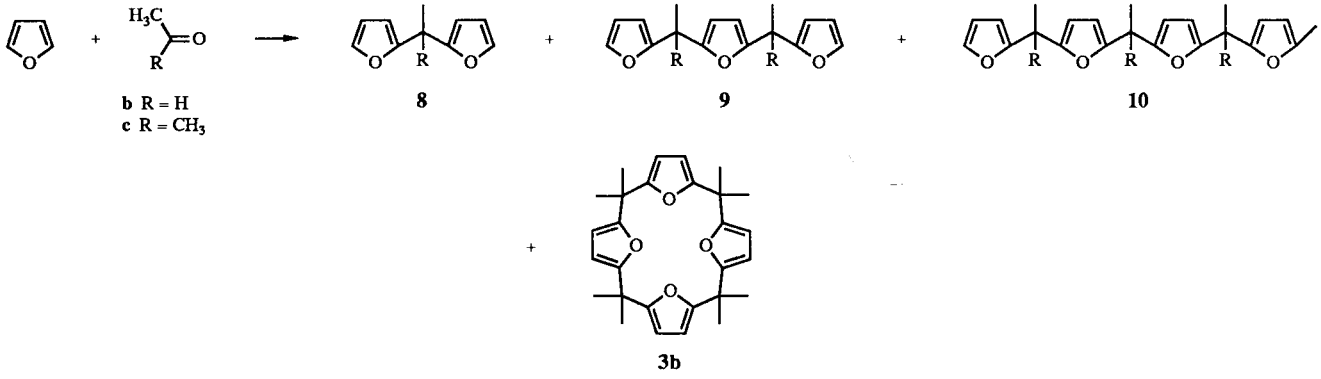
In this paper, we describe an attempt to synthesize **3a** by condensation of furan with formaldehyde. The product was identified by its mass spectrum, but it could not be isolated. We also synthesized TOQA derivatives, **3c** [2], **3d** and **3e**, and identified linear oligomers, which are intermediate products in the process.

Condensation of furan with formaldehyde in the presence of 35% hydrochloric acid as the catalyst gave linear oligomers 2,2'-difurylmethane, **4** (13%), 2,5-bis[(furfuryl)-furan], **5** (8%) and 1,1'-methylenbis[5-(furfuryl)furan], **6** (7%) as oily substances, but no cyclic tetramer, TOQA, **3a**,

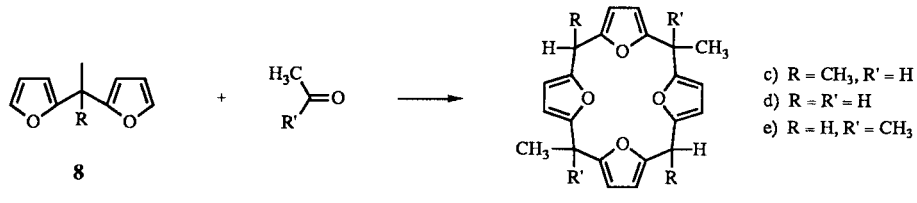
Scheme 1. Reaction between Furan and Formaldehyde



Scheme 2. Directed Method for the Preparation of TOAQ



Scheme 3. Inderect Method for the Preparation of TOAQ



could be isolated. This result is in contrast to the results of Vogel and co-workers [4] and Brown and Sawatzky [7] who obtained only **4** under the same conditions. Furthermore, reaction of **4** and formaldehyde in the presence of lithium ion with dry hydrochloric acid as the catalyst did not give **3a** as reported by Vogel and co-workers [4]. We obtained the linear hexamer, **7**, in this reaction.

Linear oligomers **4**, **5** and **6** had been prepared by Barr and Wallon [13] by another method.

In an attempt to synthesize tetramethyl TOQA, **3c**, furan was condensed with acetaldehyde in the presence of 35% hydrochloric acid as the catalyst [2] to give only the linear oligomers, **8b** (29%), **9b** (27%) and **10b** (7%). Tetramethyl TOQA **3c** was obtained in an 18% yield by treatment of 1,1-difurylethane, **8b**, and acetaldehyde in the presence of lithium perchlorate.

Treatment of furan and acetone according to the method of Brown and co-workers [6] gave linear oligomers **8c** (21%), **9c** (25%) and **10c** (5%) and octamethyl TOQA **3b** in a 5% yield. Reaction of furan and acetone in a mole ratio of 1:5 under the same conditions gave **3b** in a 12% yield. Treatment of 2,2-difurylpropane, **8c**, and acetone under the same conditions and in the presence of hydrochloric acid as catalyst gave **3b** in a 24% yield. Table 1 shows all of the above results.

The above results show that condensation of formaldehyde did not give TOQA by either the direct or indirect methods, but gave mostly furan resins. The yields of linear oligomers were also poor. Condensation of furan with acetone and acetaldehyde gave almost the same amount of linear oligomers. In the case of acetaldehyde tetramethyl TOQA **3c** was obtained only by the indirect method. In the case of acetone, octamethyl TOQA **3b** was obtained by

Table 1
Reaction Product Distribution from the Reaction of Furan and Carbonyl Compounds

Reactants	Linear oligomer				(Yield %) TOQA	
	Dimer	Trimer	Tetramer	Others	Direct Method	Indirect Method
Furan + HCHO	13	8	7	Hexamer	- [a]	-
Furan + CH_3CHO	29	26.5	7	Pentamer	-	18
Furan + CH_3COCH_3	21	25	5		12	24

[a] Detected by mass spectrum.

both the direct and indirect methods in good yields. The above results show that the production of TOQA with alkyl groups at positions 5, 10, 15 and 20 occurs with reasonable yields indicating that TOQA with alkyl groups has good thermodynamic stability.

Mixed dimethyl- and tetramethyl-substituted TOQA, **3d** and **3e**, were prepared in poor yields by treatment of 2,2'-difurylmethane, **4**, with acetaldehyde or acetone, respectively. These are new compounds which can only be prepared by the indirect method.

Preparations of tetraoxaporphyrin dications like **2** by the dehydrogenation of dimethyl TOQA **3d** and tetramethyl TOQA **3c** is now in progress.

EXPERIMENTAL

Melting points were measured on a Kofler micro hot stage and are uncorrected. Infrared spectra were taken on a Shimazu IR-435. The ^1H nmr spectra were measured in deuteriochloroform on a Hitachi R-22 instrument. Mass spectra were obtained with Hitachi MS-80 spectrometer. Column chromatography was performed with Shimazu LC-6A instrument. Microelemental analysis were performed on a Perkin-Elmer 240 analyzer.

Reaction between Furan and Formaldehyde.

1) To an ice-cooled mixture of 170 g (2.5 moles) of furan, 75 ml of ethanol and 50 ml of 35% aqueous hydrochloric acid was added dropwise, 85 ml of formalin (formaldehyde, 1.25 moles) with stirring at under 10°. The mixture was stirred for 18 hours at room temperature. The mixture was extracted with ether, washed with 5% aqueous sodium bicarbonate until the washings were not acidic, and then with distilled water, dried over anhydrous magnesium sulfate, and filtered. After evaporation of the solvent, the residue was distilled *in vacuo* to give the following linear oligomers:

2,2'-Difurylmethane **4**.

This compound had bp 95° (30 mm), yield 24.6 g (13%); ms: 149 (Calcd. for 148); ^1H nmr: δ 3.97 (2H, s), 6.03-6.14 (2H, m), 6.29 (2H, d), 7.34 (2H, d).

2,5-Bis[(furfuryl)furan] **5**.

This compound had bp 95-100° (1-2 mm), yield 15.2 g (7.6%); ms: 227 (Calcd. for 228); ^1H nmr: δ 3.93 (4H, s), 5.98 (2H, s), 6.09 (2H, d), 6.29 (2H, dd), 7.33 (2H, d).

1,1'-Methylenebis[5-(furfuryl)furan] **6**.

This compound had bp 123-125° (1-2 mm), mp 77 ~ 78°, yield 18.1 g (7.1%); ms: 308 (Calcd. for 308); ^1H nmr: δ 3.93 (6H, s), 5.96 (4H, s), 6.01-6.14 (2H, m), 6.21-6.39 (2H, m), 7.22-7.41 (2H, m).

Anal. Calcd. for $C_{19}H_{16}O_4$: C, 74.01; H, 5.23; O, 20.76. Found: C, 73.74; H, 5.12; O, 21.14.

The ^1H nmr data of compounds **4**, **5** and **6** are nearly the same as those reported by Barr and Wallon [13].

2) Treatment of 17 g (0.25 mole) of furan and 70 g (1.25 moles) of formaldehyde under the same conditions as above gave linear oligomers, **4**, **5** and **6**, and also a large amount of a resinous substance. The gc-ms analysis of the distillate residue of the linear oligomers showed a peak which had molecular weight 321 (Calcd. for **3a**: 320). Separation of this product was unsuccessful.

Reaction between Linear Oligomers **4** or **6** with Formaldehyde.

1) To 100 ml of ethanol were added, 27.5 g (0.2 mole) of **4**, 12 g (0.2 mole) of formaldehyde and 3 g of lithium chloride. Dry hydrogen chloride gas was passed through the solution for 5 days at room temperature. The mixture was dissolved in benzene, washed with 5% sodium bicarbonate and dried. After evaporation of the solvent, the residue was distilled *in vacuo* to give an orange oil, bp 180-200° (1-2 mm), which solidified. Recrystallization from ethanol gave 0.05 g of hexamer **7** as crystals, mp 100°; ms: 469 (Calcd. for 7, 468).

2) Treatment of 3 g (0.01 mole) of **6**, and 3 g (0.1 mole) of formaldehyde with dry hydrogen chloride gas as catalyst gave only resinous material.

Reaction between Furan and Acetaldehyde.

To a mixture of 204 g (3 moles) of furan, 100 ml of ethanol and 60 ml of 35% hydrochloric acid was added, 70 g (1.5 moles) of acetaldehyde at room temperature [2]. The mixture was stirred at room temperature for 20 hours, and then extracted with ether. The ethereal extract was washed with 5% sodium bicarbonate, dried, and the ether was removed. The residue was distilled *in vacuo*, giving the following linear oligomers:

1,1-Difurylethane **8b**.

This compound had bp 89-92° (17 mm), yield 69.8 g (29%); ms: 162 (Calcd. for 162).

2,5-Bis[(methylfurfuryl)furan] **9b**.

This compound had bp 123-130° (1 mm), yield 67.9 g (27%); ms: 257 (Calcd. for 256).

1,1'-Ethylidenebis[5-(methylfurfuryl)furan] **10b**.

This compound had bp 180-183° (1 mm), yield 18.6 g (7.1%); ms: 350 (Calcd. for 350).

The data for bp, mp, ms and ir (not included here) for **8b**, **9b** and **10b** were the same as those reported by Kobuke and co-workers [2].

Linear Pentamer.

The distillate residue from **8b**, **9b** and **10b** were purified by high-speed liquid chromatography. The gc-ms analysis was carried out showing a small amount of linear pentamer; ms: 377 (Calcd. for 376).

Tetramethyltetraoxaquaterene **3c**.

1) To a mixture of 30 g (0.18 mole) of **8b**, 3.8 g of lithium chloride, 30 ml of 60% perchloric acid and 60 ml of ethanol was added dropwise 26 g (0.53 mole) of acetaldehyde under 10° in a manner similar to that reported [2]. The mixture was stirred for 2 days and then extracted with benzene. The benzene solution was washed with 5% aqueous sodium bicarbonate, dried and the benzene was removed. The residue was distilled *in vacuo*, giving a yellow oil, which soon solidified. Recrystallization from ethanol gave 6.3 g (18%) of crystalline material as pillars, mp 140-143°; ms: 377 (Calcd. for 376); ^{1}H nmr: δ 1.48 (12H, d), 3.80-4.15 (4H, m), 5.93 (8H, s); ^{1}H nmr: spectrum of **3c** is nearly the same as that reported by Kobuke and co-workers [2].

2) Condensation of furan with acetaldehyde, at the mole ratios of 1:2 and 1:5 as reported above gave only linear oligomers **8b**, **9b** and **10b**, but no **3c**.

Reaction between Furan and Acetone.

To a solution of 204 g (3 moles) of furan, 100 ml of ethanol and 60 ml of 35% hydrochloric acid was added, 87 g (1.5 moles) of acetone under 10°, and the mixture was stirred for 18 hours [6]. The organic layer was separated, extracted with ether, washed with 5% aqueous sodium bicarbonate, dried, and the ether was removed. The residue was distilled *in vacuo*, giving the following linear oligomers:

2,2-Difurylpropane **8c**.

This compound had bp 44-47° (1-2 mm), yield 54.6 g (21%); ms: 176 (Calcd. for 176); ^{1}H nmr: δ 1.61 (6H, s), 6.02 (2H, d), 6.25 (2H, dd), 7.32 (2H, d).

2,5-Bis[(dimethylfurfuryl)furan] **9c**.

This compound had bp 103-105° (1-2) mm), yield 71.2 g (25%), mp 47°; ms: 284 (Calcd. for 284); ^{1}H nmr: δ 1.57 (12H, s). 5.89 (2H, s), 5.93 (2H, d), 6.24 (2H, dd), 7.29 (2H, d).

2,2'-Isopropylidenebis[5-(dimethylfurfuryl)furan] **10c**.

This compound had bp 155-158° (1-2 mm), yield 13.9 g (5%); ms: 393 (Calcd. for 392).

Octamethyltetraoxaquaterene **3b**.

1) A mixture of 85 g (1.25 moles) of furan and 362 g (6.25 moles) of acetone was allowed to stand for 6 days as reported by Brown and co-workers [6,8] whereupon crystals formed. The crystals were filtered and washed with ethanol. Recrystallization from tetrahydrofuran gave 16.1 g (12%) of **3b** as colorless needles, mp 243°; ms: 433 (Calcd. for 432); ^{1}H nmr: δ 1.44 (24H, s), 5.87 (8H, s); the ^{1}H nmr spectrum is the same as that reported by Chasteerette [12].

Oily by-product and ethanol washings were added, and then distilled *in vacuo*, to give **8c**, **9c** and **10c**.

2) In a similar manner, a mixture of 50 g (0.28 mole) of **8c**, 16 g (0.28 mole) of acetone, 375 ml of ethanol and 112 ml of 35% hydrochloric acid was stirred for 4 days and crystals formed. Recrystallization of the crystals from tetrahydrofuran gave 14.5 g (24%) of **3b**.

5,15-Dimethyltetraoxaquaterene **3d**.

A mixture of 7.4 g (0.05 mole) of **4**, 2.44 g (0.05 mole) of acetaldehyde, 100 ml of ethanol, 7.4 ml of of 60% perchloric acid and 1.06 g (0.025 mole) of lithium chloride was stirred at room temperature for 3 days. The solution was extracted with ether, the ether was washed with 5% aqueous sodium bicarbonate and dried. After removal of the ether the residue was distilled *in vacuo*, yielding **3d** as a yellow oil, bp 208-210° (1-2 mm), which solidified. Recrystallization from ethanol gave 0.13 g (1.5%) of **3d** as crystals, mp 143-145°; ms: 349 (Calcd. for 348); ^{1}H nmr: δ 1.48 (6H, d), 3.76 (4H, s), 3.99 (2H, q), 5.91 (8H, s).

Anal. Calcd. for $C_{22}H_{20}O_4$: C, 75.84; H, 5.79; O, 18.37. Found: C, 75.98; H, 5.85; O, 18.17.

5,5,15,15-Tetramethyltetraoxaquaterene **3e**.

A mixture of 12 g (0.08 mole) of **4**, 4.7 g (0.08 mole) of acetone, 120 ml of ethanol and 35 ml of 35% hydrochloric acid was stirred at room temperature for 5 days. The solution was extracted with ether, the ether was washed with 5% aqueous sodium bicarbonate, dried and the ether was removed. The residue was distilled *in vacuo*, giving **3e** as a yellow oil, bp 210° (1-2 mm), which solidified. Recrystallization from ethanol gave 0.42 g (2.7%) of **3e** as crystals, mp 199-201°; ms: 376 (Calcd. for 376); ^{1}H nmr: δ 1.49 (12H, s), 3.72 (4H, s), 5.90 (8H, s).

Anal. Calcd. for $C_{24}H_{24}O_4$: C, 76.57; H, 6.43; O, 17.00. Found: C, 76.25; H, 6.43; O, 17.32.

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