The Synthesis of Furan-derived Calixarenes

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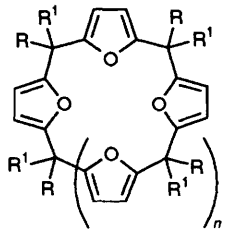
Furan and 2-hydroxymethylfuran were reacted under Lewis acidic oligomeric precursors, for a subsequent Lewis acid catalysed cyclisation to afford the furan based calixarenes, *i.e.* cyclic tetramer **2a**, and small quantities of the cyclic pentamer **2b**, hexamer **2c** and octamer **2d**.

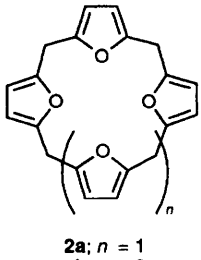
Calixarenes[1] derived from phenol derivatives have become important materials for a wide range of synthetic applications, from molecular scaffolds for building artificial enzymes to use in studying basic molecular interactions.[2] However, furan-containing macrocycles are less well known,[3] and the furan-derived calixarenes in particular have received little attention. This fact is due in part to the problem of ready accessability of such materials, and to date only structures typified by the cyclic compounds of type **1** and **2a** have been reported.[4–6]

The simplest of all these cyclic compounds, *i.e.* **2a** has been made by several groups, but yields vary from 0.5–1.0%.[5] The lack of efficient access to such compounds, coupled with the fact that the furan rings of structures of type **1** can be reduced[6] or ring opened[7] to yield efficient ionophoric compounds attracted our attention; and we report herein our endeavours to synthesise the simplest cyclic tetramer **2a** and its related larger ring oligomers **2b–d**.

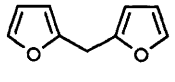
Our starting point was the preparation of non-cyclic oligomers **3** and **4** from furan **5a** and hydroxymethylfuran **5b**, to use as intermediates for cyclisation to their cyclic counter-



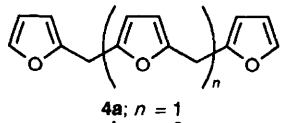
1a; n = 1, R = R^1 = Me
b; n = 2, R = R^1 = Me
c; n = 3, R = R^1 = Me
d; n = 1, R = H, R^1 = alkyl
e; n = 1, R = R^1 = alkyl



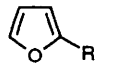
2a; n = 1
b; n = 2
c; n = 3
d; n = 5



3



4a; n = 1
b; n = 2
c; n = 3
d; n = 4
e; n = 5
f; n = 6



5a; R = H
b; R = CH_2OH

Table 1

Reactants	Catalyst	Solvent	*T*/°C	Yield (%)[a]						
(molar ratio)				**3**	**4a**	**4b**	**4c**	**4d**	**4e**	**4f**
5b (4)	$BF_3{\cdot}Et_2O$ (1)	CH_2Cl_2	0–room temp.	~5% yield of a mixture + 1.3% **2a**						
5a (2), **5b** (1)	$BF_3{\cdot}Et_2O$ (cat.)	CH_2Cl_2	−78–room temp.	16	11	1	2	~1	~1	0
5a (2), **5b** (1)	$BF_3{\cdot}Et_2O$ (cat.)	none	0–room temp.	16	11	1	2	~1	~1	0
5a (10), **5b** (1)	$BF_3{\cdot}Et_2O$ (cat.)	CH_2Cl_2	0–room temp.	28	20	4	2	0	0	0
5a (2), **5b** (1)	conc. HCl (cat.)	CH_2Cl_2	0–room temp.	0.4	0.5	0.6	0.6	<0.1	0	0

[a] All linear compounds gave satisfactory spectroscopic and analytical properties.†

Table 2

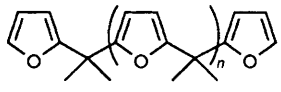
Reactants	Catalyst	Solvent	*T*/°C	Yield (%)[a]						
(molar ratio)				**4b**	**4c**	**4d**	**2a**	**2b**	**2c**	**2d**
3 (1), 37% CH_2O (4)	conc. HCl	EtOH	0–room temp.	15	0	24	0	0	0	0
3 (2), $H_2C(OMe)_2$ (2)	$BF_3{\cdot}Et_2O$ (4)	CH_2Cl_2	0–room temp.	<1	0	<1	6	0	<1	0[b]
4a (1), $H_2C(OMe)_2$ (1)	$BF_3{\cdot}Et_2O$ (2)	CH_2Cl_2	0–room temp.	0	0	trace[c]	0	0	0	0
4b (1), $H_2C(OMe)_2$ (1)	$BF_3{\cdot}Et_2O$ (2)	CH_2Cl_2	0–room temp.	10	0	0	34	0	0	2
4c (1), $H_2C(OMe)_2$ (1)	$BF_3{\cdot}Et_2O$ (2)	CH_2Cl_2	0–room temp.	0	3	0	0	3–5	0	0
4d (1), $H_2C(OMe)_2$ (1)	$BF_3{\cdot}Et_2O$ (2)	CH_2Cl_2	0–room temp.	0	0	~100	0	0	0	0
4d (1), $H_2C(OMe)_2$ (24)	$BF_3{\cdot}Et_2O$ (10)	CH_2Cl_2	0–room temp.	0	0	0	0	0	1	0

[a] All cyclic compounds had satisfactory spectroscopic and analytical properties.† [b] Small quantities of a mixture of **4b**, **4d** and **2c** were isolated as an inseparable mixture. [c] The linear hexamer **4d** was observed by TLC and NMR (present in small quantities) after the first few hours of reaction. However, no cyclic hexamer **2c** was observed and complete decomposition of all materials occurred after 4 days.

parts.† The literature procedures[8,5d] were compared with alternative reaction conditions (non-hydrolytic) that we expected would be more compatible with the reactive methylfuran moiety. The conditions and yields of the different oligomers obtained are summarised in Table 1.

From Table 1, it was observed that it was convenient to prepare precursors **3** and **4a** on fairly large scales; the conditions of choice being with a large excess of furan because under these conditions there was minimal charring of the reaction mixture and little resinous material produced. We also obtained sufficient quantities of the other oligomers **4b–e** to attempt cyclisation reactions, again under Lewis acid conditions. These reactions are summarised in Table 2.

As can be seen from the results, it was reasonably easy to cyclise the linear tetramer **4b** to the cyclic tetramer **2a** if dimethoxymethane was used for the alkylation in an aprotic solvent. By crude ^1H NMR, the reaction is approximately quantitative, however, the yield of **2a** and its oligomers are quoted after silica gel chromatography where considerable decomposition takes place. It is intriguing that the linear tetramer **4b** cyclises reasonably readily, however, as the chain



6a; *n* = 2
b; *n* = 3
c; *n* = 4

length becomes longer, the yield of cyclic material drops (*i.e.* for conversion of **4c** to **2b**) and if the chain is extended further, cyclisation is virtually non-existant (*i.e.* for conversion of **4d** to **2c**). These results strongly suggest that cyclisation of the precursor to **2a** is possible or even likely on conformational grounds, but as the chain lengthens, cyclisation becomes less likely probably owing to increased flexibility of the chain. This intriguing result contrasts markedly with the results reported[6] for the more substituted counterparts, *i.e.* oligomers **6** have been cyclised and the efficiency of the reaction seems to increase with increasing chain length and occurs under reactions conditions that destroy the unsubstituted oligomers **4b–d**.‡ This may be explained by the increased stability of oligomers **6** to hydrolysis or alcoholysis and the existence of the geminal-dimethyl groups, which may be assisting cyclisation.[9]

This conformational problem suggested to us that addition of a template to assist these cyclisation processes would be necessary for optimisation of the cyclisation, by making cyclisable conformations more easily accessible. Unfortunately, we have been unable to find any material that assists any of the cyclisations, including the addition of alkali metal and ammonium salts. This failure to template the cyclisations is probably due to the fact that unlike their non-aromatic polyether counterparts, these furan substances are poor ligands for cations and do not solvate most of the additives we tried.

† All compounds had satisfactory spectroscopic and analytical properties. Selected analytical data for linear compounds. **3** [see refs. 8(*a*), (*b*), (*d*)]; b.p. 95 °C at 30 mmHg (lit.[5d] 95 °C at 30 mmHg); **4a** [see refs. 8(*a*) and (*b*)]; b.p. 95–100 °C at 1–2 mmHg (lit.[5d] 95–100 °C at 1–2 mmHg); **4b** [see ref. 8(*a*)]; m.p. 76–78 °C (lit.[5d] 77–78 °C); **4c**; m.p. 98–100 °C (lit.[8c] 99–101 °C); **4d**; m.p. 128–130 °C (lit.[5d] 100 °C); **4e**; m.p. 140–142 °C.

All new compounds gave satisfactory spectroscopic and analytical properties. Selected spectroscopic and analytical data for cyclic compounds. **2a**; m.p. 158–160 °C (lit.[5b] 158–159 °C); accurate MS: $C_{20}H_{16}O_4$ requires *m*/*z* 320.1049, found 320.1046. **2b**; ^1H, 300 MHz, $CDCl_3$ δ 3.88 (10H, s), and 5.94 (10H, s); accurate MS $C_{25}H_{20}O_5$ requires *m*/*z* 400.1307, found 400.1311. **2c**; (^1H, 300 MHz, $CDCl_3$) δ 3.89 (12H, s), and 5.89 (12H, s); accurate MS for **2c** $C_{30}H_{28}O_6N$ requires *m*/*z* 498.1916, found 498.1924. **2d**; (^1H, 300 MHz, $CDCl_3$) δ 3.89 (16H, s), and 5.94 (16H, s); accurate MS for **2d** $C_{40}H_{36}O_8N$ requires *m*/*z* 658.2441, found 658.2433.

‡ The linear pentamer and hexamer **6b** and **6c**, respectively, were cyclised in 45 and 52% yields respectively with HCl in benzene, whereas the linear tetramer **6a** was cyclised in only 13–36% with various carbonyl compounds. See ref. 6.

In conclusion, we have isolated cyclic furan calixarene **2a** in 34% yield by cyclisation of the linear tetramer **4b**. Cyclisation of the homologous linear pentamer and hexamer **4c** and **4d** respectively, has also been achieved, providing furan calixarenes **2b** and **2c** in low yields. The fact that these compounds and octamer **2d** have been prepared and isolated at all shows that they are stable, but the low yields suggest that milder methods for their preparation need to be found.

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