

Role of Metal Salts in the Synthesis of Furan–Ketone Condensation Macrocycles: An 'Apparent' Metal Template Effect

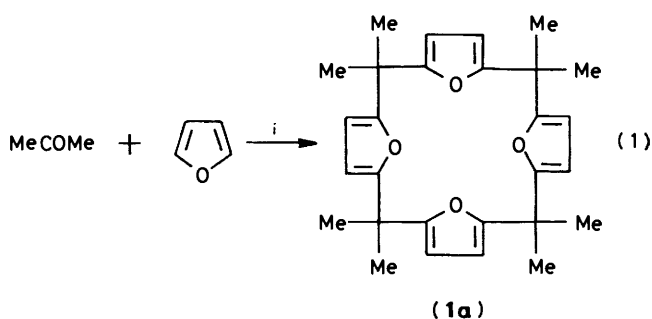
Maria de Sousa Healy and Antony J. Rest*

Department of Chemistry, The University, Southampton SO9 5NH

The acid-catalysed condensation of furan and acetone has been investigated by systematically varying the parameters of the reaction. The dramatic yield enhancement for macrocycles found on adding metal salts, and hitherto assumed to be due to a metal ion template effect, has now been demonstrated to result from pH effects. Optimisation of the condensation reaction conditions has enabled a number of tetrameric furan–ketone macrocycles to be synthesized with improved yields and a tetrameric furan–cyclohexanone macrocycle has been synthesized in a one-step reaction for the *first time*. Hexameric and octameric furan–acetone macrocycles have also been prepared. The tetrameric furan–ketone macrocycles show no binding interaction with any metal ion but the tetrameric tetrahydrofuran–acetone macrocycle binds strongly enough with LiClO_4 to form an isolable 1 : 1 complex and gives very strongly perturbed ^1H n.m.r. spectra in the cases of LiSCN and $\text{Ni}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$. Increasing the number of donor sites, as in the hexameric furan–acetone and hexameric tetrahydrofuran–acetone macrocycle, did not lead to complexation of metal ions.

The addition of metal ions to the reaction mixture often leads to dramatic increases in yields of macrocyclic products. These increases in yields are attributed to metal ions holding the reacting groups in the correct positions for cyclisation reactions to proceed, *i.e.* the metal ions behave as templates.^{1–3}

When acetone and furan were condensed in an acidic solution [equation (1)] a yield of *ca.* 18–20% of the tetrameric macrocycle was obtained, but yields were much lower for heavier ketone homologues ($\leq 10\%$).⁴ The addition of metal



Reagents: i, H^+ /EtOH, 50–60 °C

salts increased the yield of (1a) dramatically, *e.g.* up to 40–45% when LiClO_4 was added.⁵ (This yield was subsequently revised to 24–25%⁶ when it was discovered that soluble polymers of low molecular weight were also formed and that these needed to be washed from the crude reaction product, which was presumably what had been used previously⁵ to assess reaction yields). Work from this laboratory⁷ suggested that the improved yields might not be due simply to a template effect because transition-metal salts, whose metal ions show little tendency to co-ordinate ether oxygen atoms in general and furan oxygen atoms in particular, also gave improved yields of the product (1a). We now report evidence to show that increases in the yield of compound (1a) can be attributed to acidity effects (pH) rather than to a metal ion template effect. The new synthetic route exploiting the acidity effect was used to prepare tetrameric furan–ketone macrocycles in improved yields, *e.g.* a furan–cyclohexanone macrocycle was prepared for the *first*

time by a one-step reaction. Such macrocycles may be valuable alternatives to crown ethers and their potential affinity for Li^+ ions may have a bearing on the use of Li salts in the treatment of manic depression. A brief account of some of this work has appeared elsewhere.⁸

Experimental

General Remarks.—In the condensation reactions all reagents were of puriss. grade and, unless otherwise stated, were used without further purification. Ethanol was always absolute AnalaR quality. Most of the perchlorate salts † were not readily available and were, therefore, prepared as required by neutralising the appropriate metal carbonates with 72% perchloric acid. No attempt was made to dry these perchlorates exhaustively and hence water of crystallisation was present. I.r. spectra were recorded as thin films (oils and liquids) and Nujol mulls (solids) on a Pye Unicam SP200 or a Perkin-Elmer 157G grating spectrometer. ^1H N.m.r. spectra were recorded on a Perkin-Elmer R-124 (60 MHz), a Varian Associates HA-100 (100 MHz), or a Varian Associates XL-100-12 (100 MHz) spectrometer; the last instrument was also used to record ^{13}C n.m.r. spectra (25.15 MHz). Mass spectra were obtained using an AEI MS 12 spectrometer at an ionising potential of 70 eV. The major ion fragments are quoted as percentages with respect to the base peak (100%). For fragments with m/z greater than 520, the spectra were calibrated using perfluorokerosene (PFK) or *syn*-tris(perfluoroheptyl)-*s*-triazine as standard. M.p.s were determined on a Kofler hot-stage apparatus and are uncorrected. Gas-liquid chromatographic (g.l.c.) analyses were performed on a Pye Series 104 chromatograph or a Pye Unicam GCD chromatograph, both fitted with flame ionisation detectors and using glass columns. A column (length 1.5 m, internal diameter 5 mm) packed with silicone oil (5%, type OV17) on Chromosorb W (80–100 mesh) was used when separating mixtures of furan–acetone polymeric condensates. A temperature-controlled programme was required. Separation and determination of mixtures containing furan, ethanol, acetone, or mesityl oxide (4-methylpent-3-en-2-one) was achieved on a longer column

† CAUTION. Perchlorate salts may cause *explosions* when mixed and heated with combustible materials.

Table 1. Yields (%) and m.p.s (°C) of some tetrameric furan-ketone and tetrahydrofuran-ketone macrocycles

Ketone		Furan-ketone macrocycle		Tetrahydrofuran-ketone macrocycle	
		% Yield ^a	M.p. (°C)	% Yield	M.p. (°C)
Acetone	(1a)	35(7)	240–243	(2a)	38 ^b
Butan-2-one	(1b)	29(4)	170–173	(2b)	29
Pentan-2-one	(1c)	22(6)	148–151		<i>c</i>
Pentan-3-one	(1d)	13(1)	246–248		<i>c</i>
Hexan-2-one	(1e)	24(2)	138–140		<i>c</i>
Cyclohexanone	(1f)	17(4)	266–268		<i>c</i>
Heptan-2-one	(1g)	18(<1)	198–200		<i>c</i>
Heptan-4-one	(1h)	7(<1)	300–315 ^d		<i>c</i>
Octan-2-one	(1i)	5(<1)	168–170		<i>c</i>
Nonan-2-one	(1j)	4(<1)	135–140		<i>c</i>
Undecan-2-one	(1k)	4(<1)	158–160		<i>c</i>
Acetone	Cyclic hexamer (C ₆)	<i>e</i>	178–180		36
					73–75

^a The yields in parentheses were those obtained for condensation reactions carried out in the absence of metal salts. ^b 18% Yield of (3) (m.p. 163–165 °C) also obtained from this reaction. ^c Hydrogenation not attempted. ^d Melted with decomposition. ^e No strict yield comparison possible (see text and Table 3).

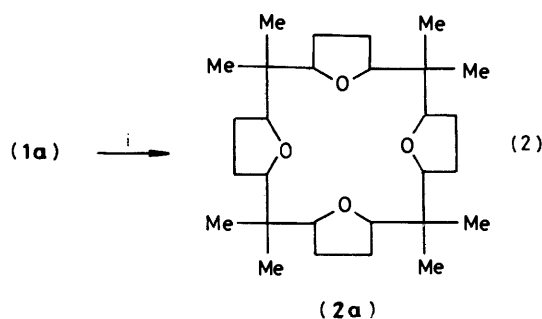
(length 2.5 m, internal diameter 2.5 mm) packed with 10% polyethylene glycol adipate on a Celite (60–80 mesh) support. The carrier gas (N₂) was maintained at a flow rate of 60 ml min⁻¹.

(i) *General Synthetic Method for Tetrameric Furan-Ketone Macrocycles.*—(a) *Acetone.* LiClO₄ (10.6 g, 0.1 mol) was dissolved in absolute EtOH (12 ml) contained in a three-necked flask (250 ml) fitted with a thermometer, coiled condenser, stirrer, and dropping funnel. Acetone (23.3 g, 0.4 mol) and conc. HCl (8 ml) were added with continual stirring. Finally, furan (13.6 g, 0.2 mol) was added rapidly. After *ca.* 20 min, the mixture became hot (60–70 °C) and turned deep red. The reaction flask was immersed in a water-bath and maintained at 60 °C for 3 h, during which time an off-white sticky mass appeared. The mixture was then stirred overnight at room temperature, water (10 ml) was added, and the suspension extracted* with benzene (50-ml aliquots) in a fume-hood. The benzene layer was washed with a 5% NaHCO₃ solution (200 ml) and dried (anhydrous MgSO₄). Evaporation of benzene afforded an off-white oily substance which, on washing with EtOH and drying *in vacuo* gave a white powder (m.p. 237–241 °C). Recrystallisation from C₆H₆ gave compound (1a) as a white solid (m.p. 240–243 °C, *c*: the literature value of 243 °C⁴).

(b) *Aliphatic, alicyclic, and aromatic ketones.* Condensation reactions with other ketones were carried out using the above procedure on a quarter-scale with the exception that extra EtOH was used (half-scale). Successful reactions were carried out with: butan-2-one, pentan-2-one, pentan-3-one, hexan-2-one, cyclohexanone, heptan-2-one, heptan-4-one, octan-2-one, nonan-2-one, and undecan-2-one. No reaction was observed for acetophenone and cyclopentanone even on extending the reaction time. Yields of macrocycles obtained by the above procedure (*i.e.* 1a–k) with and without added LiClO₄ are given in Table 1. The macrocycles were characterised by ¹H and ¹³C n.m.r., i.r., and mass spectroscopy (Table 2).

* The extraction procedure using Et₂O⁶ was found to be ineffective because large volumes (up to 1 000 ml) were required to dissolve completely the solid material obtained. Three solvents (C₆H₆, CHCl₃, C₆H₁₂) were tested for their effectiveness in comparison to Et₂O and also to establish whether any change of procedure, *e.g.* at washing and neutralisation stages, resulted in a loss of yield or changed the nature of the ratio of products. Both C₆H₆ and CHCl₃ were more efficient than Et₂O but C₆H₁₂ was as inefficient as Et₂O.

(ii) *General Synthetic Method for Tetrahydrofuran-Ketone Macrocycles.*—The synthesis of the tetrameric tetrahydrofuran-acetone macrocycle (2a) was reported to take place in absolute EtOH [equation (2)].⁵ In this work, however, the use



Reagents: i, H₂/Raney Ni, EtOH

of absolute EtOH always led to recovery of unchanged starting material. Dried tetrahydrofuran (LiAlH₄) gave cleaner reactions. Recrystallised and dried furan-acetone cyclic tetramer (10 g) was placed in a high-pressure autoclave with dry tetrahydrofuran (THF) (500 ml) and Raney Ni (10 ml). The vessel was filled with H₂ (initial pressure 120 atm) and heated with stirring (125 °C, 6 h). After the mixture had been stirred overnight the autoclave was depressurised and the spent catalyst was filtered off (Celite). The solvent was evaporated (rotary pump, 10⁻¹ Torr) leaving an off-white sticky mass which on washing with EtOH gave the tetrahydrofuran tetramer (2a) (3.89 g, 38%). The ethanolic washings were evaporated to give a 'gummy' yellow oil which would not crystallise. The oil was redissolved in EtOH and after 2 weeks a white crystalline solid had precipitated out and was found to be pure (t.l.c.). The solid was identified by mass spectroscopy (*m/z* 440) and ¹H n.m.r. spectroscopy as a macrocycle, (3) in which two *adjacent* furans had been hydrogenated. The yield of this product was 1.82 g (18%). Higher yields of compound (2a) could not be obtained by increasing the H₂ pressure (to 150 atm), raising the temperatures (to 160 °C), or lengthening the period of reaction (to 12 h). The above set of conditions were then adopted for compound (1b) and the hexameric furan-acetone macrocycle with appropriate scaling on account of the smaller amounts of

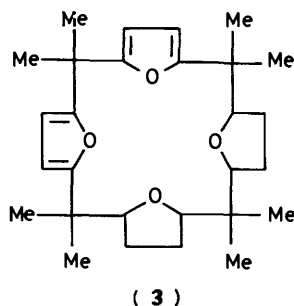
Table 2. Spectroscopic data for furan-acetone and tetrahydrofuran-acetone macrocycles

Macrocyclic	ν_{\max} (cm ⁻¹)	m/z (%) ^a	τ (p.p.m.) ^b	δ_c (p.p.m.) ^b
(1a)	1 655, 1 600, 1 560, 1 270, 1 220, 1 210, 1 155, 1 115, 1 030, 955, 795, 760	433(11), 432(34), 417(100), 201(13), 186(13)	4.12 (s, 8 H), 8.55 (s, 24 H)	158.63(s), 103.16(s), 36.62(s), 25.55(s)
(1b)	3 100—2 900, 1 610, 1 575, 1 470, 1 350, 1 320, 1 260, 1 230, 1 175, 1 145, 1 120, 1 070, 1 045, 1 025, 980, 955, 815, 790, 765, 760, 740, 730, 690	488(30), 473(100), 455(23), 216(11), 212(28)	4.20 (s, 8 H), 8.15 (q, <i>J</i> 7.5 Hz, 8 H), 8.36 (s, 12 H), 9.30 (t, <i>J</i> 7.5 Hz, 12 H)	157.84(s), 104.14(s), 40.56(s), 29.83(s), 8.21(s)
(1c)	2 900—2 775, 1 665, 1 435, 1 365, 1 305, 1 230, 1 205, 1 160, 1 105, 1 070, 1 025, 980, 945, 785, 740	544(13), 515(100), 500(9), 486(3), 457(12)	4.21 (s, 8 H), 8.20 (m, 8 H), 8.26 (s, 12 H), 8.70 (br, m, 8 H), 9.15 (m, 12 H)	157.80(s), 103.88(s), 40.26(s), 39.15(s), 22.33(s), 17.22(s), 14.53(s)
(1d)	1 605, 1 560, 1 445, 1 360, 1 325, 1 285, 1 215, 1 205, 1 140, 1 105, 1 085, 1 025, 965, 920, 880, 835, 795, 765, 720, 710, 685	544(13), 514(100), 502(9), 488(3), 458(12)	4.06 (s, 8 H), 8.14 (q, <i>J</i> 8 Hz, 16 H), 9.38 (t, <i>J</i> 8 Hz, 24 H)	156.55(s), 105.13(s), 44.32(s), 24.42(s), 7.44(s)
(1e)	2 950—2 800, 1 595, 1 450, 1 365, 1 305, 1 285, 1 240, 1 230, 1 130, 1 095, 1 075, 1 025, 860, 780, 725	600(11), 585(1), 543(100), 429(12), 372(7), 243(15), 186(7)	4.11 (s, 8 H), 8.00—8.30 (br, m, 8 H), 8.60 (s, 12 H), 8.80—8.95 (br, 12 H), 9.12— 9.20 (m, 16 H)	157.83(s), 103.92(s), 40.18(s), 36.85(s), 26.15(s), 23.18(s), 22.34(s), 14.06(s)
(1f)	3 000—2 900, 1 575, 1 495, 1 390, 1 370, 1 320, 1 290, 1 280, 1 245, 1 230, 1 220, 1 210, 1 195, 1 140, 1 085, 1 050, 1 025, 980, 925, 895, 845, 775, 730, 715, 685	592(100), 565(2), 551(4), 542(2), 445(4), 378(4), 298(5), 296(6)	4.13 (s, 8 H), 8.05 (br, 16 H), 8.60 (br, m, 24 H)	157.52(s), 103.97(s), 40.82(s), 33.47(s), 26.15(s), 22.34(s)
(1g)	2 950—2 800, 1 540, 1 455, 1 365, 1 310, 1 245, 1 210, 1 155, 1 120, 1 080, 1 025, 965, 960, 785, 735	656(7), 641(2), 585(100), 443(11), 372(6), 257(14), 186(5)	4.12 (s, 8 H), 8.10—8.26 (m, 8 H), 8.60 (s, 12 H), 8.75— 8.90 (br, m, 24 H), 9.10— 9.30 (m, 12 H)	157.86(s), 157.78(s), 103.79(s), 40.22(s), 37.66(s), 32.61(s), 34.46(s), 23.65(s), 22.78(s), 22.65(s), 22.35(s), 14.09(s)
(1h)	2 950—2 850, 1 530, 1 445, 1 360, 1 205, 1 155, 1 120, 1 025, 995, 785, 740	657(14), 656(32), 614(16), 613(40), 584(10), 527(100), 484(21), 455(31), 286(34), 285(88), 243(26), 242(79)	4.11 (s, 8 H), 8.01—8.26 (m, 16 H), 8.51 (br, s, 16 H), 9.10—9.24 (br, s, 24 H)	c
(1i)	3 000—2 750, 1 560, 1 550, 1 545, 1 365, 1 360, 1 215, 1 160, 1 130, 1 090, 1 030, 960, 785, 780, 725	712(13), 697(7), 627(100), 527(8), 457(12), 372(5)	4.11 (s, 8 H), 8.08—8.40 (br, m, 8 H), 8.55 (br s, 32 H), 8.70 (s, 12 H), 9.10—9.20 (br, m, 12 H)	157.87(s), 103.91(s), 40.21(s), 37.19(s), 32.05(s), 30.11(s), 24.04(s), 22.81(s), 22.33(s), 14.08(s)
(1j)	2 950—2 850, 1 565, 1 435, 1 360, 1 205, 1 155, 1 070, 1 025, 875, 790, 735	768(6), 753(6), 699(4), 683(4), 584(100), 499(52), 472(12), 387(16), 285(22)	4.10 (s, 8 H), 8.06—8.26 (br, m, 8 H), 8.58 (s, 12 H), 8.82 (br, s, 40 H), 9.13 (t, 12 H)	157.89(s), 103.95(s), 40.24(s), 37.22(s), 32.13(s), 30.49(s), 29.61(s), 24.15(s), 22.77(s), 22.35(s), 14.12(s)
(1k)	2 850—2 750, 1 545, 1 435, 1 375, 1 210, 1 145, 1 075, 1 030, 975, 795, 740	780(3), 767(1), 682(100), 569(1), 484(12), 384(2), 295(10)	4.11 (s, 8 H), 8.10—8.28 (br, m, 8 H), 8.59 (s, 12 H), 8.65 (br, s, 56 H), 9.15 (t, 12 H)	
Furan-CH ₃ CHO cyclic tetramer	2 980—2 880, 1 565, 1 455, 1 260, 1 230, 1 015, 955, 780, 740	377(12), 376(45), 362(24), 361(100), 346(7), 331(11), 316(8), 173(16)	4.08 (s, 8 H), 5.83—6.03 (m, 4 H), 8.51 (d, 12 H)	
Furan-Me ₂ CO cyclic hexamer (C ₆)	3 100—2 875, 1 560, 1 205, 1 150, 1 110, 1 025, 960, 795, 720	648(45), 634(58), 633(100), 618(16), 309(30)	4.25 (s, 12 H), 8.46 (s, 36 H)	
(2a)	2 900—2 750, 1 340, 1 255, 1 215, 1 080, 1 040, 1 005, 995, 970, 905, 740	449(11), 448(39), 183(29), 95(72), 71(69), 69(100)	6.10 (br, m, 4 H), 6.61 (br, m, 4 H), 8.50—8.71 (br, m, 16 H), 9.05—9.16 (br, s, 24 H)	80.72(s), 80.41(s), 26.59(s), 25.81(s), 17.43(s)

Table 2. (continued)

Macrocycle	ν_{\max} (cm ⁻¹)	m/z (%) ^a	τ (p.p.m.) ^b	δ_c (p.p.m.) ^b
(2b)	3 000—2 800, 1 240, 1 110, 1 090, 1 035, 925, 820, 760	505(10), 504(30), 312(19), 197(35), 179(20), 178(57), 125(33), 109(50), 55(100)	6.10 (br, m, 4 H), 6.42 (br, m, 4H), 7.73 (br, m, 4 H), 8.08 (s, 12 H), 8.31—8.70 (br, m, 12 H), 9.18 (t, 12 H)	84.69(s), 80.81(s), 80.64(s), 26.10(s), 25.79(s), 25.51(s), 25.30(s), 22.91(s), 22.19(s), 7.97(s)
Tetrahydrofuran— Me ₂ CO cyclic hexamer	3 000—2 875, 1 465, 1 385, 1 350, 1065	673(46), 672(100), 653(32), 561(29), 449(71), 407(26), 405(20), 337(72)	6.16—6.52 (br, m, 12 H), 8.26—8.56 (br, m, 12 H), 9.06—9.26 (br, s, 36 H)	

^a Parent molecular ion shown in italics. ^b s = Singlet, d = doublet, t = triplet, m = multiplet, br = broad. ^c Macrocycle insoluble.



starting materials. Yields of these tetrahydrofuran-ketone macrocycles are given in Table 1 and their characterisation (¹H n.m.r., i.r., and mass spectroscopy) given in Table 2.

(iii) *Synthesis of Hexameric and Octameric Furan-Acetone Macrocycles.*—(a) *Cyclic hexamer (C₆).* To a solution of LiClO₄ (2.8 g, 26 mmol) in EtOH (25 ml) was added Me₂CO (1.53 g, 26 mmol), conc. HCl (1 ml), and linear hexamer (C₆;⁹ 4 g, 7 mmol). This mixture was stirred for 2 days at room temperature and then extracted with benzene (see above). The resulting solid (2.81 g) was shown (g.l.c.) to be primarily the cyclic hexamer, C₆ (2.15 g, 50%). Similar yields were obtained for reactions in the presence of CsClO₄ (1.97 g, 46%) and in the absence of metal salts (2.07, 49%). ¹H N.m.r., i.r., and mass spectroscopic data are given in Table 2.

(b) *Cyclic octamer (C₈).* The reagents [EtOH (8 ml), Me₂CO (0.44 g, 7.7 mmol), conc. HCl (0.2 ml), and the linear tetramer (L₄;⁹ 1.5 g, 3.8 mmol)] were mixed together, refluxed for 3 h at 60 °C and stirred overnight at room temperature. Extraction with C₆H₆ followed by recrystallisation afforded a white solid (0.85 g; m.p. 218—230 °C), which was shown (¹H n.m.r.) to be a mixture of two compounds. The intense singlets (τ 4.12 and 8.55) belonged to compound (1a) and two other singlets (τ 4.20 and 8.43, 1:3) belonged to the second compound. Condensation in the presence of LiClO₄ and NaClO₄ gave lower overall yields of solid but now the unknown compound was the major product. Careful fractional recrystallisation afforded a pure sample of yellowish solid which gave an analysis (Found: C, 76.7; H, 7.4. Calc. for C₅₆H₅₄O₈: C, 77.78; H, 7.41%) and showed the presence of fragments in the mass spectrum with m/z values in the range 800—900. On the basis of this information and the simple ¹H n.m.r. spectrum, the second compound is assigned as the cyclic octamer (C₈).

(iv) *Detailed Studies of the Condensation Reaction of Furan with Acetone.*—(a) *In the presence of metal salts.* The condensation of furan with acetone was carried out in a standard manner [see section i(a)] on a quarter-scale because many metal salts were not as readily available as LiClO₄.

(b) *Reaction time.* Standard condensation reactions were carried out for 3 and 8 h and then the reaction mixtures worked up.

(c) *Effect of varying the amount of LiClO₄.* Varying amounts of LiClO₄ (0—0.2 mol), the most effective metal salt, were dissolved in EtOH (6 ml) and treated with Me₂CO (5.8 g, 0.1 mol), conc. HCl (2 ml), and furan (3.4 g, 0.05 mol) for 3 h at 60 °C, and the mixtures then stirred overnight at 20 °C. The products were extracted (C₆H₆) and recrystallised (C₆H₆) to give pure compound (1a).

(d) *Effect of varying the amount of acid.* Different amounts of conc. HCl (0—12 ml) were treated with EtOH (3 ml), furan (3.4 g, 0.05 mol), and Me₂CO (5.8 g, 0.1 mol) for 3 h at 60 °C and the mixtures then stirred overnight at 20 °C. The products were extracted (C₆H₆) and recrystallised (C₆H₆) to determine the yields of pure compound (1a).

(e) *Effect of varying the type of acid.* Furan (3.4 g, 50 mmol) and Me₂CO (5.8 g, 100 mmol) were condensed together in the presence of EtOH (3 ml) and a variety of acids (24 mmol), e.g. conc. HCl (2 ml), syrupy phosphoric acid (0.5 ml), conc. H₂SO₄ (0.66 ml), glacial acetic (1.4 ml), conc. HNO₃ (2.24 ml), 46% HBr (2.9 ml), and 72% HClO₄ (1.96 ml). The reagents were refluxed for 8 h (60 °C) and then stirred overnight (20 °C). In the reactions with H₃PO₄ and MeCO₂H, refluxing was continued for 48 h. The products were extracted (C₆H₆) and recrystallised (C₆H₆) to give the following yields of compound (1a): 15% (HClO₄), 13% (HCl), 12% (H₂SO₄), 12% (HBr), and 0% for HNO₃, H₃PO₄, and MeCO₂H.

(f) *Condensation under anhydrous conditions.* EtOH (6 ml) was saturated with dry HCl gas (generated from NaCl and conc. H₂SO₄ and dried over CaCl₂), and to this was added Me₂CO (5.8 g, 100 mmol) and furan (3.4 g, 50 mmol). The mixture was refluxed for 3 h (60 °C) and then stirred overnight. Extraction (CHCl₃) gave a 6% (0.4 g) yield of compound (1a). An identical reaction with added anhydrous LiClO₄ (2.65 g, mmol) yielded 3.1 g of solid giving a yield of (1a) of 33%.

(g) *Condensation in the presence of water.* A condensation was carried out between Me₂CO (5.8 g, 100 mmol) and furan (3.4 g, 50 mmol) in EtOH (6 ml) containing conc. HCl (2 ml) and distilled H₂O (2 ml) by refluxing the mixture for 3 h (60 °C) and then stirring it overnight (20 °C). A similar reaction was carried out with added LiClO₄ (2.65 g, 25 mmol). The yields of compound (1a) after extraction (C₆H₆) and recrystallisation (C₆H₆) were 0.04 g (<1%) and 0.5 g (9%) respectively.

(v) *Studies of Complexation Properties of Furan and Tetrahydrofuran Macrocycles by ¹H N.M.R. Spectroscopy.*—A sample of a particular macrocycle (ca. 25 mg) in CDCl₃ (0.5 ml) was prepared as normal for running a ¹H n.m.r. spectrum. A melting point tube containing the metal salt under investigation was introduced. After a spectrum of this system had been recorded, the melting point tube was broken, some additional agitation applied, and spectra recorded at regular intervals (30 min). When no further change in the spectrum occurred the undissolved metal salt was filtered off and a spectrum of the solution recorded. This solution was shaken with water before a final spectrum of the organic phase (CDCl₃) was recorded.

Table 3. Yields (%) of compound (1a) from condensation reactions in the presence of metal salts

Metal salt	Cation radius (Å)	Yields (%) of (1a) after recrystallisation	Yields (%) of (1a) by g.l.c. ^a	Other identifiable cyclic (C) and linear (L) products ^b
LiCl	0.68	16	16	L ₆ , C ₆
LiBr		17.5	18	L ₆ , C ₆
LiI		19	20	C ₆
LiSCN		0	0	L ₃ , L ₄ (20%)
LiClO ₄		35	36	L ₆ , C ₆
LiOAc		9	8.6	L ₃ , L ₄ (28%)
LiBF ₄		0	0	L ₃ , L ₄ (23%)
LiNO ₃		0	0	None
Li ₂ SO ₄		9	10	None
NaCl		0.97	8.5	8.7
NaBr	6		5.9	None
NaI	8		8.3	L ₆ , C ₆
NaClO ₄	13.6		15	L ₆ , C ₆
KCl	1.33	4	8	None
KClO ₄		8	10	L ₆ , C ₆
RbCl	1.47	5	5.7	None
RbClO ₄		3	5.3	L ₆ , C ₆
CsCl	1.67	4.3	6	L ₆ , C ₆
CsClO ₄		0.2	2	L ₃ , L ₄ , L ₆
MgCl ₂	0.66	12	13.5	None
Mg(ClO ₄) ₂		23.6	25	L ₄ , L ₆ , C ₆
Ca(ClO ₄) ₂ ·6H ₂ O	0.99	31	31.8	L ₄ , L ₆ , C ₆
Pb(ClO ₄) ₂ ·3H ₂ O	1.20	16	16	L ₆ , C ₆
CrCl ₃ ·6H ₂ O	0.63	28	28	None
Cr(ClO ₄) ₃ ·6H ₂ O		30.8	33	None
MnCl ₂ ·4H ₂ O	0.80	26	27	L ₆
Mn(ClO ₄) ₂ ·6H ₂ O		33	32	None
FeCl ₂ ·4H ₂ O	0.74	6.6	12	None
Fe(ClO ₄) ₂ ·6H ₂ O		28	27.2	L ₆
FeCl ₃ (anhydr.)	0.64	10	16	None
Fe(ClO ₃) ₃ ·9H ₂ O		15.6	22.8	L ₆ , C ₆
CoCl ₂ ·6H ₂ O	0.72	26.3	25.9	L ₆ , C ₆
Co(ClO ₄) ₂ ·6H ₂ O		33.8	33	None
NiCl ₂ ·6H ₂ O	0.69	11	11.6	None
Ni(ClO ₄) ₂ ·6H ₂ O		32	31.1	L ₆ , C ₆
NiSO ₄ ·6H ₂ O		7.4	8	None
CuCl ₂ ·2H ₂ O	0.72	17	17	L ₆ , C ₆
Cu(ClO ₄) ₂ ·6H ₂ O		30.7	29	None
ZnCl ₂ (anhydr.)	0.74	25	22	None
Zn(ClO ₄) ₂ ·6H ₂ O		29.8	32	None
AgClO ₄ ·H ₂ O	1.26	8.3	11	None

^a 5% OV17 column, detector temp. = 300 °C, injector temp. = 280 °C, column temp. = 250 °C, retention times: L₄ = 1.8 min, (1a) = 2.4 min, L₆ = 29 min, and C₆ = 30 min. With column temp. = 200 °C, retention time of L₃ = 1.5 min. ^b These oligomers accounted for ca. 2% of the remaining crude solid. The remaining unassigned products showed the same unidentified peaks which were of the same magnitude as the other oligomers.

Results

(a) *Condensation in the Presence of Metal Salts.*—In the presence of LiClO₄, LiCl, LiI, NaClO₄, and NaI, the reaction mixture became red during refluxing and solid products precipitated out; the highest yields of compound (1a) were obtained

from these reactions. In contrast, the insoluble salts LiBF₄, Li₂SO₄, NaCl, * NaBr, KCl, KClO₄, RbCl, RbClO₄, * CsCl, * and CsClO₄, gave rise to green reaction mixtures which, in some cases (*), still showed the presence of unchanged acetone even after refluxing for 48 h instead of the usual 3 h [see below,

Table 4. Comparison of the yields (%) of compound (**1a**) obtained after heating the condensation reaction between furan and acetone for different times

Metal salt	Yield after 3 h ^a	Yield after 8 h ^b
KCl	8	9.1
CsCl	6	5.4 ^c
LiClO ₄	36	34
NaClO ₄	15	17.9
KClO ₄	10	8.8
RbClO ₄	5.3	3.4 ^c
CsClO ₄	2	2
Mg(ClO ₄) ₂	25	26.8
Mn(ClO ₄) ₂ ·6H ₂ O	32	33
Ni(ClO ₄) ₂ ·6H ₂ O	31.1	29

^a Compiled from Table 3. ^b Calculated from gas chromatographs and obtained using the same conditions as before. ^c Results after refluxing for 48 h.

section i(b)]. The yield of compound (**1a**) obtained in each case was determined by recrystallisation and g.l.c. analysis (Table 3). From the gas chromatographs some of the remaining constituents of the crude reaction solid could also be identified, although, when combined, these represented less than 2% of the total solid.* Mass spectra of the crude solids showed the presence of other cyclic (C) and linear (L) oligomers: C₄ (**1a**), L₄, C₅, L₅, C₆, L₆, C₇, L₇, C₈, L₈, L₉, and L₁₀ although none of these could be obtained and identified as separate pure compounds.⁹

Condensations in the presence of alkaline-earth metal salts gave significantly better yields than many of the Li⁺ salts, e.g. Ca(ClO₄)₂·6H₂O (31%) was almost as good a 'template' agent as LiClO₄ (35%) (Table 3).

The results obtained in the presence of transition metal salts showed higher yields of products (Table 3) than for the non-transition metals with the notable exceptions of LiClO₄ and Ca(ClO₄)₂·6H₂O. Amongst the anions, metal perchlorates gave consistently higher yields of compound (**1a**) than did metal chlorides. This probably arises from solubility effects, e.g. the most insoluble salts NiCl₂·6H₂O and NiSO₄·6H₂O gave very little yield of product.

In order to investigate further the significance or otherwise of the type of cation, condensations were carried out in the presence of tetra-alkylammonium salts. Within experimental error, the reactions in the presence of NH₄BF₄, Buⁿ₄NCl, and Buⁿ₄NClO₄ gave low yields (ca. 7%), i.e. the same as in the absence of any added metal salts, while NH₄Cl seemed to inhibit not only the formation of compound (**1a**) but any condensation since only minute traces of oligomers were detected (Table 3).

(b) *Effects of Varying the Parameters of the Condensation Reaction.*—(i) *Effect of varying the reaction time.* The yield of compound (**1a**) obtained from the condensation of furan with acetone in the absence of any salts was only ca. 7%. The addition of certain metal salts enhanced the yield of the macrocycle; however the best yield (LiClO₄ = 35%) was well short of the reported value (44–45% †) ⁵ for this particular salt. It seemed possible that refluxing for only 3 h at 60 °C was insufficient to obtain the highest possible yield in the cases of

insoluble salts and that longer reflux times might increase the yield. The reactions to which KCl, CsCl, LiClO₄, NaClO₄, KClO₄, RbClO₄, CsClO₄, Mg(ClO₄)₂, Mn(ClO₄)₂·6H₂O, and Ni(ClO₄)₂·6H₂O had been added were heated for 8 h and in the cases of RbClO₄ and CsCl the refluxing period was extended to 48 h. All the results (Table 4) indicated that the reaction had effectively gone to completion after heating for 3 h, i.e. the amount of crude solid isolated from each reaction was almost the same as that obtained in the 3-h reactions.

(ii) *Effect of varying the amount of LiClO₄ on the yield of compound (**1a**).* LiClO₄ (0–0.2 mol) was added to the reaction mixture [see Experimental section iv(c)] and the yield of compound (**1a**) was determined on each occasion according to the recrystallised product. The yield of macrocycle was found to increase sharply until 0.03 mol of the salt had been added, but then a plateau was reached when increased quantities of LiClO₄ did not give corresponding increases in the yields of the macrocycle (Figure 1).

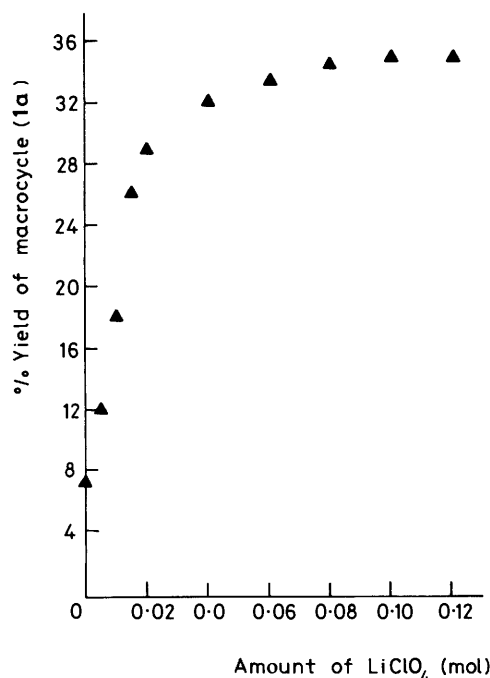


Figure 1. Graph showing the effect of varying the amount of LiClO₄ on the % yield of compound (**1a**)

(iii) *Effect of varying the amount of acid.* Since the condensation is dependent on the presence of acid, the effect of varying this parameter was determined by carrying out [see Experimental section iv(d)] the condensation in the absence of metal salts and with varying amounts of conc. HCl. The yield increased as the amount of added acid increased (Figure 2); however the maximum yield, ca. 34%, was reached after 9 ml of the acid had been added. A feature of reactions in which more than 5 ml of acid had been added was the rapid reaction and almost instant precipitation of the product on the addition of furan.

(iv) *With excess of acid in the presence of LiClO₄ and Ni(ClO₄)₂·6H₂O.* When the condensations were carried out in the presence of the optimum quantities of conc. HCl [9 ml, see Results section iii(b)] together with LiClO₄ and Ni(ClO₄)₂·6H₂O (0.03 mol, see Results section ii(b)) the yields of compound (**1a**) obtained were 37 and 32% respectively compared with 35 and 32% respectively, obtained without

* Other components of the solid must remain on the column.

† Subsequently, the authors revised this yield to 24–25%⁶ and noted that soluble polymers of low molecular weight were also formed and that these needed to be washed from the crude reaction product, which was presumably used previously⁵ to assess the reaction yield.

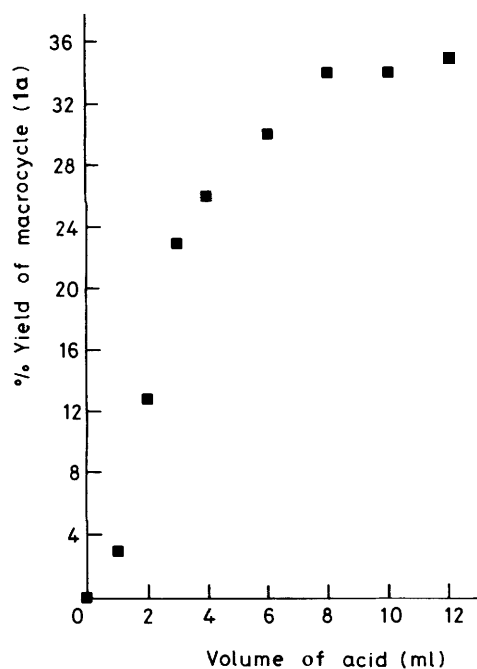


Figure 2. Graph showing the effect of varying the amount of conc. HCl on the % yield of compound (1a)

optimisation (Table 1), *i.e.* little or no improvement in yield occurs on adding metal ions to an already optimised reaction.

(v) *Effect of varying the type of acid.* A slightly increased yield of compound (1a) was found for HClO_4 compared with conc. HCl but others were less effective, *e.g.* conc. H_2SO_4 (12%) and HBr (12%) whilst HNO_3 , H_3PO_4 , and HOAc failed to promote any reaction.

(vi) *Condensation in the presence of metal salts and 72% HClO_4 .* Since a slightly higher yield of compound (1a) was achieved in the previous section [v(b)], the condensations in the presence of HClO_4 and metal salts were repeated. The reactions with alkali and alkaline-earth metal salts behaved in the same manner as with conc. HCl but yielded overall greater quantities of crude solid product leading to slightly higher yields of compound (1a), especially for the less soluble salts KClO_4 , RbClO_4 , and CsClO_4 . The largest quantity of compound (1a) came from the reaction employing LiClO_4 (38%). The reactions with transition metal salts also showed a tendency towards better yields when 72% HClO_4 was used as the acid.

(vii) *Condensations under anhydrous conditions.* There was a possibility that some relatively low yields could be due to the presence of water, *e.g.* from water of crystallisation. If macrocycle formation was inhibited by water then the increased yields for some metal salts could be due to their ability to bind water. In order to investigate this point, condensations were carried out using dry furan and acetone together with dry HCl gas rather than conc. HCl. For such a reaction system, yields without metal salt and with anhydrous LiClO_4 of 7 and 33%, respectively, were obtained, *i.e.* analogous yields to those obtained using the standard reaction procedure [see Experimental section i(a)]. In an effort to determine just how detrimental water could be, reactions were carried out in which distilled water (2 ml) was deliberately added. Less than 1% of compound (1a) was extracted from the reaction without metal salt, and only 9% for added LiClO_4 under these conditions, *i.e.* a large excess of water reduces yields dramatically, but such excesses were not present in the routine condensation reactions [see Experimental section i(a)].

Table 5. Complexing ability of compound (2a) with metal salts as demonstrated by ^1H n.m.r. spectroscopy and expressed as a function of the time taken to observe spectral changes.

Metal salt	Time (h)				
	0	$\frac{1}{2}$	2	24	48
LiCl					a
LiBr		b			
LiI	b				
LiSCN	c				
LiClO_4	c				
LiBF_4				b	
LiNO_3		b			
Li(picrate)		b			
LiOAc					b
MgI_2			b		
$\text{Mg}(\text{ClO}_4)_2$		b			
$\text{Ni}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$		c			

^a Complexation caused only a slight change in the chemical shift of the Me protons. ^b Complexation caused the ^1H n.m.r. spectrum to appear as in Figure 3b. ^c Complexation caused the ^1H n.m.r. spectrum to appear as in Figure 3c.

(viii) *The possibility of a side reaction of acetone.* If the rate of reaction between furan and acetone were to be slow then, under acidic conditions, acetone could undergo self-condensation. The usual method for condensation reactions was followed but the furan omitted. After the usual reaction period (3 h), a sample of the reaction mixture was removed and analysed by g.l.c. The chromatographs showed that only *ca.* 5% of acetone was lost, *i.e.* little acetone self-condensation occurs in the standard reaction. The product formed was mesityl oxide (4-methylpent-3-en-2-one).

(c) *Complexation Studies.*—Two common methods for measuring complexation, u.v.-visible spectroscopy and atomic absorption spectroscopy, were unsuccessful in the case of furan-acetone based macrocycles, the former because no shifts were observed in the λ_{max} values and the latter because of interference from the organic solvents which partitioned into the aqueous phase. The ^1H n.m.r. method, however, was successful.

The cyclic tetramers derived from furan condensed with acetone, butan-2-one, cyclohexanone, and acetaldehyde together with the furan-acetone cyclic hexamer (C_6) were tested with a variety of metal salts. The ^1H n.m.r. spectra of all of these macrocycles were identical without and with added non-paramagnetic metal salts; *i.e.* no complexation occurred.

The saturated macrocycle, (2a), underwent a definite change on addition of metal salts (Figures 3a and b). When an actual analysable complex between compound (2a) and a metal salt was isolated, a more dramatic change in the ^1H n.m.r. spectrum was observed, *e.g.* the complex of (2a) with LiClO_4 (Figure 3c). The Me groups, which were initially inequivalent (Figure 3a), become equivalent on tight binding to Li^+ . Over a long period (48 h) no complexation was observed between compound (2a) and the following salts: NaCl , NaBr , NaI , NaClO_4 , $\text{Na}(\text{picrate})$, KCl , KClO_4 , RbCl , RbClO_4 , CsCl , and CsClO_4 . Some evidence for complexation was observed with other metal salts (Table 5). The macrocycle appeared to form a complex with LiI , LiSCN , and LiClO_4 , as noted previously,⁵ and for these salts substantial changes in the Me resonances took place almost immediately on mixing. Other salts took longer to bind to the macrocycle but, once bound, all such complexes were stable since shaking the CDCl_3 solution with water did not cause the spectra to revert to that of the uncomplexed form (Figure 3a).

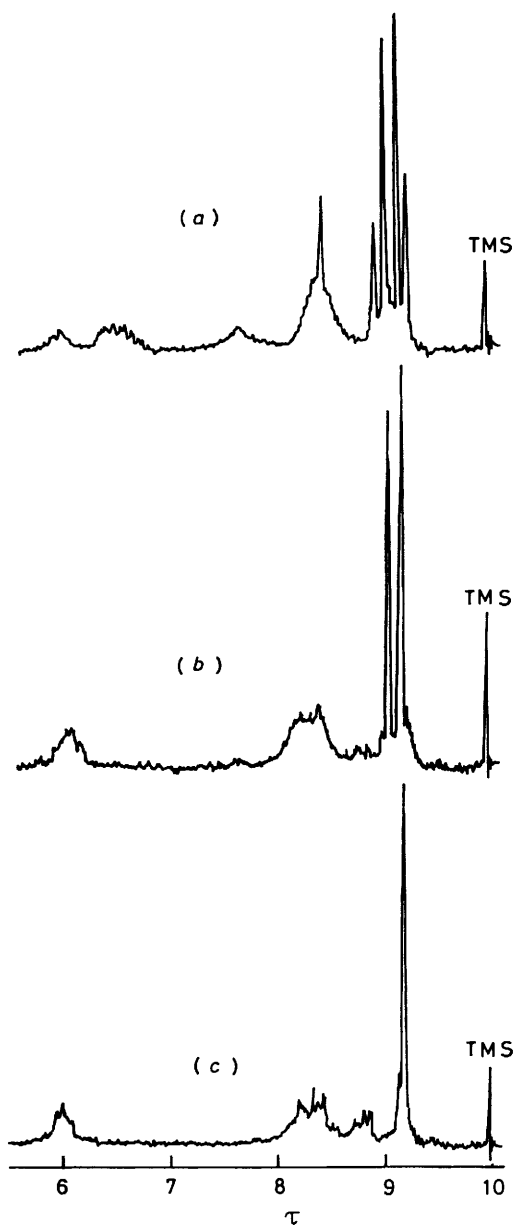


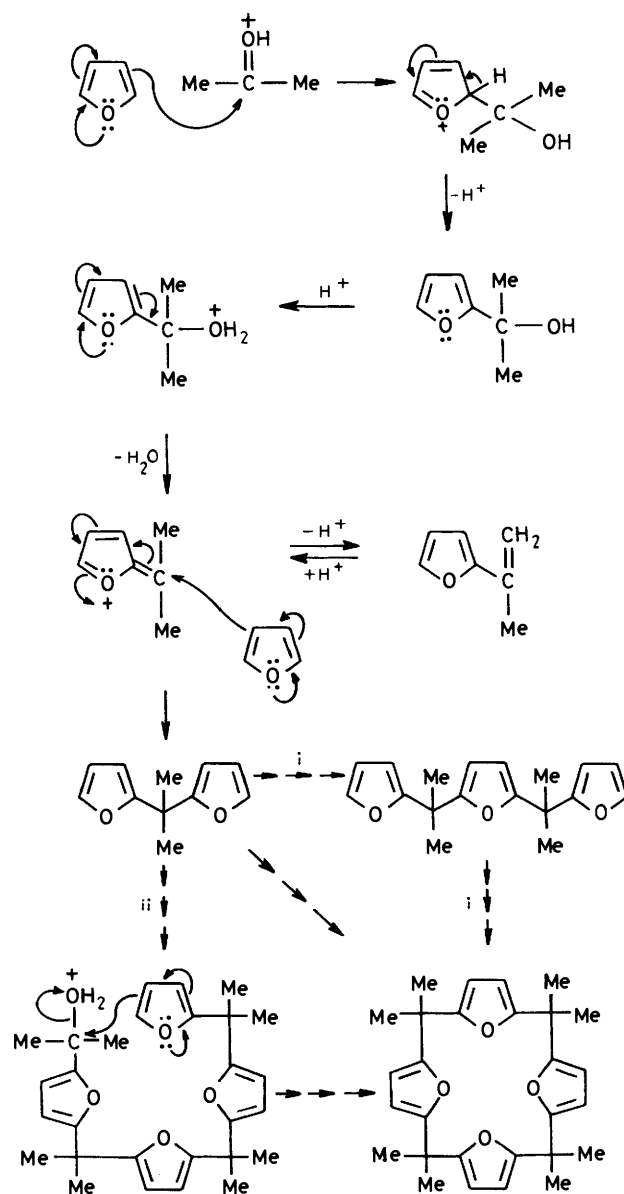
Figure 3. ^1H N.m.r. spectra (100 MHz) of compound (2a): (a) in the absence of metal ions, (b) in the presence of a weakly binding ion, and (c) in the case of the LiClO_4 complex with compound (2a)

No complexation was detected between the tetrahydrofuran–butan-2-one cyclic tetramer nor the tetrahydrofuran–acetone cyclic hexamer and any of the metal salts.

Variable-temperature ^1H n.m.r. spectra were recorded over the range -40 to 68°C but no evidence of Me signal collapse, which would indicate conformational changes, could be detected.

Discussion

At the outset it seems likely that certain metal ions would behave as templates in the condensation of furan with acetone to give enhanced yields of compound (1a),^{5,7} although there were some doubts about the details.⁷ It was proposed, therefore, to harness the metal ion template effect to synthesize new furan–ketone type macrocycles with larger ring sizes, con-



Scheme. Reagents: i, H^+ , THF, Me_2CO ; ii, H^+ , Me_2CO

taining substituents and heteroatoms, e.g. by using thiophene, and to synthesise existing macrocycles in increased yields by single-step rather than multi-step reactions.

The formation of compound (1a) in the absence of metal salts had been proposed to involve the cyclisation of linear dimers, trimers, and tetramers (Scheme).^{4,10} The roles for the metal ion in the processes shown in the Scheme would seem to be two-fold: (1) the metal ion could co-ordinate to the linear tetramer bringing the reacting ends of the molecule close together and facilitating cyclisation by lowering the activation energy; (2) a co-ordination effect could be in operation whereby the metal ion co-ordinates two dimers affording the proximity and favourable orientation for cyclisation. An equilibrium template could also be postulated where the function of the metal would be to complex to compound (1a) and remove it from the equilibrium as a macrocycle–metal complex.

At first sight the results (Table 1) would seem to indicate a strong possibility of a template effect, i.e. the ca. 10% yield of compound (1a) in the absence of metal ions compared to >30%

in the presence of metal salts. If a co-ordination template effect were to be operating then factors such as cation size, charge on the cation, type of counter anion, ligand preference (HSAB), and solubility of the salt should all be important. The variation in cation size (Table 3) should firstly have led to different macrocycles, *i.e.* the larger cations Pb^{2+} , Ag^+ , K^+ , Rb^+ , and Cs^+ might have been expected to yield a cyclic hexamer (C_6) rather than the tetramer (**1a**) which is actually found. Indeed it might have been predicted that these ions would not act as templates for compound (**1a**) because the macrocyclic cavity diameter, estimated from molecular models, is only 1.4–1.7 Å.¹¹ Secondly, transition metal salts, which have a greater affinity for *N*-donor ligands, would not have been expected to afford high yields of compound (**1a**). In reality the transition metal salts gave better yields of compound (**1a**) than most of the alkali-metal salts with the exception of $LiClO_4$ (Table 3). Thirdly, if a template effect were involved, then the formation of metal-(**1a**) complexes would have been expected but none, not even for $LiClO_4$, was observed by 1H n.m.r. spectroscopy. Fourthly, in the absence of metal ions it was found that the yield of compound (**1a**) was crucially dependent on the concentration of conc. HCl (Figure 2)* such that ultimately a yield of 35% was obtained, which is equivalent to the 'best' yield obtained with $LiClO_4$ in a 'normal' reaction. Even more significantly, having optimised the concentration of acid, no further improvement in yield could be achieved by adding $LiClO_4$ and $NiClO_4 \cdot 6H_2O$. It would seem therefore, that the role of the metal salts is in some way connected with the acidity of the reaction medium because, like conc. HCl, the yield depends on the concentration of metal salt, *e.g.* for $LiClO_4$ and an optimum is reached corresponding to the plateau in Figure 1. Aspects of the effective acidity in the reaction medium were confirmed by experiments with a variety of acids, *i.e.* $HClO_4 > HCl > H_2SO_4 \approx HBr \gg HNO_3, H_3PO_4, MeCO_2H$, because these acids will dissociate to differing extents in the furan-acetone-ethanol solution.

The addition of neutral salts to solutions of strong acids in water has been found to have a profound effect on the acidity of these solutions. Some salts, *e.g.* $LiCl$, $NaCl$, $NaBr$, $NaClO_4$, and KCl , produced an increase in acidity whereas large tetra-alkyl ammonium salts, *e.g.* Me_4NBr and Et_4NBr , gave a reduced acidity. The acidity of aqueous $HClO_4$ and HCl in the presence of neutral salts has been measured and found to depend linearly on the concentration of added salt [equation (3)]¹² where $pH_m = pH$ of the solution after the addition of a

$$pH_m = pH_o - 0.0555 M_s(Z_+Z_-)[(h_+/r_+) - (h_-/r_-)] \quad (3)$$

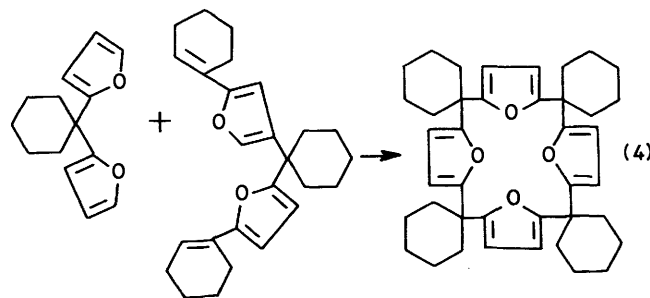
salt of concentration M_s , $pH_o = pH$ of the dilute acid solution, Z_+ and Z_- = charges on the cation and anion respectively, r_+ and r_- = ionic radii of the cation and anion respectively, and h_+ and h_- are functions related to the hydration numbers of the ions. From equation (3) it can be seen that the parameters which will be most important in determining the acidity of a solution are h and r . For a large increase in acidity the added salt must have a cation with a small radius and high hydration factor while the anion must be large and poorly hydrated such that the term $[(h_+/r_+) - (h_-/r_-)]$ will be large and positive. Reported data¹² for aqueous solutions show h_+/r_+ is large for

* It might appear unlikely that acids would promote cyclic polymerisation as opposed to linear polycondensation. In 1886, however, von Baeyer (A. von Baeyer, *Ber.*, 1886, 19, 2184) reported the formation of the tetrapyrrole analogue of compound (**1a**) from the violent reaction of pyrrole with dry acetone on the addition of one drop of HCl. Subsequently, the reaction was made less violent and an 88% yield was obtained (P. Rothmund and C. L. Gage, *J. Am. Chem. Soc.*, 1955, 77, 3340).

Li^+ , Mg^{2+} , Ca^{2+} , and the first row transition metal cations, while h_-r_- decreases along the series $NO_3^- > SCN^- > Cl^- > ClO_4^- > Br^- > I^-$. The maximum acidity would thus be expected for the above-listed cations together with ClO_4^- , Br^- , and I^- anions. The solvation factors (h_+ of Na^+ and K^+) are less than that for Li^+ and hence the heavier alkali metals would be expected to have less effect on the acidity. Non-metal salts whose cations are bulky and poorly hydrated, *e.g.* Et_4N^+ , have been found¹² to decrease the acidity of solutions.

The results obtained for the yields of compound (**1a**) in the presence of metal and non-metal salts show a good correlation (Table 3) with the predictions from equation (3), bearing in mind the extrapolation from an aqueous solution to an EtOH-acetone-furan solution containing variable quantities of water depending on the state of hydration of the salts used. The condensation yields in the presence of Li^+ salts follow closely the expected trend of acidity, *i.e.* increasing in the series $LiCl < LiBr < LiI < LiClO_4$ (Table 3). The anomalous position of $LiClO_4$ in this series may be explained by differences in solubility, *viz* decreasing solubility in the series $LiClO_4 > LiI > LiBr > LiCl$. Other similar anomalies could be also attributed to solubility effects which would prevent the metal salt from exerting the expected effect or affect the acidity [equation (3)].

The condensation of furan with methyl ketones ($MeCOR$, where $R = Et, Pr^n, Bu^n, n-C_5H_{11}, n-C_6H_{13}, n-C_7H_{15}, n-C_9H_{19}$) apparently led to the isolation of macrocyclic tetramers as single isomers (^{13}C n.m.r. spectroscopy) although chemical shift coincidences cannot be ruled out. The isolation of a single isomer could imply that condensations may be influenced by steric factors. The importance of such factors is also suggested in the condensations of furan with cyclopentanone and cyclohexanone where, chemically, these ketones are very similar yet a macrocyclic product was only found for the latter. Models showed that the steric interactions for cyclohexanone are minimal since the ring puckers, but this is not possible for cyclopentanone. Significantly, the presence of metal salts has enabled the furan-cyclohexanone macrocycle to be prepared in a one-step reaction for the first time (16% yield).



Reagents: i, Dry HCl, dioxane

The previous reaction was from the condensation of oligomers [equation (4), 9%¹³].

The decreasing yield of tetrameric macrocycles as the chain length increases in the series $MeCOC_nH_{2n+1}$ is analogous to that found in the synthesis of the analogous porphyrinogens,¹⁴ *e.g.* the condensation of pyrrole with acetone gave 94% yield, with butan-2-one 54%, and benzophenone 3%. This decrease probably arises from differences in the stability of the protonated carbonyl group. For acetone, the inductive effects of the Me group are small and, therefore, the carbonyl group is more electrophilic than for those ketones with larger alkyl chains. The lack of reactivity of acetophenone presumably arises from lack of protonation of its carbonyl group.

In contrast to the successful yield enhancement for long chain ketones, especially in the presence of metal salts, condensations of furan with functionalised ketones were much less successful and only one macrocyclic product was isolated. For example, monochloroacetone was the only ketone to give an identifiable product, the dimer, while condensations with 4-methylpent-3-en-2-one, acetylacetone, and pyruvic acid could not be sufficiently controlled to yield identifiable products in place of tarry resins. The aldehydes, HCHO and MeCHO should have been suitably reactive since their carbonyl groups would be expected to be easily protonated. In the event both HCHO and MeCHO underwent self-condensation. However, some of the macrocyclic tetramer was isolated from the condensation of acetone with MeCHO, although the yield was small (Table 2). The variability in reactions illustrates the importance of the protonation of the carbonyl group, *i.e.* in some cases there is too little while in others too much leads to self-condensation.

The attempted condensation between 3,4-disubstituted furans* and acetone were also unsuccessful, for two possible reasons: firstly steric effects were probably crucial and secondly some substituents in 3,4-disubstituted furans were electron-withdrawing, *e.g.* CO₂H and CO₂Et. These groups could reduce the nucleophilicity of the furan ring to such an extent as to prevent its attack on the protonated acetone. Additionally, some attempted condensations failed because the substituents were so acid-sensitive, *e.g.* CH₂OH and CH₂Cl, that self-condensation predominated over reaction with acetone. The addition of metal salts effected no improvements in the yields. Condensations between furan and thiophene did not lead to macrocyclic products.

The structure of the furan (1a) and tetrahydrofuran (2a) macrocycles resemble those of crown ethers and so similar complexing abilities were expected especially since their cavity diameters (1.4–1.7 Å)¹¹ are able to accommodate a range of metal ions, *e.g.* Li⁺, Mg²⁺, Cr³⁺, Mn²⁺, Fe²⁺, Fe³⁺, Co²⁺, Ni²⁺, Cu²⁺, and Zn²⁺. The use of n.m.r. spectroscopy for diamagnetic ions is a very convenient technique for assessing the degree of complexation. In the cases of furan macrocycles there was no tendency to form complexes with any of the salts tested, which highlights the weak donor ability of the furan oxygens. Increasing the number of donors to 6, as in C₆, did not render this macrocycle any more able to accommodate metal ions so hole size and steric incompatibilities are eliminated. The fully hydrogenated tetrahydrofuran macrocycle (2a) did show evidence of complexation from the changes in spectra (Figures 3a–c) but no complexation was found for the partially hydrogenated macrocycle (3) or the macrocycle (2b). In the cases of the partially hydrogenated macrocycle it is presumably the poor donating ability of the furan units which is still crucial, while for compound (2b) steric factors may be unfavourable. Indeed a model of this macrocycle showed that the Et groups

on the methine bridge are able to rotate freely over the macrocycle cavity and to block the path of incoming cations. Increasing the cavity size and the number of donors to six as in the tetrahydrofuran–acetone cyclic hexamer did not lead to isolable complexes. For this macrocycle complexation was only achieved for CsClO₄ and this complexation was much weaker, *i.e.* less perturbation of the ¹H n.m.r. spectrum than for compound (2a).

Conclusions

This work set out initially to utilise a reported template synthesis to prepare new furan–ketone macrocycles and to improve the yields of known furan–ketone macrocycles. However the demonstrated dependence of yield on pH has shown that the contribution from the template effect is of minor importance in these condensation reactions. A suitable explanation for the action of metal salts has been found in terms of their effect on the acidity of the reaction medium. It appears, therefore, that the role of metal ions in promoting the syntheses of macrocycles is not as simple as it might first appear. Much more attention should be paid, therefore, to the details of reaction conditions, *e.g.* the acidity (*vide supra*). Interestingly, basicity effects have been found¹⁵ to be important in the base-promoted syntheses of 12-crown-4, 15-crown-5, and 18-crown-6 in the presence of alkali and alkaline-earth metal cations.

Acknowledgements

We thank the University of Southampton for support (to M. H.).

References

- 1 M. de Sousa Healy and A. J. Rest, *Adv. Inorg. Chem. Radiochem.*, 1978, **21**, 1.
- 2 C. J. Pedersen, 'Synthetic Multidentate Macrocyclic Compounds,' Academic Press, New York, 1978, ch. 1.
- 3 D. H. Busch, *Acc. Chem. Res.*, 1978, **11**, 392.
- 4 R. G. Ackman, W. H. Brown, and G. F. Wright, *J. Org. Chem.*, 1955, **20**, 1147.
- 5 M. Chastrette and F. Chastrette, *J. Chem. Soc., Chem. Commun.*, 1973, 534.
- 6 M. Chastrette, F. Chastrette, and J. Sabadie, *Org. Synth.*, 1977, **57**, 74.
- 7 A. J. Rest, S. A. Smith, and I. D. Tyler, *Inorg. Chim. Acta*, 1976, **16**, L1.
- 8 M. de Sousa Healy and A. J. Rest, *J. Chem. Soc., Chem. Commun.*, 1981, 149.
- 9 M. de Sousa Healy, Ph.D. Thesis, University of Southampton, 1981.
- 10 W. H. Brown and R. J. Hutchinson, *Can. J. Chem.*, 1978, **56**, 617.
- 11 A. Corsini and J. M. Panoyan, *J. Inorg. Nucl. Chem.*, 1977, **39**, 1449.
- 12 K. Schwabe, *Electrochim. Acta*, 1967, **12**, 67.
- 13 W. H. Brown, B. J. Hutchinson, and M. H. Mackinnon, *Can. J. Chem.*, 1971, **49**, 4017.
- 14 R. L. N. Harris, A. W. Johnson, and I. T. Kay, *Quart. Rev. Chem. Soc.*, 1966, **20**, 211.
- 15 B. R. Bowsher and A. J. Rest, *J. Chem. Soc., Dalton Trans.*, 1981, 1157.

* Condensation with 3,4-disubstituted furans bearing electron-donating substituents may have been more successful but such reagents were not available and their synthesis was beyond the scope of this investigation because the synthetic routes are very complicated.