Role of Metal Salts in the Synthesis of 1,1,7,7,13,13,19,19-Octamethyl-[1.1.1.1](2,5)Furanophan

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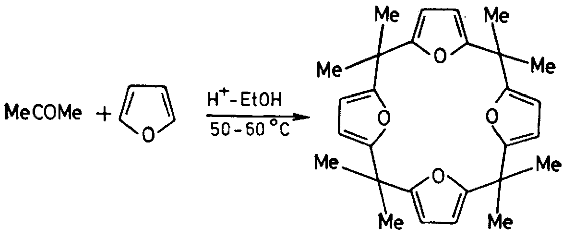
Summary The importance of pH, rather than a metal ion template effect, in the synthesis of a macrocycle is demonstrated for the first time; the results are correlated with the effect of added salts on the acidity of the reaction medium.

The addition of metal ions often leads to dramatic increases in yields in syntheses of macrocycles; these increases 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] Template effects fall into three broad categories:[1] (i) kinetic or co-ordination template effects, where a macrocyclic product is formed which is not formed in the absence of metal ions; (ii) thermodynamic template effects, where the *same* macrocycle is formed in the presence and absence of metal ions but the metal ion promotes macrocycle formation by removing it from the equilibrium mixture as a macrocycle–metal complex; (iii) equilibrium template effects, which represent a combination of the two previous effects except that *different* products are formed in the metal-assisted and metal-free reactions.

When acetone and furan are condensed in an acidic medium (equation 1) an increased yield of the macrocycle (**1**) was obtained[4] in the presence of metal salts [up to 40—45% ($LiClO_4$)† compared to 18—20% (conc. HCl alone)[6]]. The increase in yield was attributed[4] to a template effect between the furan rings and the metallic cations, although these cations showed no tendency to form isolable complexes with (**1**).



(1)

(1)

Work from this laboratory[7] suggested that the improved yields might not simply be due to a template effect, because transition metal salts whose metal ions show little tendency to co-ordinate ether oxygens in general, and furan oxygens in particular, also gave improved yields of (**1**). We now report evidence to show that increases in the yield of (**1**) can be attributed to acidity (pH) effects rather than to a metal ion template effect.

On varying the acid concentration in the reaction (equation 1)‡ it was found that the yield§ of (**1**) depended critically on the acid concentration, such that a maximum yield of 34% was obtained in the reaction employing 8 ml of conc. HCl, and further addition of conc. HCl gave no improvements in yield (Table 1). Addition of varying amounts (up to 0·2 mol) of good templating agents, *e.g.* $LiClO_4$[4] and $Ni(ClO_4)_2.6H_2O$,[7] no longer had any impact on the yield of macrocycle. The role of metal salts, therefore, must be connected in some way with the acidity (pH) of the reaction medium.

Table 1. The effect of varying quantities of conc. hydrochloric acid on the yield of (**1**).

Volume of conc. HCl/ml	Yield/%
0	0
1·0	2·8 ± 0·2
2·0	12·9 ± 0·6
3·0	22·8 ± 1·1
4·0	25·1 ± 1·3
5·0	28·2 ± 1·4
6·0	31·3 ± 1·6
7·0	32·7 ± 1·6
8·0	33·7 ± 1·7
9·0	34·3 ± 1·7
10·0	34·1 ± 1·7

Schwabe[9] has shown that the effect of added salts on the acidity of an aqueous solution depends on the size, charge, and solvation properties of the ions according to equation (2)

$$\mathrm{pH_m} = \mathrm{pH_0} - 0{\cdot}0555\, \mathrm{M_S}(Z_+Z_-)\,[h_+/r_+ - (h_-/r_-)] \qquad (2)$$

where $\mathrm{pH_m}$ = pH of the solution after the addition of a salt of concentration $\mathrm{M_S}$; $\mathrm{pH_0}$ = pH of the dilute acid solution; Z_+ and Z_- = charges on the cation and anion

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† Subsequently the authors revised this yield to 24–25%[5] 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 previously[4] to assess the reaction yield.

‡ Acetone (0·1 mol) and conc. HCl were added to absolute ethanol (3 ml) with continuous stirring and then furan (0·05 mol) was added rapidly. The reaction flask was immersed in a water bath and maintained at 60 °C for 3 h. After stirring overnight at room temperature, water (25 ml) was added and the suspension was extracted with benzene (30 ml). The benzene layer was washed (5% sodium hydrogen carbonate solution) and dried (anhydrous $MgSO_4$). Evaporation of the solvent gave an off-white oily substance which, on washing (EtOH) and drying *in vacuo*, gave a white powder, which was recrystallised (benzene) to give a white solid characterised as (**1**),[4–6] m.p. 240—243 °C, by ^1H n.m.r. [τ 4·12 (s, 8H) and 8·55 (s, 24H)].

§ Yields (%) were based on furan and were initially determined from the weight of pure recrystallised product. This was a lengthy procedure because the crude reaction product was a mixture. G.l.c. [Pye-Unicam GCD chromatograph, column (length 1·5 m, internal diameter 5 mm) packed with silicone oil (5% type OV17) on Chromosorb w (80—100 mesh), detection temp. 300 °C, injection temp. 280 °C, column temp. 250 °C] proved[8] to be an accurate (± 5%) and rapid means of determining the composition of the crude reaction product.

respectively; r_+ and r_- = ionic radii of the cation and anion respectively; and h_+ and h_- are functions related to the hydration requirements of the ions. From equation (2) 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 of small radius with a high hydration factor while the anion must be large and poorly hydrated so that the term $[(h_+/r_+) - (h_-/r_-)]$ will be large and positive. Reported data[9] for aqueous solutions show that h_+/r_+ is large for Li^+, Mg^{2+}, Ca^{2+}, and the first row divalent 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 abovementioned 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 these ions would be expected to have less effect on the acidity. Non-metal salts whose cations are large and poorly hydrated, *e.g.* Et_4N^+, have been found[9] to *decrease* the acidity of solutions. The results obtained for the yields of (**1**) in the presence of metal and non-metal salts show a good correlation (Table 2) with the predictions from equation 2, bearing in mind the extrapolation from an aqueous solution to an EtOH–acetone solution containing variable quantities of H_2O depending on the state of hydration of the salts used. Additionally, when the reaction was carried out in the presence of equimolar amounts of acids, the yield of (**1**) again could be correlated with acid strength,¶ *i.e.* $HClO_4 > HCl, H_2SO_4, HBr >> H_3PO_4, CH_3CO_2H$.

TABLE 2. The effect of salts (0·1 mol) on the yield of (**1**).[a]

Salt	Yield/%[b]	Salt	Yield/%[b]
LiCl	16·0 ± 0·8	$CrCl_3 \cdot 6H_2O$	28·0 ± 1·4
LiBr	17·5 ± 0·9	$Cr(ClO_4)_3 \cdot 6H_2O$	30·8 ± 1·5
LiI	19·0 ± 1·0	$MnCl_2 \cdot 4H_2O$	26·0 ± 1·3
$LiClO_4$	35·0 ± 1·7	$Mn(ClO_4)_2 \cdot 6H_2O$	33·0 ± 1·6
		$FeCl_2 \cdot 4H_2O$	6·6 ± 0·3
NaCl	8·5 ± 0·4	$Fe(ClO_4)_2 \cdot 6H_2O$	28·0 ± 1·4
NaBr	6·0 ± 0·3	$CoCl_2 \cdot 6H_2O$	26·3 ± 1·3
NaI	8·0 ± 0·4	$Co(ClO_4)_2 \cdot 6H_2O$	33·8 ± 1·7
$NaClO_4$	13·6 ± 0·7	$NiCl_2 \cdot 6H_2O$	11·0 ± 0·5
		$Ni(ClO_4)_2 \cdot 6H_2O$	32·0 ± 1·6
KCl	4·0 ± 0·2	$CuCl_2 \cdot 2H_2O$	17·0 ± 0·8
$KClO_4$	8·0 ± 0·4	$Cu(ClO_4)_2 \cdot 6H_2O$	30·7 ± 1·5
		$ZnCl_2$	25·0 ± 1·2
$MgCl_2$	12·0 ± 0·6	$Zn(ClO_4)_2 \cdot 6H_2O$	29·8 ± 1·5
$Mg(ClO_4)_2$	23·6 ± 1·2		
$Ca(ClO_4)_2 \cdot 6H_2O$	31·0 ± 1·5	$[Bu^n_4N]Cl$	5·0 ± 0·3
		$[Bu^n_4N]ClO_4$	6·4 ± 0·3

[a] In the absence of salts the reaction [absolute ethanol (12 ml), acetone (0·4 mol), furan (0·2 mol), and conc. HCl (8 ml)] gave a 7·0% yield of (**1**). [b] The yield was estimated on the basis of a pure recrystallised product rather than on the crude reaction product, as in ref. 4. Hence these yields are lower than those reported in ref. 4. Other contributions to the yield of crude reaction products came from linear tetramer, linear hexamer, and cyclic hexamer, and amounts of these varied with the different metal ions (Ref. 8).

The size, charge, and solvation property requirements for metal ions in respect of acidity (equation 2) are very similar to the factors which govern the ability of metal ions to act as templates for macrocycle synthesis; *cf.* the original proposal[4] for the increased yield of (**1**) in equation (1). It appears that the role of metal ions in promoting the synthesis of macrocycles is not necessarily as simple as might first appear. Much more attention should be paid, therefore, to the details of reaction conditions, *e.g.* acidity (*vide supra*). Interestingly, basicity effects have been found[10] to be important in the base-catalysed synthesis of 12-crown-4, 15-crown-5, and 18-crown-6 in the presence of alkali and alkaline-earth metal cations.

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¶ 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 (**1**) from the violent reaction of pyrrole with dry acetone on the addition of *one* drop of hydrochloric acid. Subsequently, the reaction was made less violent and an 88% yield was obtained (P. Rothemund and C. L. Gage, *J. Am. Chem. Soc.*, 1955, **77**, 3340).

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