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The Template Synthesis of 2,2,7,7,12,12,17,17-Octamethyl-21,22,23,24-tetraoxaquaterene: Factors Affecting the Choice of Template Agent

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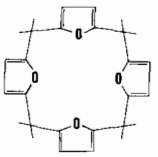
Introduction

The major problem in many macrocycle syntheses is the low yield of the reaction due to other, more favourable, competing reactions. The addition of a metal ion can often bring about a dramatic increase in the yield of macrocycle and this increase is ascribed to the "template effect" action of the metal.[1]

The reaction between acetone and furan in strong acid shows a template effect in the presence of a number of group I and group II metal salts, leading to an improved yield of the macrocycle I.[2]



I

The metal ions used[2] were those known to bind strongly to macrocyclic polyethers.[1] The template effect of transition metals with respect to I was not investigated[2] in spite of their known template effect in the synthesis of nitrogen and sulphur macrocycles.[3-5] We report the use of transition metals in the synthesis of I and discuss factors affecting the optimum choice of template agent.

Experimental

All reactions were performed under similar conditions unless specified. A mixture of metal salt (0.1 mol), ethanol (30 ml), acetone (0,4 mol) and concentrated hydrochloric acid (16 ml) was stirred vigorously at 20 °C in a 250 ml conical flask fitted with an *efficient* reflux condenser. Furan (0.2 mol) was added rapidly with stirring. After 48 hours water (10 ml) was added with stirring and the product extracted into benzene (3 X 50 ml aliquots). Removal of the benzene left an off-white oily solid, which, on washing with ethanol gave a white crystalline product. Yields were estimated on this product after careful vacuum drying (10^{-2} torr, 2 hours) to remove ethanol. M.Pt. (235–40; 243–44 °C after recrystallising from benzene) agreed with the literature value.[6]

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TABLE I. Influence of Metal Salt on the Yield of I.

Metal Salt	% Yield	
	This work[a]	Ref. 2[b]
$LiClO_4$	43–48[a,c]	40–45
$Mg(ClO_4)_2$	38–40[d]	39–43
$Ni(ClO_4)_2 \cdot 6H_2O$	35–39[d]	
LiCl	30–35	27–30
$MCl_2 \cdot 6H_2O$ (M = Mn, Co, Ni, Cu)	25–32	
NaCl	6–10	no effect[e]
KCl	5– 6	no effect[e]
Li_2SO_4	26–30[d]	
No metal added	1–2; 1[d]; 15–18[f]	18–20

[a] Reaction at 20 °C for 48 hours unless otherwise stated. [b] Reaction at 60 °C for 8 hours and then stirred overnight. [c] Reaction at 20 °C for 1 hour. [d] Reaction at 40–50 °C for 3½ hours. [e] No yield enhancement over and above the no added metal reaction. [f] Reaction at 40–50 °C for 48 hours.

Results and Discussion

The results (Table I) show a good agreement with previous work[2] for the metals common to both studies in spite of the differences in reaction conditions. The beneficial effect of alkali and alkaline earth metals had been noted previously[2] but we report here that transition metals give enhanced yields of I, Yield enhancement with a common metal varies in the order $ClO_4^- > Cl^- > SO_4^{2-}$. The trend $ClO_4^- > Cl^-$ had been observed previously[2] but the more extensive data in our study underlines the importance of the counter anion in the template effect. The determining factor is not merely solubility (NaCl and KCl almost totally insoluble; $M(H_2O)_6Cl_2$ salts only slightly soluble) as was suggested previously$_2$ to explain the lack of effect of NaCl and KCl, but a combination of solubility and the ability of the salt to dissociate in the reaction medium. For a particular anion the nature of the metal is important in determining the degree of dissociation which is related to ionic size, hence the

effectiveness of Li^+. The preference of metals for types of ligands, as a means of choosing an effective template agent, is clearly not crucial as demonstrated by similarity in yield of I (Table I) for Ni and Mg.

It would seem that considerations of ligand preference and coordination preference are not the only factors in the choice of a template agent to give the optimum yield of a particular macrocycle but that often the nature of the template effect is very subtle so that a variety of metal salts should be investigated.

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