Template Effect in Synthesis of Furan Compounds

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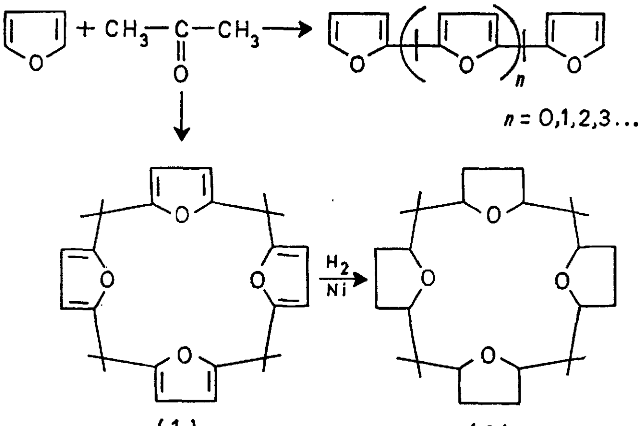
Summary A template effect between furan rings and several metallic cations leads to an improved yield of a 16-membered heterocyclic ring which does not form any addition complex with salts, while the corresponding saturated ring gives 1 : 1 complexes with lithium perchlorate and thiocyanate.

The complexing ability of macrocyclic polyethers for metallic cations is well established; several template syntheses of these compounds have been performed.[1] We now report results concerning a polyoxygenated heterocyclic compound in which the oxygen atoms, being involved in aromatic heterocycles, are only weakly basic.

It is known[2] that compound (**1**), a 16-membered ring with 4 oxygen atoms, is obtained in low yield when acetone and furan are condensed in an acidic medium in the correct amounts; products of linear condensation are formed together with (**1**). We found that, in the presence of several salts, the yield of the cyclic compound (**1**) is much enhanced. For example, when acetone (0·2 mol) reacts with furan (0·1 mol) at 50—60° in ethanol (15 ml) and concentrated hydrochloric acid (8 ml), 18—20% of (**1**) is obtained; in the presence of 0·03—0·1 mol lithium perchlorate, 40—45% of (**1**) is obtained. Other perchlorates behave similarly (calcium, zinc, magnesium; yield of cyclization 39—43%). With tetrabutylammonium perchlorate no effect is observed



(1) (2)

(19% yield). Some chlorides also enhance the yield of cyclization, although to a lesser extent than the perchlorates (lithium, calcium, magnesium; 27—30% yield); tetrabutylammonium chloride markedly decreases the yield of cyclization ($\leqslant 10\%$). Some salts (potassium perchlorate, sodium and potassium chlorides) appear to have no effect, because of their insolubility.

It appears that in the presence of a metallic salt, the oxygen atoms of the furan rings in the transition state are disposed around the cation, so that cyclization is favoured with respect to linear condensation; in the presence of a tetrabutylammonium salt the furan rings, solvating the Bu_4N^+ cation to a small extent, are randomly disposed and lead mostly to linear condensation.

The difference between perchlorates and chlorides may be due to a catalytic effect of the ClO_4^- anion, as suggested by an experiment in which the addition of 0·03 mol $HClO_4$ led to a 28% yield of cyclization, and/or to a smaller dissociation of chlorides. The absence of effect with tetrabutylammonium perchlorate shows that a template effect is operating.

This observed template effect indicates that even in a furan ring oxygen has a noticeable donor strength towards cations. This strength is low, and we were unable to prepare addition complexes between (**1**) and metallic salts. When hydrogenated at 170° at 16×10^6 Nm^{-2} with Raney nickel in ethanol, (**1**) led to (**2**) which gave, as expected, addition complexes with lithium salts (perchlorate† and thiocyanate). These products, soluble in chloroform, have i.r. and n.m.r. spectra which distinguish them from uncomplexed (**2**). Their n.m.r. spectra show only one peak for all the CH_3 protons and one multiplet for the α protons (adjacent to the oxygen atom on the rings), while the spectrum of uncomplexed (**2**) shows several kinds of CH_3 protons and two kinds of α protons. So when complexed by Li^+, the macrocycle takes a particular conformation. The influence of complexation on the geometry of polyoxygenated compounds has been reported.[1b,c] No complexes between (**2**) and other salts could be obtained.

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† 1 : 1 stoicheiometry from microanalysis.

[1] (a) C. J. Pedersen and H. K. Frensdorff, *Angew. Chem. Internat. Edn.*, 1972, **11**, 16; (b) J. Dale and P. O. Kristiansen, *Chem. Comm.*, 1971, 670; *Acta Chem. Scand.*, 1972, **26**, 1471; (c) J. Dale and J. Krane, *J.C.S. Chem. Comm.*, 1972, 1012; (d) R. N. Greene, *Tetrahedron Letters*, 1972, **18**, 1793.

[2] R. G. Ackman, W. H. Brown, and G. F. Wright, *J. Org. Chem.*, 1955, **20**, 1147.