Formation of substituted macrocyclic ethers by radical cyclisation

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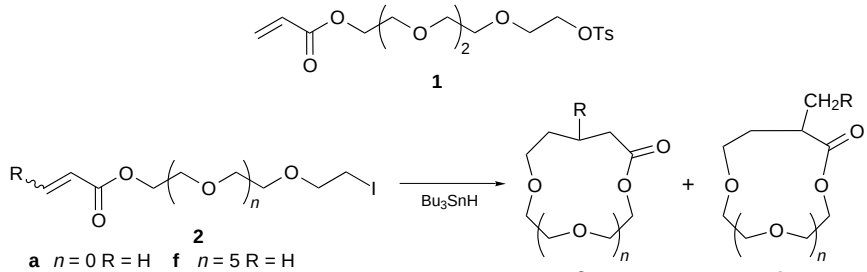
ω-Iodopolyoxaalkyl acrylates and related compounds undergo radical cyclisation when treated with tributylstannane to afford substituted macrocylic polyethers.

3-Oxahex-5-enyl radicals (CH_2=$CHCH_2OCH_2CH_2$·) undergo *exo* cyclisation about 25 times more rapidly at 80 °C than do hex-5-enyl radicals.[1,2] Similarly the 2-allyloxyphenyl radical cyclises much more rapidly than its all carbon analogue.[3] The effect of an oxygen atom in the chain on the rates of cyclisation of these and related species has been attributed to the decrease in the strain energy of the cyclisation transition structures resulting from the replacement of a carbon atom by oxygen,[1,4] an hypothesis supported by molecular mechanics calculations.[4] These observations suggested that the ring closure of radicals derived from suitable polyether precursors might proceed relatively rapidly. Here we show that such radicals do indeed cyclise more readily than their all-carbon analogues, and that this method provides a viable alternative to ionic reactions as a route to macrocyclic polyethers of potential utility as ionophores.

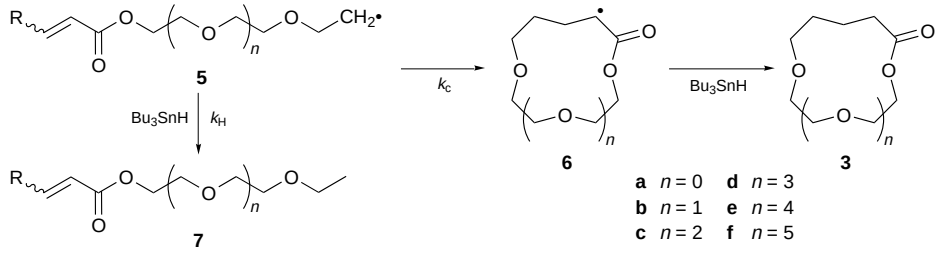
Suitable radical precursors **2a–j** were readily prepared from ethylene glycol oligomers. In a typical example, treatment of the monotosylate of tetraethylene glycol[5] with acryloyl chloride and Hünig's base gave the acrylate **1** (92%) which was converted into the iodide **2c** (95%) on stirring with sodium iodide in acetone. In some cases the oligomeric ethylene glycol was first esterified by treatment with an acid chloride and triethylamine and the iodide was then prepared *via* the mesylate. Heating of each of the compounds **2b–j** with 1.1 molar equivalents of tributylstannane (0.01 mol dm^{-3}) and AIBN as catalyst in benzene under reflux for 2 h gave the corresponding cyclic polyethers **3b–j** (and in some cases **4g–j**), but no cyclised product could be obtained from **2a**. Uncyclised products formed by direct hydrogen atom transfer to the initially formed radicals were also detected. Their formation allowed the estimation of the rate constants for cyclisation on the basis of the mechanism shown in Scheme 1. Accurate GC analysis of the product mixtures and treatment of the data in the usual way[6] gave values of k_c/k_H which, when combined with the rate constant for hydrogen transfer from tributylstannane to a primary radical (k_H = 6.3 × 10^6 dm^3 mol^{-1} s^{-1} at 80 °C),[7] gave k_c at 80 °C. The results presented in Table 1 show that the radicals **5b** and **5c**, respectively, cyclise 30 and 10 times faster than their all-carbon-chain analogues (k_c = 4.8 × 10^3 and 1.2 × 10^4 s^{-1} at 80 °C, calculated from data in the literature[8]).

Each of the substrates **2b–f** undergoes exclusive *endo* cyclisation to give **3b–f**, but substrates **2g–j** bearing an activating substituent at the remote end of the acrylate double bond also undergo some *exo* cyclisation. Interestingly, the maleate ester **2h** and the corresponding fumarate **2g** cyclise with slightly different *endo* : *exo* ratios of 43 : 57 and 58 : 42, respectively. As measured approximately by NMR the ratio was 1 : 1 for cyclisation of **2i**. In an attempt to improve the *endo* : *exo* selectivity we examined the behaviour of the ester **2j**[9] bearing the bulky *tert*-butyl group. However, once again the **3j** : **4j** ratio was about 1 : 1.

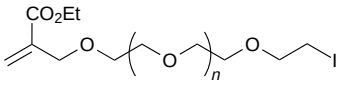
Consideration of the competing reactions available to the various radicals involved in these cyclisations suggested that the



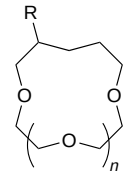
Scheme 1



formation of cyclised products should be improved by conducting the experiments with very low concentrations of both the iodoacrylate and Bu_3SnH, thus respectively decreasing of the formation of oligomers and the rate of hydrogen atom transfer to uncyclised radicals. Because such high dilution conditions require the use of very large quantities of solvent for the production of small amounts of products, they are of no interest for preparative purposes. However, the same effect was obtained by the separate slow addition with syringe pumps of both Bu_3SnH and iodoacrylate to a solution of AIBN in benzene (method A). Under these conditions cyclised products were isolated in modest to good yield (Table 2). In an alternative procedure the precursors were heated with 1.1 molar equivalents of Bu_3SnH (0.01 mol dm^{-3}), AIBN and sodium tosylate (method B). The role of the sodium tosylate is still uncertain but it certainly promotes cyclisation. Each of these methods is suitable for the convenient preparation of macrocyclic polyethers on a gram scale.



8 $n = 1$
9 $n = 2$



10 $n = 1$ R = CO_2Et
11 $n = 2$ R = CO_2Et
12 $n = 2$ R = CO_2H
13 $n = 2$ R = CH_2OH

Table 1 Cylisation rate constants for polyether radicals in benzene at 80 °C

Radical	$k_c \times 10^{-4}/s^{-1}$	Radical	$k_c \times 10^{-4}/s^{-1}$
5b	15 ± 4	**5c**	13 ± 1
5d	5.1 ± 0.8	**5e**	10 ± 2
5f	3.0 ± 04		

Table 2 Formation of macrocyclic polyethers by radical cyclisation

Substrate	Ring size	Products [yield (%)]
2a	9	**3a**
2b	12	**3b** (78[a])
2c	15	**3c** (72[a], 78[b])
2d	18	**3d** (70[a], 87[b])
2e	21	**3e** (63[a], 90[b])
2f	24	**3f** (30[a])
2g	12/11	**3g** (37[a] **4g** (21[a])
2h	12/11	**3h** (43[a,c]) **4h** (57[a,c])
2i	15/14	**3i** (36[d]) **4i** (36[d])
2j	15/14	**3j** (29[d]) **4j** (29[d])

[a] Method A (see text); isolated yields. [b] Method B (see text); yields determined by GC with an internal reference. [c] Relative yield; for this reaction the absolute yield was not determined. [d] Method B; total yield determined by GC; relative yields by NMR.

Finally we examined the preparation of macrocycles that do not contain a lactone group within the ring and hence should be able to survive robust manipulation of the side chain. Thus treatment of the ester **8** with Bu_3SnH in the usual way gave **10** (64%) with a rate constant for cyclisation of $k_c = 2 \times 10^4\ s^{-1}$ at 80 °C, while **9** gave **11** (87%). An advantage of products such as **10** and **11** is that the side chain can be readily converted into functionality suitable for tethering the macrocycle to other ionophores or to fluorescent agents. Thus **11** readily underwent hydrolysis with KOH in methanol to afford the acid **12** (84%) while reduction with LAH in THF gave the alcohol **13** (79%).

In conclusion it appears that, as in the case of simple hexenyl species, the introduction of oxygen atoms into suitable long chain precursors enhances the rate of radical cyclisation sufficiently to allow the preparation of substituted macrocyclic polyethers in modest to good yield under convenient experimental conditions. These results therefore complement those describing other applications of radical macrocyclisation in synthesis.[10,11] Preliminary experiments indicate that some of the macrocyclic polyethers described above may be useful as complexing agents.

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