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Synthesis of soluble combinatorial libraries of crown ether-ester analogues *via* the cyclodepolymerisation of linear polyesters

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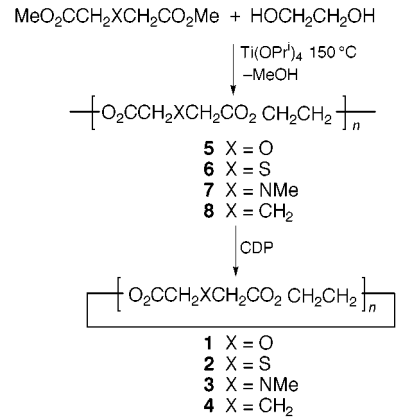
Cyclodepolymerisation of functional linear polyesters gives macrocycles which, on equilibration *via* transesterification, give soluble combinatorial libraries of crown ether-ester analogues, one consisting of 30 different 18- or 27-membered rings and another consisting of 29 different 24- or 36-membered rings.

Combinatorial chemistry has great potential to assist in solving a wide variety of chemical problems.[1,2] Most frequently to date it has involved the synthesis of combinatorial libraries on insoluble polymer supports and the target molecules have been peptides[3] or potential pharmaceuticals.[4] There are, however, other synthetic approaches and other targets of interest, for example, the synthesis of libraries in solution[5] and the synthesis of libraries to assist in the optimisation of recognition properties.[6]

Cyclic oligomers can often be prepared efficiently by the cyclodepolymerisation (CDP) of condensation polymers.[7,8] CDP involves treating a dilute solution, typically *ca.* 2% w/v, of an appropriate polymer with a catalyst that brings about the cleavage and reformation of the polymer linkages. At low concentrations the formation of cyclics is much more likely than the formation of chains. Thus, treating linear polyesters in dilute solution with a transesterification catalyst affords cyclic oligoesters in excellent yields.[7] Crown ethers are an important class of compounds, many of which can recognise cations, and we now report that CDP can be used to synthesise soluble libraries of crown ether-ester analogues made up of 18-membered and 27-membered rings containing all the combinations of the moieties in cyclics **1**–**4** and of 24- and 36-membered rings made up of all the combinations of the moieties in cyclics **13** and **14**. Although in the 18-membered ring family the binding of cations is expected to be achieved mainly *via* the ether, thioether or *tertiary* amine moieties,[9] as the rings become larger binding may also be achieved through the ester carbonyl groups. The natural ionophore valinomycin, for example, a depsipeptide which has a 36-membered ring, binds K^+ with high selectivity using the carbonyl groups of six ester linkages.[10]

Polymers **5**–**8** were synthesised by standard procedures from the appropriate dimethyl ester, ethylene glycol, and a catalytic amount of titanium isopropoxide (Scheme 1). The yields and the molecular weight data of the products are summarised in the Table. Treatment of 2% w/v solutions of each individual polymer in chlorobenzene with 2 mol% of di-*n*-butyltin oxide at 183 °C brought about CDP and the formation of the expected series of cyclic oligomers.[11] Although the reactions were substantially complete in 24 h, they were nevertheless carried out for 7 days to ensure that equilibrium was reached. It is evident from the results, summarised in Table 1, that the cyclic fractions from polymers **5**–**8**, generally isolated by passing the crude product down a short column of alumina, consisted of 61–80% of the 18-membered ring dimers (**1**–**4**; $n = 2$), and 14–18% of the 27-membered ring trimers (**1**–**4**; $n = 3$). Larger cyclic oligomers were also present[11] but only the dimers and trimers were considered to be present in sufficient amounts to be useful in the present project. It is clear that none of the functionalities involved caused the formation of, say, a particular cyclic trimer to be much more heavily favoured than any other. Thus, the various motifs present were expected to 'mix' well in combinatorial experiments.

When an equimolar mixture of the cyclics from each of the three polymers **5**, **6** and **8**, as a 2% w/v solution in chlorobenzene, was treated with 3 mol% of di-*n*-butyltin oxide

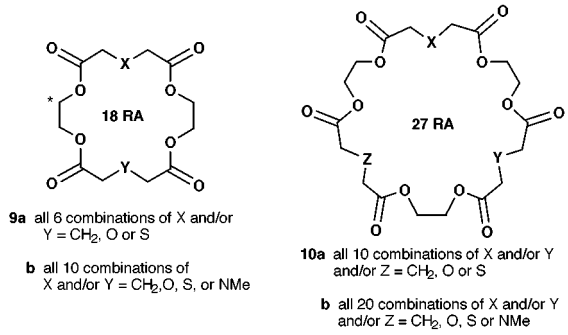


Scheme 1

Table 1 Properties of polymers and the composition of the CDP products

Starting polymer	Yield (%)	$\overline{M}_n$[a]	$\overline{M}_w$[a]	Yield of cyclic oligomers (%)	Composition of CDP product (%)[b]		
					Cyclic dimer	Cyclic trimer	Other cyclics
5	92	1 500	2 300	53	74	17	9
6	56	3 000	4 300	70	66	18	16
7	54	19 200	28 700	69	80	14	6
8	74	14 300	25 400	94	61	17	22
11	81	1 700	2 200	71	51	21	14
12	83	2 900	4 300	61	48	19	31

[a] By GPC relative to polystyrene standards. [b] By GPC on a column specifically designed to analyse oligomers. The materials unaccounted for were either linear oligomers or polymer.



9a all 6 combinations of X and/or Y = CH_2, O or S

b all 10 combinations of X and/or Y = CH_2,O, S, or NMe

10a all 10 combinations of X and/or Y and/or Z = CH_2, O or S

b all 20 combinations of X and/or Y and/or Z = CH_2, O, S or NMe

at 183 °C for 7 days, equilibration was achieved through transesterification and the product contained all the six expected combinations of the cyclic 'dimers' **9a** (75% by weight by GPC analysis) and all the ten expected combinations of the cyclic 'trimers' **10a** (15% by weight). Similar mixtures could be prepared directly by mixing the polymers **5**, **6** and **8** and subjecting them to CDP. The positive-ion chemical ionisation mass spectrum of the equilibrated products showed major signals for every expected combination. The relative sizes of the signals in mass spectra do not accurately reflect the proportions of the various species present, but by ^{13}C NMR spectroscopy it was shown that the amounts of all the cyclic 'dimers' were the same within a factor of 2, the most useful signal being that asterisked in **9**. The position of this signal is sensitive to the type of groups at both X and Y. This region of the ^{13}C NMR spectrum is shown in Fig. 1. There is no reason to doubt that the cyclic 'trimers' **10a** were also all present in comparable amounts. A mixture of the four polymers **5**–**8** was equilibrated similarly. The positive-ion chemical ionization mass spectrum of the product showed significant signals for all 10 combinations of 'dimers' **9b** and all 20 combinations of 'trimers' **10b**.

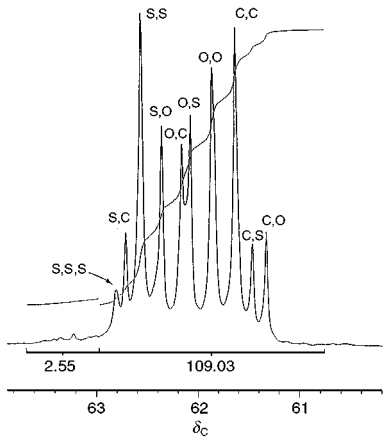
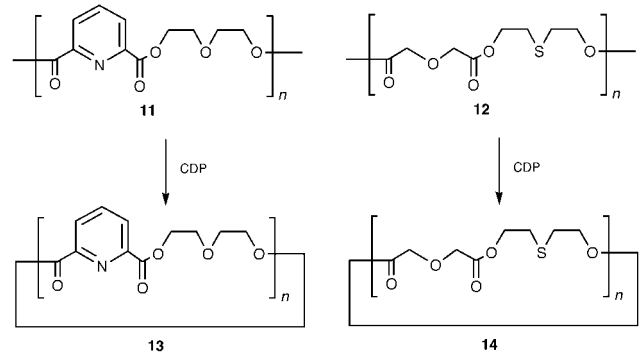
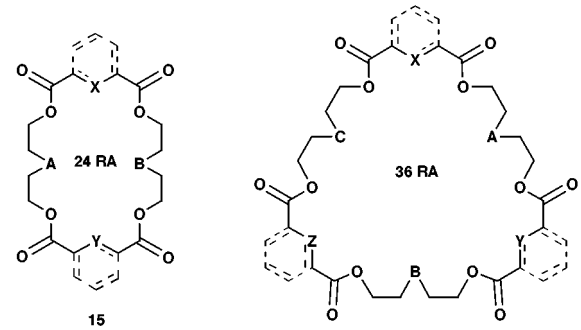


Fig. 1 Part of the ^{13}C NMR spectrum of the mixture obtained by equilibrating cyclic oligomers **1**, **2**, and **4**. The part of the spectrum shown is due to the asterisked carbon atoms in **9**. Assignments were made on the basis of studies of the NMR spectra of the pure cyclic dimers and combinatorial mixtures prepared from just two types of cyclic oligomers.

Polymers **11** and **12** were similarly prepared, characterised and subjected to CDP (Scheme 2, Table 1). In these cases the proportions of the cyclic dimers (24-membered rings) and trimers (36-membered rings) were *ca.* 2.:1 by weight. Equilibration of the cyclics from the two polymers gave solutions containing, as judged by positive-ion chemical ionisation and MALDI-TOF mass spectrometry, libraries of all nine combinations of the 24-membered rings (**15**) and all 20 combinations of the 36-membered rings (**16**). In this system the total number of possible combinations is enhanced because there is a choice in both the diacid and diol segments of the macrocycles, and, in some 'trimers', a choice in the sequence of the segments which results in isomer formation.



Scheme 2



All 9 combinations of X and/or Y = O or pyridine and A and/or B = O or S

All 20 combinations of X and/or Y and/or Z = O or pyridine and A and/or B and/or C = O or S

Research related to the above has been carried out by Sanders' group.[12–14] They have prepared macrocyclic esters directly from monomers and equilibrated *pairs* of families of the macrocycles. In their work most of the building blocks were rigid,[12–14] and, unlike in the present study, not all pairs of rings 'mixed' well.[13] Successful mixing could, however, be achieved by including ephedrine derivatives, which are relatively flexible, in the equilibrating system.[14]

Having shown that libraries of cyclic recognition systems can be prepared *via* CDP of polyesters, work is currently in hand to prepare other types of soluble libraries by CDP and to develop methods for screening the various soluble libraries.

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