'Living' macrolactonisation: thermodynamically-controlled cyclisation and interconversion of oligocholates

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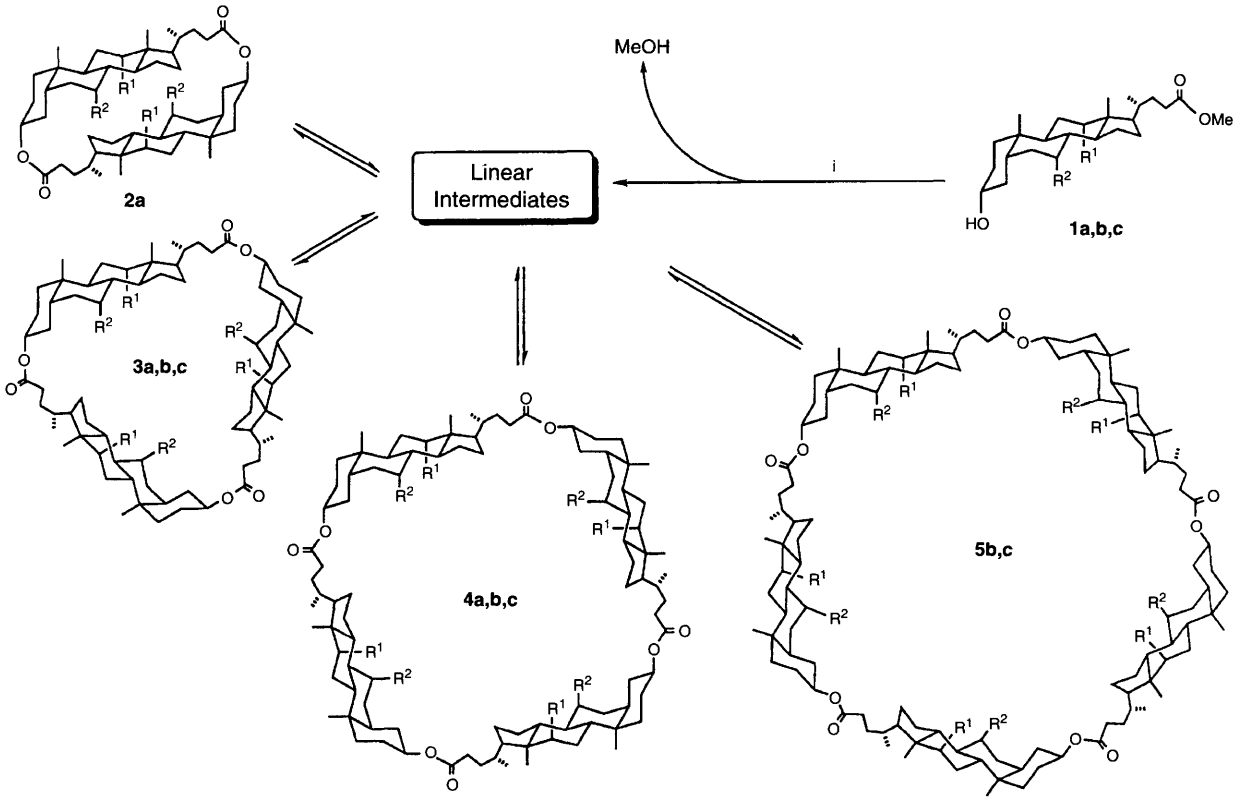
Cyclocholates are efficiently and rapidly synthesised from suitable monomers by transesterification under thermodynamic, equilibrating conditions using a potassium methoxide–crown ether complex.

We report here the development of a reversible, thermodynamically-controlled macrolactonisation procedure and its use in the synthesis of steroid-derived macrocycles. Macrolactonisation[1] has become an important reaction in the field of natural product synthesis[2] and in the construction of large host molecules for supramolecular studies.[3] In most of these cases, the distribution of the products has been determined kinetically, but we wished to explore the possibilities of thermodynamically-templated[4] chemistry using a range of supramolecular building blocks. Thermodynamic translactonisation has been used intramolecularly by Corey for the synthesis of medium ring monocyclic lactones[5] and by several groups intermolecularly for the cyclisations of β-alkanolactones.[6] Ring-size distributions in the latter experiments gave good agreement with theoretical expectations.[7]

The chemistry we envisaged for thermodynamic cyclisation of large building blocks is straightforward:

$$RCO_2Me + R'OH \rightarrow RCO_2R' + MeOH$$
$$RCO_2R' + R''OH \rightleftharpoons RCO_2R'' + R'OH$$

Each building block is therefore equipped with a methyl ester group at one end and a hydroxy group at the other. A transesterification catalyst is required, and the reaction is driven to oligomer formation by azeotropic removal into molecular sieves of the initially released methanol.[8] To test these ideas we first focussed on cyclocholates[9,10] derived from cholic acid and 7-deoxycholic acid (Scheme 1). We required each monomer to possess a 3-hydroxy and a 24-CO_2Me group for transesterification and a characteristic chromophore attached to C7 and/or C12 to facilitate quantitative spectroscopic analysis. The monomer deoxycholate **1a** and cholates **1b** and **1c** were prepared by conventional methods.† In addition, authentic samples of the cyclic oligomers (**2–5a–c**) were synthesised under kinetic conditions as before[9] and separated by preparative flash chromatography. For the cyclisation of **1a–c** a number of different transesterification catalysts were investigated [Ti-$(Pr^iO)_4$,[11] acid, dibutyl tin oxide–dibutyl tin chloride[12]] but these resulted in little or no cyclic material. However, addition of 5 mol% of the complex[13] of potassium methoxide and dicyclohexyl-18-crown-6 to a 5 mmol dm^{-3} solution of cholate



Scheme 1 *Reagents and conditions*: i, KOMe, Dicyclohexyl-18-crown-6, MePh

monomer in toluene refluxing through 4 Å sieves in a Soxhlet extractor effected complete and clean macrocyclisation within 10 mins. As the chromophore within each series was the same, the distribution of material between different ring sizes could be calculated from on-line UV analysis of HPLC effluents.‡

Fig. 1 summarises the product distributions observed in these cyclisations. Cyclic dimer is obtained only when there is no C7-substituent. Similar behaviour had previously been found in the kinetic cyclisation of cholates with a small C7 substituent.[9] The other cholates have their distributions weighted towards the trimer, the bis-methoxybenzyl derivative **1c** less strongly so than the methoxyethoxymethyl-benzyl derivative **1b** as the former has larger side chain groups pointing into the cavity with correspondingly greater repulsions.

To demonstrate that the distribution obtained is both thermodynamic and reversible, pure cyclic oligomers were resubjected to the reaction conditions; in each case, the same ratio of products was obtained whether the starting material was monomer or cyclic tri- or tetra-mer, the equilibrium being re-established within minutes. This transformation of one cyclic oligomer into another is reminiscent of the 'molecular mitosis' observed in the transformation of calix[8]- into calix[4]-arenes.[14] However, ring enlargement for calixarenes remains to be unambiguously proven. Theoretical treatments of thermodynamic cyclisation have been established for two extreme cases: The equations derived by Jacobsen and Stockmeyer, and developed further by Mandolini *et al.*[7] assume that material is completely strain free with unrestricted rotations and predict an exponentially decaying dependence of concentration on ring size. At the other extreme, for rigid building blocks with fixed internal angles, such as Stang's squares[15] or Ogura's hosts,[16] cyclisation gives rise to essentially one structure-directed product with negligible amounts of any other products. We expect that the translactonisation of cyclocholates will be an intermediate case but the relative importance of statistical and structure-directed effects is not yet clear.

In future papers we will show that this chemistry is applicable to other building blocks and that the composition of an equilibrating mixture will respond to the addition of a new component or of a template that can selectively bind one oligomer. This thermodynamic transesterification process can be labelled 'living' macrolactonisation by analogy with the responsiveness of anionic polymerisation mixtures to added monomers.[17] Furthermore, although the macroscopic composition of an equilibrating mixture is time independent, individual monomer units will be continuously changing partners and finding themselves in different sized rings. This is reminiscent of the behaviour of individual carbon atoms predicted§ by von Doering and Roth[18] in bullvalene undergoing degenerate Cope rearrangements.

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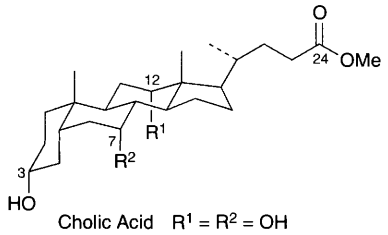

Cholic Acid $R^1 = R^2 = OH$

1a $R^1 = OCH_2C_6H_4Ph$, $R^2 = H$

b $R^1 = OCH_2Ph$, $R^2 = OCH_2OCH_2CH_2OMe$

c $R^1 = R^2 = OCH_2C_6H_4OMe$

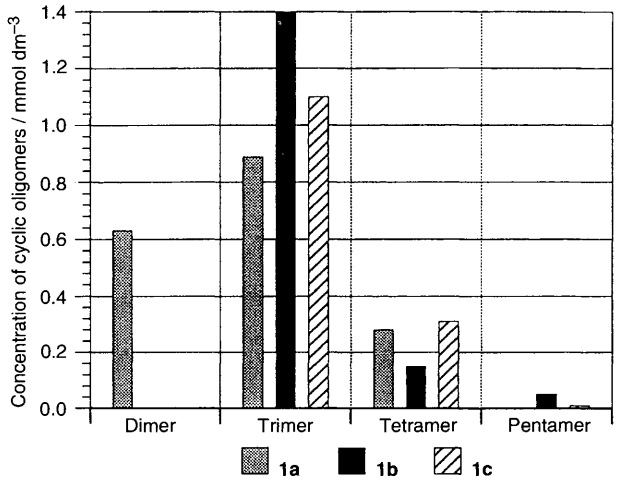

Fig. 1 Product distribution for thermodynamic cyclisation of **1a–c** (5 mmol dm^{-3}) under the conditions of Scheme 1

Footnotes

† All new compounds were fully characterised spectroscopically.

‡ HPLC separations were carried out using hexane–isopropanol mixtures on a Hewlett Packard 1050 system, with a 25 cm × 4 mm Spherisorb S5W normal phase column and detection by a Hewlett Packard HP1050 Diode Array UV detector.

§ 'Bullvalene.....will of necessity be a molecule in which no two carbons remain bonded to each other, and all ten carbon atoms inevitably wander over the surface of a sphere in ever changing relationship to each other.'[18]

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