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Synthesis and Kinetic Cyclisation of Quinine-Derived Oligomers

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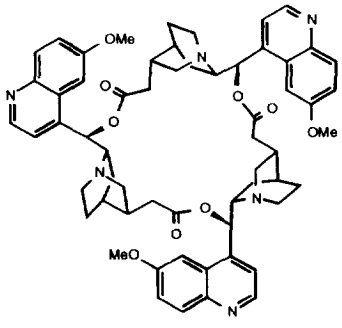
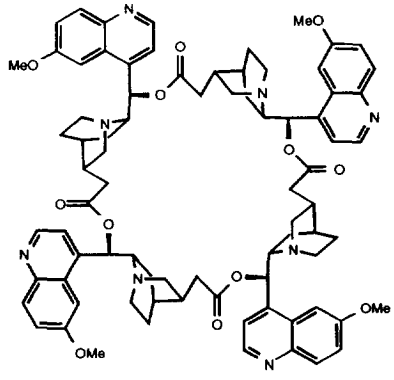
Abstract: The synthesis and kinetic cyclisations of a series of linear quinine oligomers are described. The distribution of cyclic oligomers is different from that observed in the corresponding thermodynamic cyclisation: cyclic tetramer is observed in the kinetic cyclisations, indicating that its absence under thermodynamic conditions is not due to any kinetic barrier to its formation. Copyright © 1996 Elsevier Science Ltd

In traditional organic synthesis, most reactions are carried out under kinetic control with the aim of obtaining a single product, but recently we have been investigating the synthesis of large macrocycles by thermodynamic processes,[1] including the cyclo-oligomerisation of a new quinine-derived building block.[2] In this thermodynamic cyclisation we only obtained what we believed to be cyclic trimer (**1**). This is contrary to the wide distribution we would expect from theory,[3] and in order to confirm that other macrocycles such as the cyclic dimer or tetramer (**2**) were not present, authentic samples of these "missing" oligomers were required. Successful preparation of these oligomers would also confirm that they are accessible kinetically and so help to show that the result of the "thermodynamic" reaction is indeed due to thermodynamics rather than any kinetic barrier. We show here that tetramer (**2**) and higher oligomers are in fact accessible and that the thermodynamic approach[2] is indeed the best for cyclic trimer.



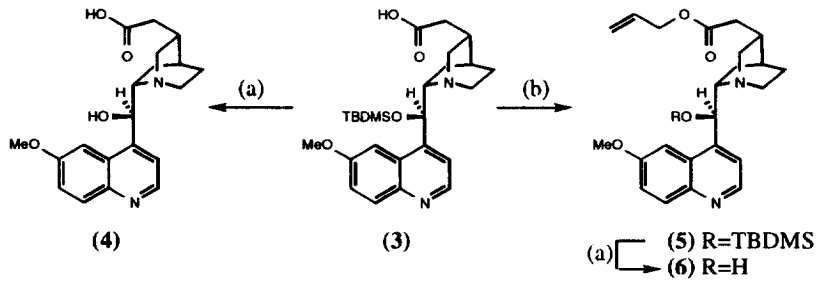
(**1**)



(**2**)

The approach taken to these cyclic oligomers was to prepare samples of the linear oligomers (monomer through tetramer) and cyclise them under kinetic conditions. The acid alcohol monomer unit (**4**) was prepared (Scheme 1) by deprotection of the previously synthesised TBDMS-protected monomer (**3**),[2] using TBAF/THF, in 50% yield. The other linear acid-alcohol molecules were prepared by a stepwise approach. The basis of the strategy was to utilise the two differently mono-protected monomer units (**3**) (acid

with protected alcohol) and (**6**) (alcohol with protected acid). (**6**) was obtained as outlined in Scheme 1. Starting with acid (**3**) an allyl protecting group was added using Yamaguchi esterification[4] conditions to give (**5**) in 90% yield. The TBDMS group could then be removed, as before, to obtain the allyl protected monomer (**6**) (66% yield).



(a) TBAF, THF, room temp., 2–3 hrs; (b) 2,6-dichlorobenzoyl chloride, allyl alcohol, Et_3N, DMAP, CH_2Cl_2, room temp., 3–4 hrs.

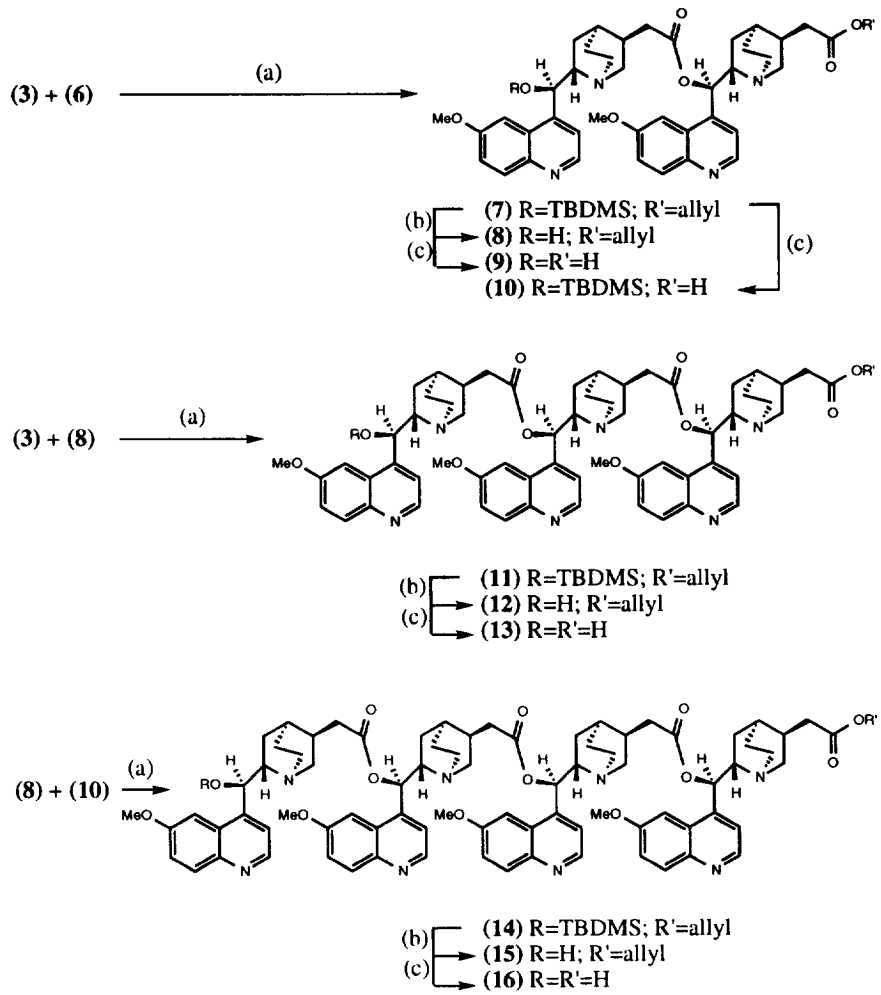
Scheme 1

Scheme 2 outlines the synthetic route used to obtain the desired linear oligomers. (**6**) was reacted, again under Yamaguchi esterification conditions, with (**3**) to give, in 90% yield, the diprotected linear dimer (**7**) . Linear dimer (**9**) was prepared by di-deprotection of (**7**) in two steps using TBAF/THF (yields (**8**) in 81%) and $Pd(PPh_3)_4$/morpholine/THF[5] (yields (**9**) in 99% yield). Linear trimer (**13**) was obtained by reacting the mono-protected dimer (**8**) with the monomer acid unit (**3**) under Yamaguchi conditions to give the diprotected linear trimer (**11**). This was then deprotected as before via (**12**) to give (**13**) (in 69% and 66% yield, respectively). Finally the synthesis of linear tetramer (**16**) was achieved by reacting the two mono-protected dimers (**10**) [prepared in 69% yield by allyl deprotection of (**7**)] and (**8**), under Yamaguchi esterification conditions to give the diprotected linear tetramer (**14**) in 97% yield. (**14**) was then deprotected in the usual manner (via (**15**), 34% yield) to the linear tetramer (33%).

Cyclisations of the linear molecules were carried out under kinetic conditions with the aim of obtaining authentic samples of cyclic dimer, trimer and tetramer. The cyclisation conditions employed were a modification of the Yamaguchi macrolactonisation method (Scheme 3), using a small amount of DMF to help solubilise the starting materials. Typical conditions used were as follows: to a stirred mixture of (**4**) (20 mg, 5.6×10^{-5} moles) in DMF (1.2 ml) was added triethylamine (16 ml, 1.15×10^{-4} moles) and 2,6-dichlorobenzoyl chloride (12 ml, 8.9×10^{-5} moles). This was then stirred at room temperature for 30 minutes, until all the starting material had dissolved. The reaction mixture was diluted to 5 mM with CH_2Cl_2 (10 ml) and DMAP (27 mg, 2.2×10^{-4} moles) was added. The reaction was then stirred for a further 16 hours and worked up by washing with water. The organic solvent was then removed, under vacuum, and the sample was analysed by ^1H NMR and electrospray mass spectrometry. The reactions were carried out at 5 mM (a) in order to ensure the formation of cyclic molecules and (b) to keep the concentration the same as the thermodynamic experiment.

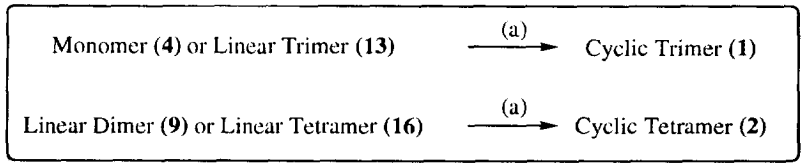
Linear dimer (**9**) does not cyclise to give the cyclic dimer but instead gives mainly cyclic tetramer (**2**) with a small amount of cyclic hexamer. 44% of the linear dimer is converted into cyclic tetramer with the remainder being incorporated into a mixture of higher oligomers. In theory for kinetic cyclisations,[6] a wide distribution of cyclic products should be obtained, starting from the smallest possible ring and going upwards. This result suggests that cyclic dimer is too strained to be formed, as predicted by inspection of CPK models and explains the lack of cyclic dimer in the thermodynamic reaction. However it does not

explain the absence of cyclic tetramer in the thermodynamic process. Linear trimer **(13)** gives the expected cyclic trimer **(1)** (48% of linear trimer units), the remaining products being cyclic hexamer and other higher oligomers. Similarly linear tetramer gives mainly cyclic tetramer **(2)** (45% of linear tetramer units) with the rest being cyclic octamer and other oligomers. The isolated cyclic trimer obtained from the linear trimer reaction gives ^{1}H NMR and ES-MS spectra identical to the product obtained in the thermodynamic cyclisation, confirming that the major product in that reaction is indeed cyclic trimer **(1)**. Finally, cyclisation of the monomer **(4)** gave no cyclic monomer or dimer. The main product obtained was the cyclic trimer **(1)**, as in the thermodynamic reaction, but with a wider distribution of products. ^{1}H NMR[7] spectra showed that monomer was converted into **(1)**: **(2)**: other higher oligomers in the proportions of 37%: 23%: 40% respectively. This corresponds to a molar trimer: tetramer ratio of *ca.* 2:1.



(a) 2,6-dichlorobenzoyl chloride, Et_3N, DMAP, CH_2Cl_2, room temp., 3–4 hrs; (b) TBAF, THF, room temp., 2–3 hrs; (c) $Pd(PPh_3)_4$, morpholine, THF, room temp., 1–2 hrs.

Scheme 2



(a) 1. 2,6-dichlorobenzoyl chloride, Et_3N, DMF. 2. DMAP, CH_2Cl_2, room temp., 18 hrs.

Scheme 3

In summary, we have demonstrated that both linear and cyclic oligomeric quinine derivatives can easily be obtained. Scheme 3 shows the major product obtained in each of the individual kinetic cyclisations. We have shown that cyclic oligomers from trimer to octamer can be prepared kinetically and in doing so we have confirmed that our previous thermodynamic cyclisation indeed yields only cyclic trimer (**1**). In theory, both kinetic and thermodynamic reactions should give a distribution of products. From this point of view, the kinetic reaction is well behaved, with trimer as the most abundant product (37% of monomer units) and ever decreasing amounts of larger rings being obtained. Kinetic cyclisations are dependent on the energy of the transition state and in our system the rate of cyclisation of the different linear species is broadly comparable, as demonstrated by the wide distribution of the cyclic products obtained. This confirms that all these cyclic products other than dimer are kinetically accessible and therefore that the absence of the larger oligomers in the thermodynamic reaction is not due to a kinetic effect on ring formation.[8] The high yield of the cyclic trimer (**1**) in the thermodynamic reaction (>90% of monomer units), which should be influenced by the energy of the ring system, suggests that this is a particularly stable molecule, relative to the other ring systems. We believe this is due to a degree of rigidity in our molecule which preorganises it to favour the cyclic trimer (**1**). This selectivity suggests that, if a particular oligomer can be stabilised by an external agent (rather than by the internal preorganisation, as here) the distribution should be shifted towards that oligomer. This would be thermodynamic templating, and is currently being investigated. We are also currently examining the possibility of mixing cinchona-derived alkaloids with other building blocks already used in our supramolecular chemistry such as cholic acids and porphyrins.

ACKNOWLEDGEMENTS

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7. The diagnostic peak in the ^1H NMR spectra is that relating to the 2' hydrogen. Cyclic trimer (**1**) δ = 8.76; Cyclic tetramer (**2**) δ = 8.73; Other cyclic oligomers δ = 8.70–8.65; Linear oligomers δ = 8.40 (monomer (**6**)), 8.53–8.59 (dimer (**8**)). 8.57-8.63 (trimer (**12**)); 8.64-8.68 (tetramer (**15**)).
8. It follows therefore that the rate of ring opening for (**1**) is less than that for (**2**) and higher oligomers.

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