Directed Macrocyclisation Reactions

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Macrocyclic hosts are prepared in 80–90% yields by using intramolecular hydrogen-bonding interactions to direct the cyclisation; in the absence of such effects, intermolecular hydrogen-bonding interactions template the formation of catenanes.

The potential recognition and catalytic properties of macrocycles that have cavities large enough to complex organic substrates make them attractive synthetic targets.[1] However, such compounds are difficult to obtain in reasonable quantities because large rings do not close efficiently and polymers are often major side-products. High dilution, which reduces the probability of intermolecular polymerisation reactions, is the most popular macrocyclisation technique,[2] but recently supramolecular approaches to this problem have been developed. In template-directed macrocyclisation, non-covalent intermolecular interactions with the template hold the reaction intermediate in a conformation that favours cyclisation.[3] In this communication, we demonstrate the use of non-covalent intramolecular interactions to direct macrocyclisation.[4]

We have reported the synthesis of three macrocyclic quinone receptors **1**, **2** and **3**.[5–7] **3** binds *p*-benzoquinone because it adopts the folded conformation illustrated. This folding can be understood on the basis of the conformational preferences of the individual diamide subunits shown in Fig. 1.[7] In the 2,6-pyridyl derivatives, intramolecular hydrogen bonds between the pyridine lone pair and the amide protons lock the amides into the NH *cis* conformation [Fig. 1(*a*)]. In the *iso*-phthaloyl derivatives, the amide–amide interactions are minimised in the *trans* conformation [Fig. 1(*b*)]. We reasoned that it should be possible to use the intramolecular hydrogen-bonding interactions to direct the synthesis of the macrocycles.

1, **2** and **3** were synthesised in two steps as shown in Scheme 1.[6] The key cyclisation intermediate is shown in Fig. 2(*a*). The *trans* conformation of the *iso*-phthaloyl diamide subunit holds the acid chloride and amine too far apart to react. The diamide must flip into the high energy NH *cis* conformation before reaction can occur. An alternative cyclisation intermediate in which *iso*-phthaloyl is replaced by 2,6-pyridyl is shown in Fig. 2(*b*). Here the preferred NH *cis* conformation of the 2,6-pyridyl diamide subunit should hold the acid chloride and amine in close proximity facilitating cyclisation.

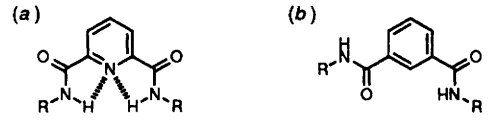
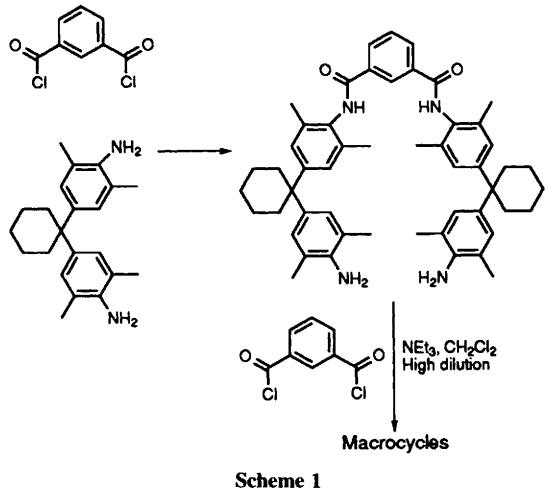


Fig. 1 Conformational preferences of the diamide subunits. (*a*) 2,6-Pyridyl diamides adopt an NH *cis* conformation owing to the intramolecular hydrogen-bonds shown. (*b*) *iso*-Phthaloyl diamides prefer the *trans* conformation.



Scheme 1

We have investigated the scope of this directed macrocylisation using the reactions shown schematically in Fig. 3.† All reactions were carried out under identical conditions: 100 cm^3 of a 0.01 mol dm^{-3} solution of the acid chloride in dichloromethane and 100 cm^3 of a 0.01 mol dm^{-3} solution of the amine and triethylamine (2 equiv.) in dichloromethane were added simultaneously *via* a motor driven syringe pump to dichloromethane (1000 cm^3) over 24 h. The yields summarised in Fig. 3 are for chromatographed and recrystallised products.‡

Reactions (*iii*) and (*iv*), which proceed *via* the Fig. 2(*b*) intermediate, give very high yields of the dimeric macrocycles,

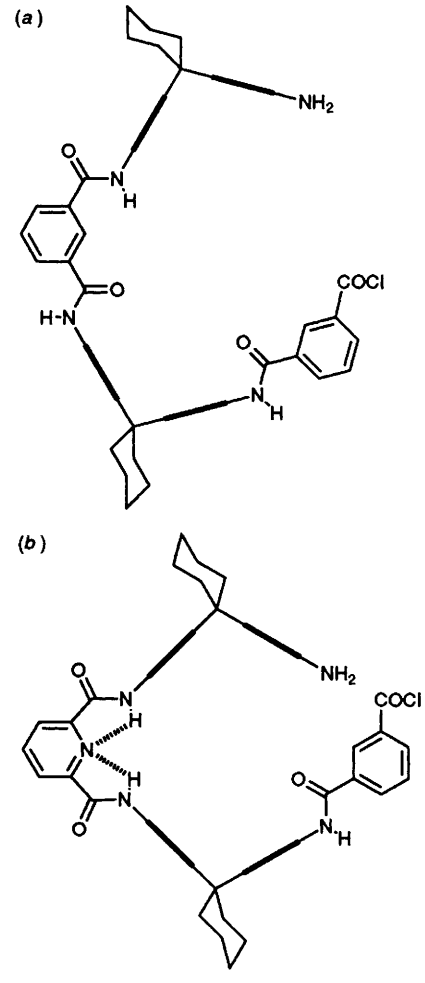


Fig. 2 Conformational preferences of the cyclisation intermediates. (*a*) The *trans* conformation of the *iso*-phthaloyl subunit holds the reactive groups too far apart to react. (*b*) The *cis*-conformation of the 2,6-pyridyl subunit holds the reactive groups in close proximity facilitating cyclisation.

2 and 6. Polymerisation is completely eliminated. The proposed intramolecular hydrogen bonds do indeed organise the intermediate to direct the macrocyclisation.

We were surprised to find that reaction (*ii*) did not produce polymer, but gave a high yield of the tetrameric macrocycle, 3. However, on consideration of possible intermediates, the reason is clear (Fig. 4). Macrocyclisation of 3 is directed by the same intramolecular interactions which cause 3 to fold and which direct the cyclisations in reactions (*iii*) and (*iv*).

The catenane products complicate a more detailed analysis of these systems. We do not yet understand how the catenanes are formed, but it is clear that reactions (*iii*) and (*iv*) in which macrocyclisation is efficient produce low yields of catenane. In reactions (*i*) and (*ii*), catenane formation can be rationalised by the formation of an intermolecular complex between the cyclic dimer and the intermediate shown in Fig. 2(*a*). If complexation stabilises the otherwise unfavourable NH *cis* conformation of the *iso*-phthaloyl subunit, then templated cyclisation to form the catenane will be promoted. In these cases, it is intermolecular hydrogen-bonding interactions which control the conformation of the intermediate and direct the macrocyclisation. Reaction pathway (*i*) produced the

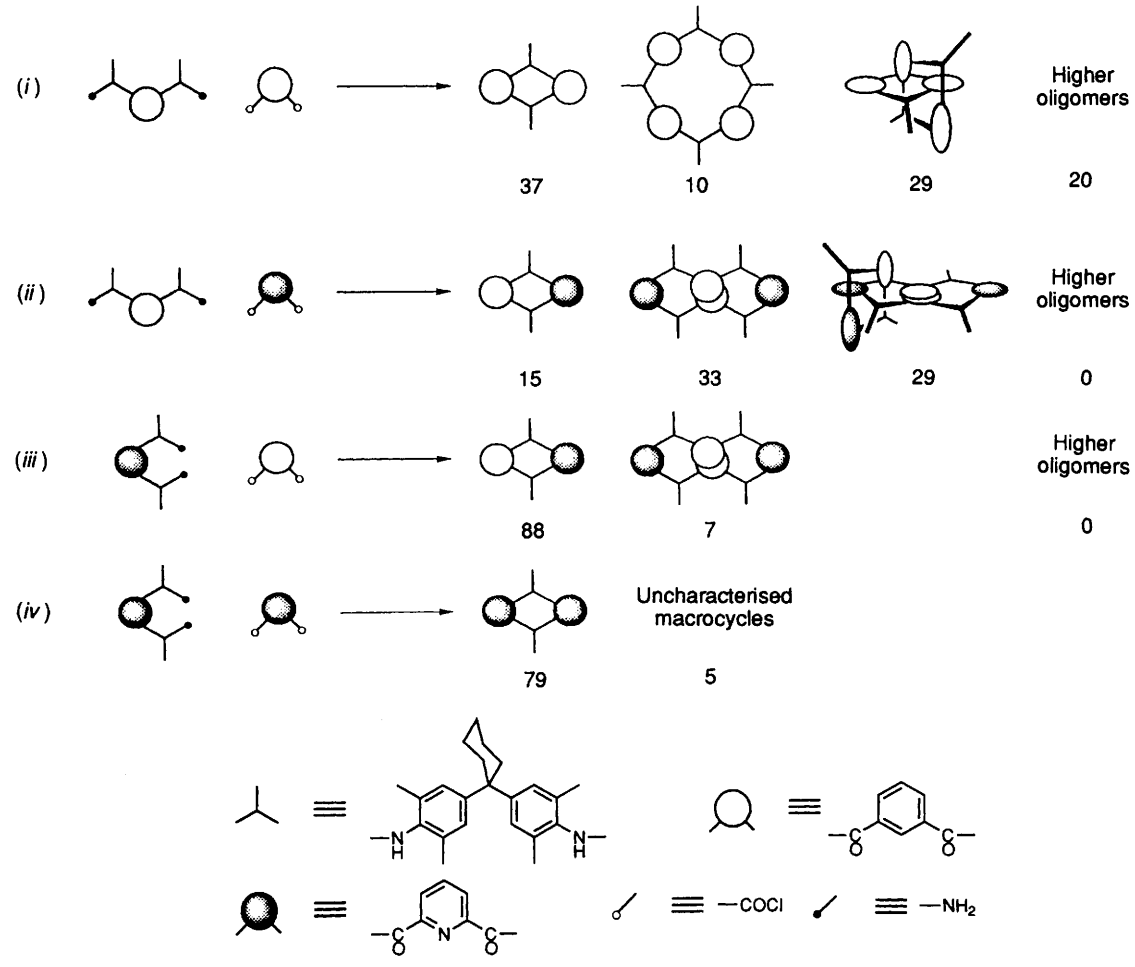


Fig. 3 Products and percentage yields obtained from four different macrocyclisation reactions carried out under identical conditions. A key for the schematic representations is provided. The uncharacterised macrocyles from reaction (*iv*) could not be identified as they could not be separated chromatographically.

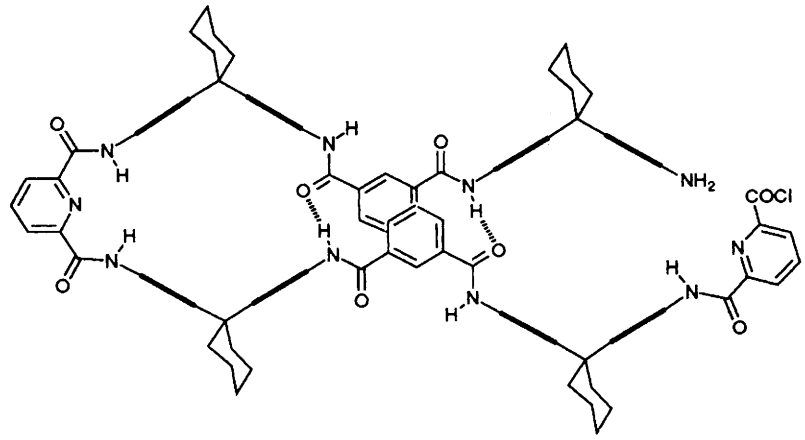
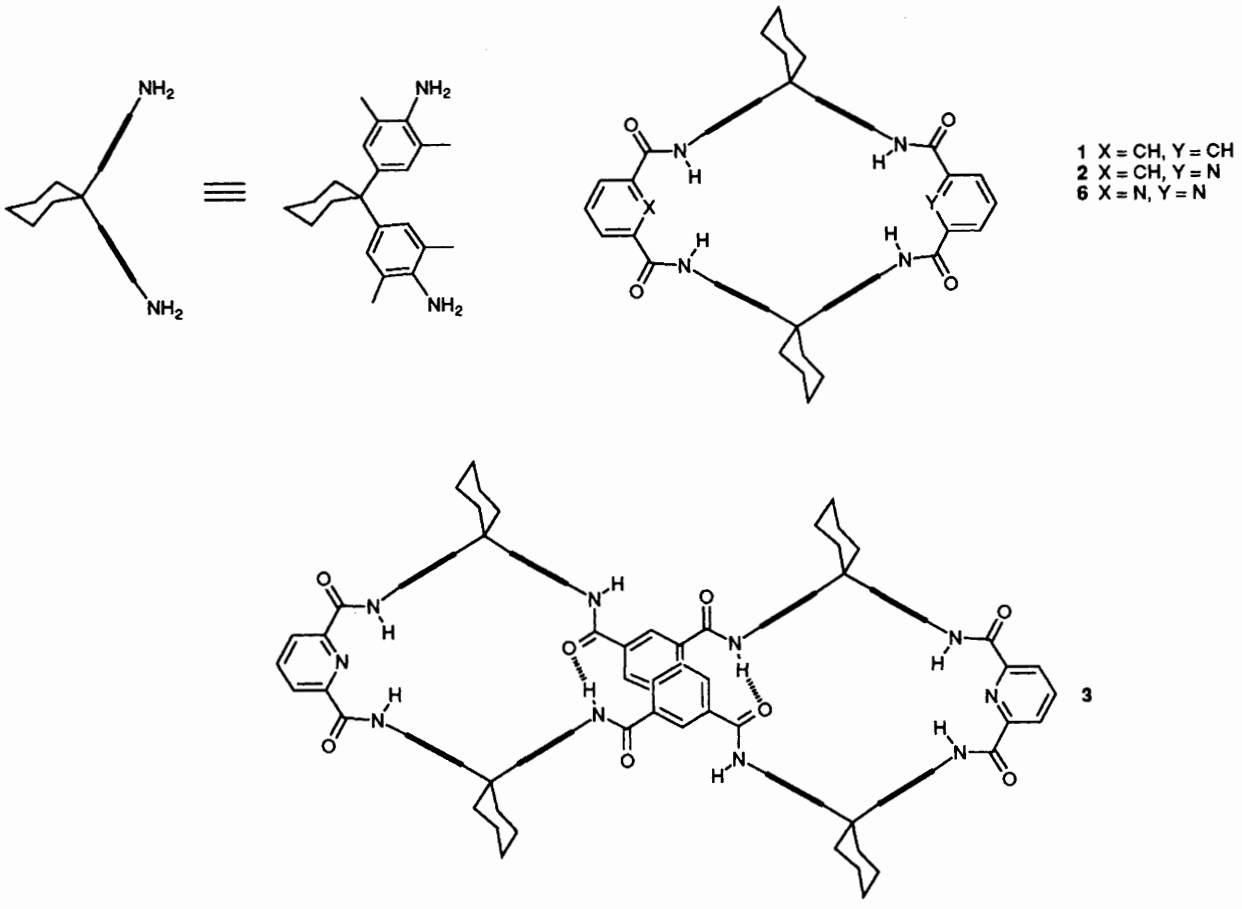


Fig. 4 The conformation of the cyclisation intermediate for reaction (*ii*) which leads to a high yield of 3



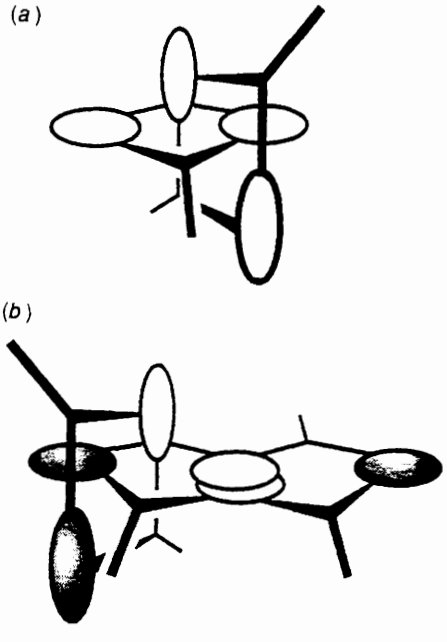


Fig. 5 (*a*) The major catenane product from reaction (*i*). (*a*) The major catenane product from reaction (*ii*).

simple dimer–dimer [2]-catenane illustrated in Fig. 5(*a*), but surprisingly we have not been able to detect any of the analogous dimer–dimer [2]-catenane in the products from reaction (*ii*). In contrast, reaction (*ii*) produced the tetramer-dimer [2]-catenane [Fig. 5(*b*)] in high yield as well as traces of the dimer–dimer–tetramer [3]-catenane.

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Footnotes

† All new compounds gave satisfactory spectroscopic data (NMR, FAB and electrospray MS). The catenane mass spectra show characteristic fragmentation patterns which distinguish them from simple macrocyles. The catenanes also have characteristic temperature-dependent ^{1}H NMR spectra which contain many non-equivalent signals when cooled into the slow exchange regime (see ref. 6).

‡ All yields are averages of more than one experiment. The percentage recovery was slightly lower for reactions (*ii*) and (*iv*) than for reactions (*i*) and (*iii*). This may reflect the fact that the 2,6-pyridyl diacid dichloride was prepared from the diacid and thionyl chloride and was used without purification assuming a quantitative yield. *iso*-phthaloyl dichloride was purchased from Aldrich. The yields for reaction (*i*) differ from those previously reported.[6]

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