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Alicyclophanes: a new range of cyclophanes containing rigid alicyclic subunits in place of the aromatic rings

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Abstract

Norbornenosuccinimides have been coupled stereoselectively with 2,5-bis(trifluoromethyl-1,3,4-oxadiazole to prepare alicyclic scaffolds **5** and **20**. Alkylations of the terminal succinimido-nitrogens of **5** with bis-alkylating agents have produced macrocyclic compounds in a short, high-yielding procedure. Alicyclophanes containing one scaffold subunit were obtained from 1,6-dibromohexane, 1,5-dichloro-3-oxapentane, 1,11-dibromo-3,6,9-trioxaundecane and 9,10-bis(chloromethyl)anthracene. Larger alicyclophanes incorporating two spacer subunits were formed by intermolecular cyclisation of **5** with 1,2-dibromoethane or **19** with *m*- or *p*-xylylene dibromide. Reaction of **5** with propargyl bromide, followed by oxidative coupling (CuCl) of the pendant acetylenes provided bis-acetylenic alicyclophane **13**.

Keywords: alkylation; cyclophanes; macrocycles; 1,3,4-oxadiazoles; norbornenes; cycloaddition; succinimides.

The cyclophanes are a well established sub-class of macrocycles[1] which contain one or more aromatic component(s) embodied in the cyclic frame.[2] In this paper, we report the facile synthesis of a novel type of modified cyclophane, the alicyclophanes (Fig. 1), in which some or all of the aromatic rings have been replaced by a rigid, alicyclic subunit comprised of fused bicyclic rings. An advantage of such compounds is that the alicyclic scaffold components can bear specific substituents (effectors)[3] and be designed to have a variety of individual framework topologies (curved, rod-like)[4] or properties (polarofacial, lipophilic, etc.).[5] While isolated examples of macrocycles incorporating multiply-bridged components have been reported in the chemical literature,[6] no systematic synthetic methodology for alicyclophane construction has been described heretofore.

Reaction of the *endo*-adduct **3**, formed by cycloaddition of cyclopentadiene **1** with maleimide **2**,[7] with 2,5-bis(trifluoromethyl)-1,3,4-oxadiazole **4** effected efficient, stereoselective coupling at the norbornene π-bond to furnish the *syn*-orientated bis-succinimide **5**.[8] This compound acts as a

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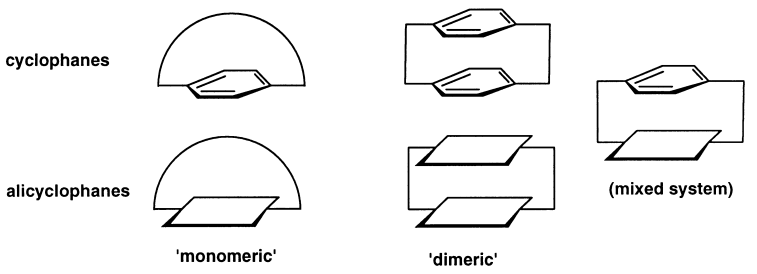


Figure 1.

key prototype spacer unit in this study, but a range of related systems is potentially available using our BLOCK coupling techniques.[3]

In a typical procedure, the scaffold bis-succinimide **5** was warmed (60°C) with 1,6-dibromohexane **6** in DMF containing solid potassium carbonate for 5 days to afford the macrocyclic alicyclophane **7**[8] in excellent yield (93%). The cyclic structure of **7** was fully supported by the single crystal X-ray structure analysis[9] presented in Fig. 2a. In particular, this structure shows that the methylene chain is conformationally highly ordered with the four central methylene subunits adopting the low energy, non-eclipsed conformation (Scheme 1).

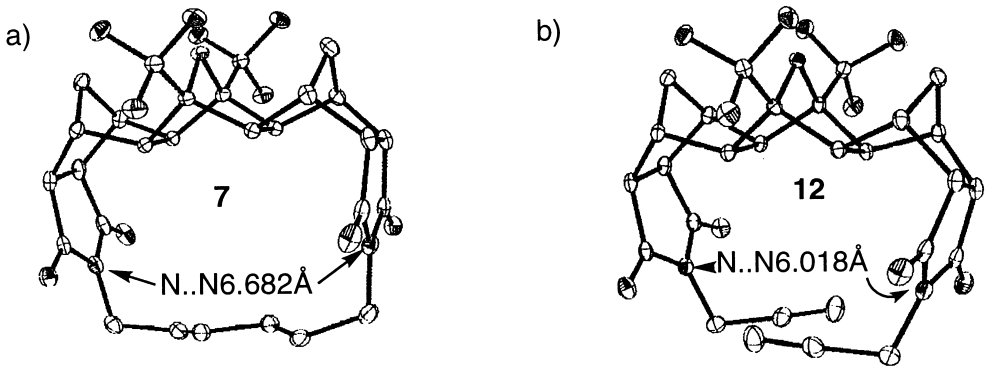
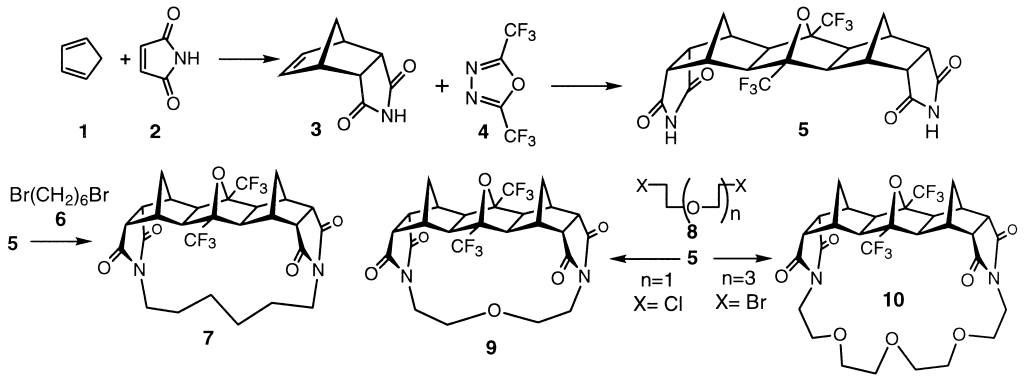


Figure 2. X-ray structures of a) alicyclophane **7** and b) open-chain diacetylene **12**

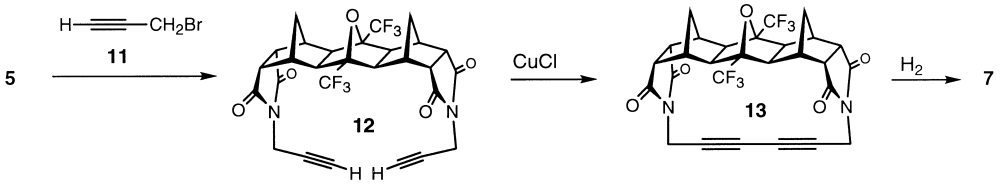


Scheme 1.

Functionality can be incorporated into the macrocyclic ring by the prior positioning of it into the bis-alkylating agent. Thus, treatment of bis-succinimide **5** with 1,5-dichloro-3-oxapentane **8** ($n=1$) afforded the cyclic ether product **9** in 93% yield. The structure of **9**[8] was supported by NMR spectroscopy and mass spectometry ($m/z=574$). That larger ring macrocycles can be produced was established by reaction of **5** with 1,11-dibromo-3,6,9-trioxaundecane **8** ($n=3$) to furnish the crown ether **10**,[8] although the yield dropped off (42%) with the longer bis-alkylating agent.

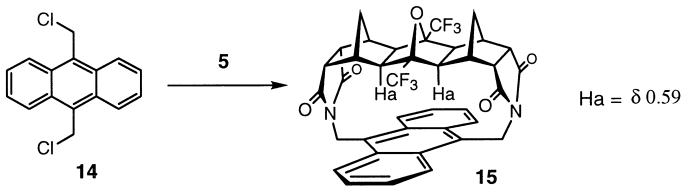
Molecular modelling (AM1) of these alicyclophanes indicated that the N–N separation of the succinimide nitrogens in **5** is 6.30 Å and that this distance expands to 6.63 Å upon conversion to the alicyclophane **7**. This calculated distance agrees well with that obtained from the X-ray structure of **7** (6.68 Å). Again, the calculated N–N separation remains essentially the same (6.56 Å, MM2) in crown ether **10**.

In a second route to alicyclophanes, short pendent arms were attached to the succinimide nitrogen centres and linked by intramolecular cyclisation. Thus, reaction of bis-succinimide spacer **5** with excess propargyl bromide **11** using the standard basic conditions (K_2CO_3, DMF) provided the open-chain bis(*N*-propargyl) derivative **12**[8] (X-ray structure,[9] Fig. 2b), which was cyclised to the diacetylenic alicyclophane **13**[8] by treatment with Cu[1] (Scheme 2). The requisite high symmetry of the cyclic product **13**[8] was evident in the ^{13}C NMR spectrum (10 resonances) and the size of the macrocyclic ring was established by hydrogenation (Pd/H_2) to alicyclophane **7**. Attempts to form **13** directly, by treatment of bis-succinimide **5** with 1,6-dibromohexa-2,4-diyne were not successful, thereby confirming the complementarity of the cyclisation methods, a conclusion reinforced when attempts to form the cyclic ether **9** from cyclisation of the *N,N*-bis(2-hydroxyethyl) derivative of **5** by reaction with mesyl chloride/pyridine or DCC were without reward.



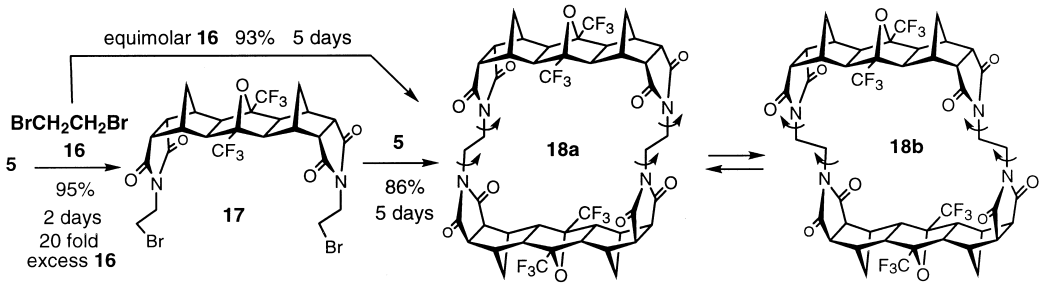
Scheme 2.

Introduction of an aromatic ring into the alicyclophanes was also readily achieved by treating the bis-succinimide spacer **5** with an appropriate aromatic bis-alkylating agent, e.g. 9,10-bis-(chloromethyl) anthracene **14** produced the alicyclophane **15**[8] (Scheme 3). The structure was based on the mass spectrum ($m/z=706$) and the ^1H NMR spectrum which displayed the typical through space, transannular shielding by the anthracene ring. In particular, the *endo*-protons (Ha) of the alicyclic spacer unit in **15** were upfield-shifted by 1.72 ppm relative to those in the starting scaffold **5**.



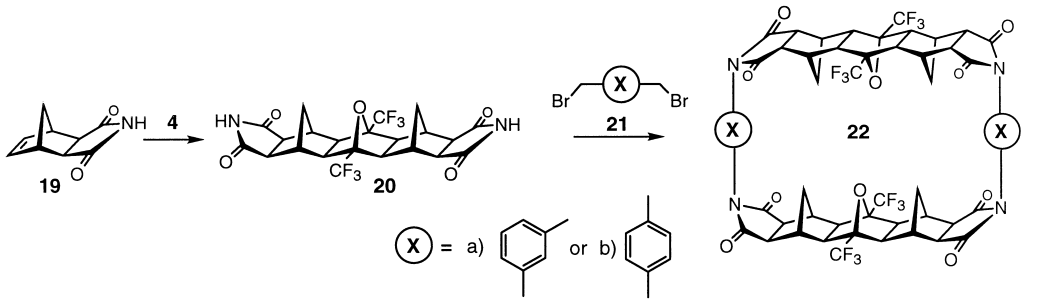
Scheme 3.

Macrocycles containing two alicyclic spacer units were accessed using short-chain bis-alkylating agents, whence dual intramolecular alkylation was obtained. Reaction of **5** with an equimolar equivalent of 1,2-dibromoethane **16** gave the cyclic product **18**[8] ($m/z = 1083$, M+Na$^+$) in 93% yield, while the same reaction reagents produced the bis(2-bromoethyl) derivative **17**[8] when a large excess (20 fold) of **16** was employed. Separate reaction of the dibromide **17** with spacer **5** produced the macrocycle **18** in excellent yield (86%). The ^{1}H NMR spectrum of **18** in $CDCl_3$ is broad and ill-defined at room temperature and does not symmetrise until the temperature exceeds 90°C. We interpret this phenomenon, tentatively, in terms of conformational rotation (**18a** = **18b**) occurring in the ethano linkers (arrows, Scheme 4) and such 'crankshaft' mobility may have potential in the design of molecular devices. The incorporation of two aromatic rings into a 'dimeric' type of macrocycle (cf. Fig. 1) can be achieved using *o*-xylylene dibromide as the bis-alkylating agent and this will be discussed elsewhere.[10]



Scheme 4.

In addition to the 'southern hemisphere'[11] macrocycles discussed above, in which the linking chain is positioned on the bottom face of the alicyclic spacer unit, we have now found that their 'northern hemisphere' counterparts are also accessible. Thus, bis-alkylation of *exo*-fused bis-succinimido spacer **20** (Scheme 5), formed by coupling of *exo*-succinimide **19**[13] with the 1,3,4-oxadiazole **4**, with *m*-xylylene dibromide **21a** produced 'dimeric' alicyclophanes **22a** ($m/z = 1235$, M+Na$^+$), in which the methano-bridged faces of the alicyclic scaffolds are inward-facing, i.e. 'northern hemisphere'[11] as assessed by molecular modelling. Similarly, **22b** was produced by treatment of **20** with *p*-xylylene dibromide **21b**.



Scheme 5.

In conclusion, given the simplicity of the preparation of the bis-succinimide spacers and the efficiency of their *N*-alkylation leading to macrocycles, we expect alicyclophanes to offer

molecular architects a new arena in which to demonstrate their creativity, and where we will be contributing further in due course.

Acknowledgements

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