Ring closing metathesis of a 4,6-diallyl-*myo*-inositol orthoformate as a model for an inositol cyclopolymer

Tae-Hyun Kim,[a,b] Mark Giles[b] and Andrew B. Holmes*[a,b]

[a] *Department of Chemistry, University Chemical Laboratory, University of Cambridge, Lensfield Road, Cambridge, UK CB2 1EW. E-mail: abh1@cam.ac.uk*

[b] *Melville Laboratory for Polymer Synthesis, Department of Chemistry, University of Cambridge, Pembroke Street, Cambridge, UK CB2 3RA*

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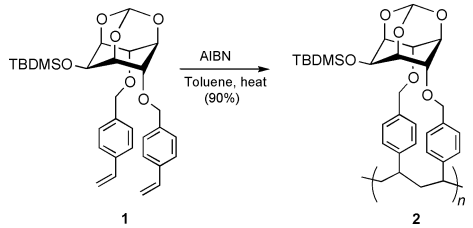
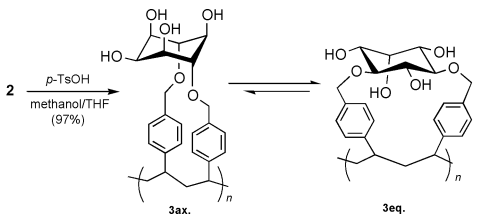
Ring closing metathesis (RCM) of the diallyl inositol derivative 5 gave the product 6 which after cleavage of the orthoester served as a model for assignment of the preferred conformation of the analogous deprotected inositol cyclopolymer 3.

In the preceding Communication the cyclopolymerisation of the conformationally locked 4,6-bis(4-vinylbenzyl)-*myo*-inositol **1** to the novel cyclopolymer **2** was reported (Scheme 1).[1]



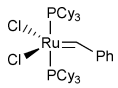
Scheme 1 Polymerisation of the monomer **1** to cyclopolymer **2**.

The rigid inositol unit of the monomer **1** acts as a template to bring both polymerisable styryl groups into close proximity for cyclopolymerisation. The monomer **1** was polymerised at high dilution (0.1 mmol ml^{-1}) in toluene with 2–3 wt% of AIBN as a radical initiator to give a soluble linear cyclic polymer **2** in high yield (80–90%) with molecular weight M_n of 10 000–20 000 as determined by GPC.† It was hoped that removal of the orthoester and silyl groups would release a hydrophilic polymer with oriented fiunctionality. Thus the polymer **2** was heated in a mixture of THF and methanol in the presence of toluene-*p*-sulfonic acid to give the hydroxylated polymer **3** (Scheme 2). The polymer **3** would be expected to exhibit interesting hydrophilic and metal binding properties if all five hydroxy groups remained axial **3ax**.[2,3] However, the alternative conformation **3eq**. would also be feasible. Unfortunately the polymer **3** shows very broad ^{1}H and ^{13}C NMR spectra, making the full conformational interpretation difficult, and hence conformational studies using model small molecules were carried out to gain insight into this feature.



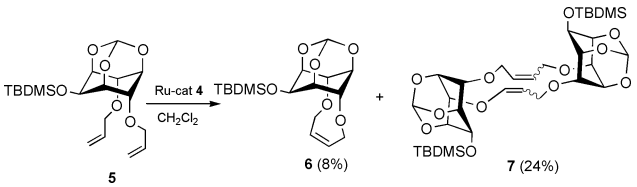
Scheme 2 Deprotection of polymer **2** to give two alternative conformations of **3**.

The model compounds were thought to be accessible by ring closing metathesis (RCM)[4,5] of the monomer **1** using the ruthenium based alkylidene catalyst **4**.[6] However, attempted ring closure of the monomer **1**, under high dilution (11.2 mM),



4

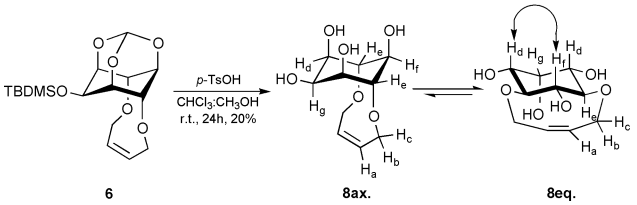
failed and gave only oligomeric products. This was ascribed to the rigid steric arrangement of the two styryl groups in a single unit of **1**, making the formation of another ring difficult. RCM of an alternative monomer with flexible alkyl linking groups was therefore carried out. The diallyl inositol **5** was formed in 78% yield by treating **1** with allyl bromide and sodium hydride in DMF. On treatment of the monomer **5** with the ruthenium initiator **4**, the ring closed product **6** and 'dimer' **7** were obtained, together with starting material (35%) and oligomeric products (Scheme 3). The double bond stereochemistry of these symmetrical products has not been assigned, but it is reasonable to assume that compound **6** has the *Z*-double bond configuration.



Scheme 3 RCM of the diallyl inositol **5**.

The RCM product **6** was deprotected to give the model compound **8** (Scheme 4).‡

Analysis of the ^{1}H NMR spectrum of the deprotected product **8** indicated that the preferred ring conformation was **8eq**. The protons H_d (δ 3.20, dd, *J* 9 and 3), H_e (δ 3.31, br t, *J* 9, 9) and H_f (δ 2.92, dt, *J* 6 and 9) were all axial and the measured coupling constants were in good agreement with those predicted by computer modelling.[7] A strong ^{1}H NMR NOE effect was also observed between the signals due to H_d and H_f (see Scheme 4) and between H_a (δ 5.75, br s) and H_e.



Scheme 4 Deprotection of the ring closed product **6** showing the observed NOE for **8eq**.

Variable temperature (VT) ^{1}H NMR experiments were carried out for both the deprotected RCM product **8** and the analogous 'dimer' in DMSO over the temperature range 300–330 K. However, although the signals due to the OH peaks altered as a result of the breaking of hydrogen bonds, there were

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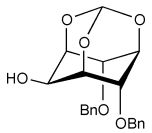
no dramatic changes in the other signals. This demonstrates the rigidity of the structure in inhibiting inositol ring-flipping.

The ^{1}H NMR signals of the inositol ring protons of the 4,6-dibenzyl-*myo*-inositol orthoformate **9**[5] occurred at δ 4.45



9

(1H, m), 4.30 (2H, m) and 4.23 (3H, m) and resembled closely the analogous signals in the polymer **2** (δ 4.5–4.2, br multiplet), indicating that the ring conformation was maintained, as expected, in the polymer. The ^{1}H NMR chemical shifts (δ 3.60–2.92) of the ring protons of the deprotected metathesis product **8eq.** are shifted upfield compared with those in the model **9**. Similarly the inositol ring protons of the deprotected polymer **3** (δ 3.7–3.0) are shifted upfield from which it is concluded that the inositol ring in **3** has the conformation **3eq.** The ^{13}C NMR spectra peaks of **3** were too broad to be assigned.

In conclusion, we have established the conformation of the novel inositol polymer **3** using the model compound **8** prepared by ring closing metathesis. The ^{1}H NMR analysis strongly suggests that the polymer **3ax**. is converted into **3eq**. when deprotected.

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Notes and references

† Full details of the synthesis and properties of polymers based on the monomer **1** will be described in a full paper.

‡ A similar sequence of reactions was carried out using 'dimer' **7**, and the spectroscopic properties of the inositol ring atoms were very similar to those discussed for the small ring analogue **6**.

1 T.-H. Kim, P. Dokolas, N. Feeder, M. Giles, A. B. Holmes and M. Walther, *Chem. Commun.*, 2000; preceding paper DOI: 10.1039/b007057m.
2 S. J. Angyal, *Tetrahedron*, 1974, **30**, 1695.
3 K. Hegetschweiler, M. Ghisletta, T. F. Fässler, R. Nesper, H. W. Schmalle and G. Rihs, *Inorg. Chem.*, 1993, **32**, 2032.
4 R. H. Grubbs and S. Chang, *Tetrahedron*, 1998, **54**, 4413.
5 S. K. Armstrong, *J. Chem. Soc., Perkin Trans. 1*, 1998, 371.
6 G. C. Fu and R. H. Grubbs, *J. Am. Chem. Soc.*, 1992, **114**, 5426.
7 F. Mohamadi, N. G. J. Richards, W. C. Guida, R. Liskamp, M. Lipton, C. Caufield, G. Chang, T. Hendrickson and W. C. Still, *J. Comput. Chem.*, 1990, **11**, 440.
8 H. W. Lee and Y. Kishi, *J. Org. Chem.*, 1985, **50**, 4402.