Synthesis and Conformational Analysis of Novel Polymeric Ligands based on myo-Inositol

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ABSTRACT. Synthesis of novel polymeric ligands based on myo-inositol was performed. Cyclopolymerization, whose mechanism and the cyclic structure were proved, was first attempted to build a conformationally rigid inositol polymer. Comparative spectroscopic methods were introduced to verify the conformation of the prepared cyclohexane polymers. A conformationally rigid polymeric ligand was successfully prepared using myo-inositol carbonate.

Keywords: myo-Inositol, Conformationally Rigid Polymer, Metal-binding Ligand, Conformational Analysis of Cyclohexane Polymers

INTRODUCTION

The search for new polymeric ligands capable of binding certain metal ions has continued over the last decade. The performance of such functional polymers is governed by a large number of functional groups present in these macromolecules. The functional groups are responsible for the desired interaction with a substrate, whereas the polymer backbone provides a structural and mechanical stability. It is well known that nature uses only a small variety of functional groups such as carboxylates, amines, amides, alcohols and thiols. Biological macromolecules, however, achieve high performance and unparalleled selectivity by orienting these functional groups via non-covalent interactions. This concept of oriented functionalities has not been cited to any great extent for synthetic polymers, largely because there is no simple way of controlling the conformation of synthetic macromolecules in bulk or solution. If the functional groups are situated on a rigid scaffold within the monomer unit, their relative orientation is fixed, and hence increased performance, together with higher selecti-
ity, can be achieved. We were, therefore, interested in developing a novel polymer with an organized backbone and oriented functional groups. Inositol (cyclohexane-1,2,3,4,5,6-hexaol) scaffolds were considered to be suitable to deliver such features. It was known that as few as three neutral O atoms in a cyclohexane can form well-defined and fairly stable complexes with cations, provided that the O atoms are located in suitable steric arrangements. The steric requirements of the cyclohexane polysaccharides to form complexes with cations are, however, rather strict and the three O atoms on a cyclohexane ring have to be located axially at the 1, 3 and 5 positions. This arrangement (syn-triaxial) is not common in nature and the only example is cis-inositol. There are many cyclohexane derivatives containing three equatorial hydroxyl groups at the 1, 3 and 5 positions including myo-inositol, but complexation with cations does not generally provide sufficient energy to preferentially adopt one chair conformation. Many works have been focused on the preparation of structurally rigid inositol platforms that have the syn-triaxial arrangement, but none of these compounds is readily available, especially in large scales. We hereby introduce synthetic approaches to prepare conformationally rigid polymers, having all-axial triols, based on the readily available myo-inositol.

RESULT AND DISCUSSION

Cyclopolymerization of the difunctional monomer 1 was previously pursued to obtain a conformationally locked inositol polymer 2. The rigid inositol unit, introduced by the orthoformate group, acts as a template for bringing two polymerizable groups into close proximity to enable cyclopolymerization. Another key structural feature offered by this monomer 1 includes the orthoformate group which, after the cyclopolymerization reaction, can be easily deprotected to yield (ideally) an all-axial triol repeat unit. The cyclopolymerizable groups were, therefore, anticipated to work as both polymerizable and ring locking groups.

Heating a toluene solution of the monomer 1 at 65 °C in the presence of 2-3 wt% of AIBN as a radical initiator afforded an organically soluble polymer which is formulated as a linear cyclopolymer 2 (Scheme 1). The evidence for the cyclopolymer 2 came from the trapping of the first formed cyclic intermediate 4 (Scheme 2). The TEMPO radical trapping technique was used to isolate the reactive compound.
radical intermediate generated during cyclopolymerization.

The mechanism of trapping cyclic intermediate is suggested in Scheme 3 and involves 'trapping' carbon-based radicals with suitable nitrooxide reagents. Thermal decomposition of the AIBN initiator would give the cyanoisopropyl radical (I) which would add selectively to the less substituted end of the vinyl group as depicted by 5. If cyclization is fast enough, the radical formed should then add to the next vinyl group intramolecularly to give 6. Finally, the radical trapping agent (T-.) can react with the resulting secondary radical to afford the trapped product 4. The structure determination of the cyclic product 4 was carried out by 1H NMR TOCSY and NOE experiments. Selective 1H TOCSY experiments assisted in determining the connectivity sequence of atoms. Mutual NOE effects were also observed between two methine protons (Hα and Hε), further indicating that both are part of the same cyclic structure.

The cyclopolymer 2 was then deprotected in the presence of toluene-p-sulfonic acid to give the hydroxylated polymer 3 (Scheme 4). The deprotected polymer 3 was expected to exhibit interesting hydrophilic and metal binding properties if all five hydroxyl groups remained axial (3ax). However, the alternative conformation (3eq) would also be feasible (Scheme 1).

Conformational studies using a model small molecule were performed to gain an insight into the conformation, as the polymer 3 showed very broad 1H and 13C NMR spectra. The diallyl inositol derivative 7 was obtained in a similar manner to 1. The ring closing metathesis (RCM) of 7 using ruthenium catalyst afforded the cyclized product 8, which was finally deprotected to give the hydroxylated product 9 (Scheme 4).

Analysis of the 1H NMR spectrum of the model compound 9 indicated that the preferred ring conformation was 9ax. With this result in hand, the conformation of the deprotected polymer 3 was verified. The 1H NMR signals of the inositol ring protons of the RCM product 8 occurred at 4.4-4.6 ppm and resembled closely the analogous signals in the polymer 2 (δ 4.5-4.1), indicating that the ring conformation was maintained, as expected, in the polymer. The 1H NMR chemical shifts of the ring protons of the deprotected metathesis product 9 were shifted upfield (δ 3.6-2.9) compared with those in the model 8. Similarly the inositol ring protons of the deprotected polymer 3 were shifted upfield (δ 3.5-3.0), from which it is concluded that the inositol ring in 3 has the conformation 3eq. It was thought that such a large ring system generated by the cyclopolymer was not rigid enough to hold the conformation of the deprotected polymer 3 to get its desired axial conformation (3ax). The metal chelating properties would, therefore, not be achieved using this polymer 3 (or 3eq).

Alternatively, we have prepared the inositol polymer based on yno-inositol carbonate 10 (Scheme 5).
Here, the carbonate group was introduced as a short bridge between O-4 and O-6 of α-myo-inositol and was expected to hold the conformation of the cyclohexane to have three axial hydroxyl groups.

The 4,6-diallylated α-myo-inositol derivative 11 was first prepared, followed by the isomerization of the diallyl groups to end ethers using Wilkinson's catalyst\(^\text{5}\) to give 12. Introduction of the styrenyl moiety as a polymerizable group to the free alcohol, followed by hydrolysis of the end ethers using mercury(II) acetate produced the diol 13 in 84% yield over two steps. Further treatment with triphosgene in the presence of pyridine afforded the carbonate 14 in a moderate yield (60%). Myo-inositol carbonate monomer 14 was then copolymerized with styrene by a radical polymerization to afford the inositol copolymer 15 in 80% yield. Homopolymerization of the monomer 14 gave only an insoluble product. Finally, removal of the orthoformate group in polymer 15 was accomplished in the presence of p-TsOH to give the desired hydroxylated inositol polymer 10. The \(^{13}\text{C}\) NMR spectrum of 10 showed the absence of the characteristic signal corresponding to the orthoformate carbon (\(\delta=102\)), whilst preserving the carbonate signal (\(\delta=145\)). IR spectrum also confirmed the presence of the carbonate group (\(\text{C}=\text{O}\) peak at 1750 cm\(^{-1}\)). At last, the conformation of the deprotected polymer 10 was determined by the \(^1\text{H}\) NMR spectrum: the signals of the cyclohexane ring protons appear at the region between \(\delta=4.5\) and 4.0, strongly indicating that the axial conformation was maintained (\textit{vide supra}). It was, therefore, concluded that the inositol carbonate-based polymer 10 had the desired conformation, having all-triaxial hydroxyls, for metal binding.

**EXPERIMENTAL**

Melting points were determined using Büchi 510 melting point apparatus and uncorrected. IR spectra were recorded on a Nicolet MAGNA 560-FTIR spectrometer. \(^1\text{H}\) NMR spectra were recorded on a Bruker Advance DPX-300 and DPX-500 spectrometer with TMS as an internal standard. Mass spectra were obtained on a JEOL JMS-AX505WA instrument. The solvents were purified according to the conventional methods.

**Polymerization of 2-silyloxy-4,6-di((vinylbenzyl)oxy) inositol orthoformate to give polymer 2:**

The inositol monomer 1 (5.0 g, 9.3 mmol) and AIBN (150 mg, 3\% wt%) were dissolved in distilled toluene (93 mL). The solution was freeze-thaw degassed using liquid nitrogen (4 cycles), and was allowed to warm to r.t. before the solution was
heated at 65 °C for 48 h. The solution was concentrated in vacuo to give an oil. The oil was dissolved in THF (10 mL) and the solution was added dropwise to vigorously stirred methanol (100 mL). The colorless precipitate was collected and reprecipitated into methanol (100 mL) from THF (10 mL). The precipitate was collected and dried in vacuo to give the polymer 2 as a free flowing colorless powder (4.5 g, 90%); Found: C, 69.2; H, 7.5. C₅H₅O₇Si requires C, 69.4; H, 7.5%; v_m(ν(KBr/cm⁻¹) 2930, 2857, 1619, 1515, 1003 and 843; ¹H NMR (300 MHz, CDCl₃, δ) 6.8-6.0 (8H, br signal, 8-4H), 5.5 (1H, br signal, orthoformate), 4.8-4.6 (4H, br signal, 2-CH₂Ar), 4.5-4.1 (6H, br signal, 6-CH₂(CH₃), 1.8-0.8 (15H, br signal, 2-CH and 2-CH₃ from polymer backbone, and SiC(CH₃)₃) and 0.3-0.0 (6H, br signal, Si(CH₃)₂); GPC (CHCl₃, RI/Da Mₜ 18.3×10⁴, Mₜ 9.1×10⁴ and Mₚ/Mₜ 2.7.

Deprotection of polymer 2 to give the hydroxylated polymer 3: A solution of the inositol polymer 2 (1.0 g) and p-toluenesulfonic acid (0.1 g, 10 wt.%) in a mixture of THF (20 mL) and methanol (10 mL) was heated at 45 °C for 24 h. The large amount of precipitate that had formed was broken up with a spatula and the solution was heated for further 24 h at 45 °C. The solution was allowed to settle and the excess solvent was decanted off. The solid was filtered through a glass frit and washed with THF (2 mL). The solid was collected and dried to give the hydroxylated polymer 3 as an off-white solid (0.74 g, 90%); v_m(ν(KBr/cm⁻¹) 3400-3000 (O-H), 2911, 1512, 1422, 1103 and 1055; ¹H NMR (300 MHz, DMSO-d₆, δ) 7.6-5.9 (8H, br signal, 8-4H), 4.7-4.4 (4H, br signal, 4-CH₂), 4.3-4.1 (4H, br signal, 2-CH₂Ar), 3.5-3.0 (6H, br signal, 6-CH₂(CH₃), 2.3-0.5 (6H, br signal, 2-CH and 2-CH₃ from polymer backbone).

**TEMPO trapping experiment: Preparation of 4:** The inositol monomer 1 (78 mg, 0.15 mmol), AIBN (22 mg, 0.14 mmol) and TEMPO (9 mg, 0.05 mmol) were dissolved in distilled benzene (5 mL). The red-orange solution was freeze-dried degassed using liquid nitrogen (4 cycles) and was allowed to warm to r.t. under argon before the solution was heated for 12 h at 65 °C. The solvent was evaporated to give a liquid, which was purified by column chromatography (3:1 hexane:EtOAc and 2:1 hexane:ether). The unreacted inositol monomer 1 (70 mg, 90%) was first eluted, followed by the TEMPO adduct 4 as a colorless oil (2.5 mg, 0.2%); R, 0.27 (3:1 hexane:EtOAc), v_m(ν(KBr/cm⁻¹) 2956, 2858, 1472, 1401, 1259, 1165, 1003 and 852; ¹H NMR (500 MHz, CDCl₃, δ) 5.79 (2H, br s, vinyl CH), 5.33 (1H, s, orthoformate), 4.45 (1H, m, ring CH), 4.28 (1H, m, ring CH) or 4.25-4.20 (4H, m, ring CH or...
OCH₂), 4.18-4.03 (4H, m, OCH₂ or ring CH₄), 0.87 (9H, s, C(CH₃)₃) and 0.07 (6H, s, Si(CH₃)₃); ¹³C NMR (125.7 MHz, CDCl₃, δ) 127.7, 103.1, 74.4, 73.1, 69.1, 67.7, 61.7, 26.0, 18.5 and -1.6; m/z (CH₂) 357 ([M+H]⁺, 100%); 356 [M⁺, 70%]; [Found: (M+H)⁺ 357.1728. C₆H₆O₃Si requires M, 357.1733].

Deprotection of the acetylated orthoformate 8 to give the model compound 9: A solution of the cycloalkene 8 (20 mg, 0.056 mmol) and p-toluene-sulfonic acid (6 mg, 30 wt%) in a mixture of chloroform (5 mL) and methanol (1 mL) was stirred at r.t. for 24 h. The heterogeneous solution was filtered and the solid was washed with chloroform (5-2 mL) and methanol (5-1 mL). The solid was collected and dried under reduced pressure to give the tetralin 9 (2 mg, 20%) as a white solid; m.p. 281-283 °C (from methanol); νmax (KBr/cm⁻¹) 3500-3100 broad (O-H), 2961, 2931, 2872, 1457, 1363, 1250, 1156, 1108, 1058, 995 and 893; ¹H NMR (500 MHz, DMSO-d₆, δ) 5.75 (2H, br s, CH₂), 4.64 (1H, br s, OH), 4.58 (3H, m, OH), 4.12 (4H, ABq, J = 14.0, H₁ and H₂), 3.60 (1H, br s, H₃), 3.31 (2H, dd, J = 9.0 and 9.0, H₄), 3.20 (2H, multiplet containing dd, J = 9.0 and 3.0, H₅) and 2.92 (1H, ddd, J = 6.0, 9.0 and 9.0, H₆); ¹³C NMR (125.7 MHz, DMSO-d₆, δ) 129.7, 81.1, 74.3, 74.0 and 71.0; m/z (EI) 233 ([M+H⁺, 5%] and 173 (100%); [Found: (M+H)⁺ 233.1004. C₁₅H₁₃O₃ requires M, 233.1019].

8,9-Bispropenoyloxy-2,4,10-trioxa-tricyclo[3.3.1.1³⁷]decan-6-ol (12): The diallyl ether 11 (16.8 g, 62.2 mmol) and DABCO (7.0 g, 62.2 mmol) were added in a mixture of ethanol-toluene-water (7:3:1. 100 mL), followed by heating to 80 °C for 0.5 h to obtain a clear solution. The solution was cooled to r.t. and the tris(triphenylphosphine) rhodium (I) chloride (2.87 g, 3.1 mmol) was added, and the solution was left to stir overnight at 100 °C. The TLC analysis showed complete conversion to the isomerized form. The solution was passed through a short plug of Celite, washed with ethyl acetate and dried in vacuo. The isomerized product was purified by column chromatography (3:1 hexan:EtOAc) as a pale yellow oil (14 g, 83%); R: 0.35 (3:1 hexan:EtOAc); νmax (CHCl₃)/cm⁻¹ 3480 (O-H), 3050, 2967, 1672, 1170, 1000 and 900; ¹H NMR (300 MHz, CDC₁₃), δ limited data due to the presence of ca. 1:1 mixture of geometric isomers: 6.02 (1H, multiplet containing doublet, J = 13.5, OCH₂CH of trans), 5.93 (1H, multiplet containing doublet, J = 8.0, OCH₂CH of cis), 5.43 (1H, s, orthoformate CH), 1.49 (6H, m, 2-CH₂); m/z (FAB) 99 (100%), 115 (85%) and 289 (5%); [Found: (M+H)⁺ 271.1186. C₁₅H₁₃O₃ requires M, 271.1181].

9-(4-Vinylbenzoxyl)-2,4,10-trioxa-tricyclo[3.3.1.1³⁷]decan-6-8-carbonate (14): To a solution of the diol 13 (3.0 g, 9.8 mmol) in dry pyridine (60 mL), trisphosgene (8.7 g, 29.4 mmol) was carefully added at r.t. under N₂. The reaction mixture was stirred at r.t. for 18 h before it was quenched by the addition of sat.-NH₄Cl solution (20 mL). The aqueous layer was separated and was extracted with ethyl acetate (3-5 mL). The combined organic layers were washed with brine (20 mL), dried over MgSO₄ and evaporated. The milky oil was purified by column chromatography (1:1 hexane:EtOAc) to give the carbonate 14 as a white solid (1.93 g, 60%); m.p. 155-156 °C; R: 0.43 (1:1 hexane:EtOAc); νmax (KBr)/cm⁻¹ 3010, 2931, 1750 (carbonate C=O), 1601, 1594, 1180, 1105, 995 and 970; ¹H NMR (500 MHz, CDCl₃, δ) 7.44-7.34 (4H, m, ArH), 6.73 (1H, dd, J = 17.5 and 11. CH₂=CHAr), 5.78 (1H, d, J = 17.5, CH₂=CHAr), 5.60 (1H, br s, orthoformate CH), 5.28 (1H, d, J = 11, CH₂=CHAr), 5.05 (2H, ABq, J = 9.5, OCH₂Ar), 4.65 (2H, m, ring CH₂), 4.60-4.24 (4H, m, ring CH₂); ¹³C NMR (125.7 MHz, CDCl₃, δ) 143 (carbonate C), 138.3, 138.0, 136.6, 136.5, 114.7, 102.0 (orthoformate C), 72.3 (CH, ring C), 70.0 (CH, OCH₂Ar), 69.7 (CH, ring C), 66.6 (CH, ring C) and 60.0 (CH, ring C); m/z (FAB) 136 (80%), 154 (100%) and 335 (13%); [Found: (M+H)⁺ 333.0968. C₁₅H₁₃O₅ requires M, 333.0974].

Copolymerization of 9-(4-Vinylbenzoxyl)-6,8-carbonate in situ orthof ormulate 14 with styrene (15): The isostil monomer 14 (0.71 g, 2.1 mmol), styrene (0.25 ml, 2.1 mmol) and AlBN (0.025 g, 2.5 wt% relative to monomers) were dissolved in dry THF (42 mL; 0.1 M of monomers). The solution was freeze-thaw degassed using liquid nitrogen (4 cycles), and was allowed to warm to r.t.
before the solution was heated at 65 °C for 48 h. The solution was concentrated \textit{in vacuo} to give an oil. This was then dissolved in THF (5 mL) and the solution was added dropwise into a vigorously stirred methanol (50 mL). The precipitate was collected and reprecipitated into hot hexane (50 mL) from THF (5 mL). The precipitate was collected and dried to give the copolymer 15 as a white solid (750 mg, 80%); \( \nu_{\text{as}} \) (KBr)/cm\(^{-1} \) 3049, 3025, 2926, 2851, 1770 (carbonate C=O), 1600, 1456, 1446, 1385, 1366, 1062, 753 and 698; \( ^{1}H \) NMR (500 MHz, Acetone-\( \delta \), \( \delta \)) 7.2-6.2 (30H, br signal, 30-\( \text{ArH} \)), 5.6 (1H, br signal, orthoformate CH\(_{2} \)), 4.9 (2H, br signal, OCH\(_{3}\)/Ar), 4.6-4.2 (6H, br signal, 6-ring CH\(_{2} \)) and 1.9-1.0 [18H, br signal, CH and CH\(_{2} \) from inositol unit, 5-(CH and CH\(_{2} \) from styrene backbone)]; \(^{13}C \) NMR (125.7 MHz, Acetone-\( \delta \), \( \delta \)) selected data 146 (C, carbonate), 102.8 (CH, orthoformate); GPC (THF, RI): \( \tilde{M}_{n} \) 1.10×10\(^{3} \), \( \tilde{M}_{w} \) 3.89×10\(^{3} \) and \( \tilde{M}_{w}/\tilde{M}_{n} \) 3.5.

Deprotection of the copolymer 15 (10): A solution of the copolymer 15 (450 mg) and \( p \)-toluenesulfonic acid (100 mg, 22 wt%) in THF-methanol (2:1, 3 mL) was stirred at r.t. for 48 h. After this time, the solvent was removed \textit{in vacuo} to give a white solid. This was dissolved in THF (0.5 mL) and the solution was added dropwise into a vigorously stirred methanol (20 mL). The precipitate was collected and dried to give the deprotected polymer 10 as a white solid (322 mg, 78%); \( \nu_{\text{as}} \) (KBr)/cm\(^{-1} \) 3468 (O-H), 3073, 3059, 2913, 2858, 1750 (carbonate C=O), 1603, 1490, 1449, 1347, 1261, 1159, 1059, 748 and 700; \(^{1}H \) NMR (300 MHz, Acetone-\( \delta \), \( \delta \)) 7.2-6.2 (30H, br signal, 30-\( \text{ArH} \)), 5.0-4.6 (2H, br signal, OCH\(_{3}\)/Ar), 4.5-4.0 (6H, br signal, 6-ring CH\(_{2} \)), 3.8-3.2 (3H, br signal, 3-\( \text{OH} \)) and 2.9-1.0 [18H, br signal, CH and CH\(_{2} \) from inositol unit, 5-(CH and CH\(_{2} \) from styrene backbone)]; \(^{13}C \) NMR (75.4 MHz, Acetone-\( \delta \), \( \delta \)) selected data 145 (C, carbonate).

CONCLUSION

A conformationally rigid polymeric ligand having syn-triaxial hydroxyls has been successfully synthesized using the readily available \( \text{MeO-Tris} \)-inositol. We have also established an effective method to verify the conformation of the cyclohexane polymers by the comparative spectroscopic techniques. Polymeric analogues of inositol should be useful as a novel metal binding ligand as polymers are generally valued as chelating agents due to their advantages of easy use and removal after chelation. We are currently investigating the metal binding properties of this polymer.

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REFERENCES

7. Another possible steric requirement of the cyclohexane polyols for metal binding is such that the three O atoms on three consecutive carbon atoms in cyclohexane must be in axial, equatorial and axial positions.
10. Ring closing metathesis of 1 only produced oligomeric products.