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Polyketide Library Synthesis: Conformational Control In Extended Polypropionates.

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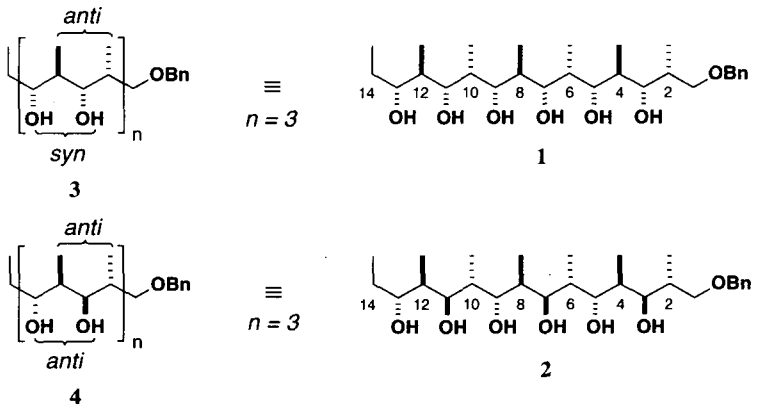
Abstract: The stereoregular heptapropionates **1** and **2** display contrasting conformational properties. The mutually reinforcing conformational determinants in hexol **1** lead to the population of essentially a single extended conformer with a helical twist. © 1997 Elsevier Science Ltd.

The biological activity of polyketide natural products is generally dependent on specific non-covalent interactions, where conformational preorganisation not only directs functional groups in space for target recognition but reduces the entropic penalty involved in binding. In the preceding paper,[1] we outlined a versatile strategy for the synthesis of libraries of unnatural polyketides, as demonstrated by the preparation of **1** and **2** shown below. We now report some of our results on conformational preorganisation in such designed polypropionates, which depends on the interplay of specific intramolecular hydrogen bonding patterns and the avoidance of *syn*-pentane steric interactions along the otherwise flexible hydrocarbon backbone. In the hexol **1**, these conformational determinants are found to be mutually reinforcing, leading to the population of essentially a single extended conformer having a helical twist.



The combination of stereoregular 1,3-*anti* methylation (*cf.* syndiotactic polypropylene) with 1,3-*syn* or *anti* related hydroxyl groups suggested that the polypropionate sequences **3** and, to a lesser extent, **4** should exhibit distinctive conformational properties. This methylation pattern is known to favour an extended main chain, where destabilising *syn*-pentane interactions are avoided.[2,3] Initially, the monomeric *syn*-diol **5** (≡ **3**, for n = 1) was examined (**Fig 1**). The calculated global minimum **6** (MM2, MacroModel,[4] v 4.5) has an extended alkane backbone with the methyl groups at C_2 and C_4 oriented to avoid *syn*-pentane interactions, reinforced by an intramolecular hydrogen bonding network. To obtain experimental evidence for this preorganisation, we related the observed vicinal ^{1}H NMR coupling constants[5] to those predicted by MacroModel, based on a Karplus-type relationship.[6] For H_3, the experimental ^3J values (1.4 and 9.5 Hz) agree with those calculated

(1.7 and 9.2 Hz; Boltzmann weighted over the conformer population at 300 K), reflecting the dihedral angles (80°, 162°) associated with the *trans-trans* (*tt*)[7] conformational preference. This strong divergence of coupling constants indicates a substantial predominance of a single conformation.

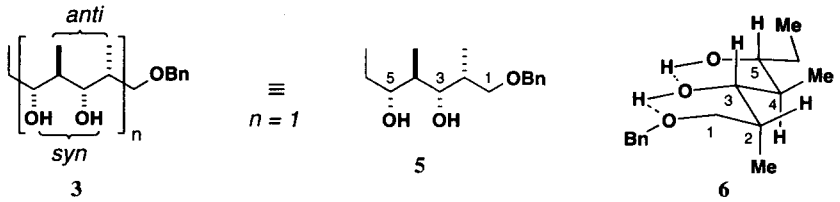


Fig 1: Hydrogen-bonded global minimum conformer of *syn*-diol **5**

To ascertain whether this local conformational control could be applied to a longer polypropionate chain, as occurs in **3** for n > 1, the heptapropionate **1** was studied (**Fig 2**). Monte-Carlo exploration of the accessible conformational space gave **7** as the global minimum conformer.[8] In this conformation, the alkane backbone has a helical twist with a mean dihedral angle of 168° (range 159 to 181°), indicative of near *tt* conformations throughout the main chain. In an analogous manner to **6**, this conformer is additionally stabilised by an extended hydrogen bonding network (mean OH–H distance 1.88 Å), terminating on the benzyl ether oxygen. Experimental evidence for this conformational preference was again sought, initially from the vicinal ^{1}H NMR coupling constants. For the methine protons α to the hydroxyl groups in **1**, the calculated ^3J values (Boltzmann weighted at 300 K) fell into two distinct ranges, 0.6–1.7 Hz and 10.1–10.6 Hz, reflecting the dihedral angles of the *tt* conformational preference for the main chain. Although these protons have inherently similar chemical environments, the observable ^3J values of 1.2, 1.3, 1.5, 1.7 and 9.3, 9.4 Hz (500 MHz, C_6D_6)[5] provide support for a strong bias in the conformer equilibrium of hexol **1** in solution, towards that calculated *in vacuo*.

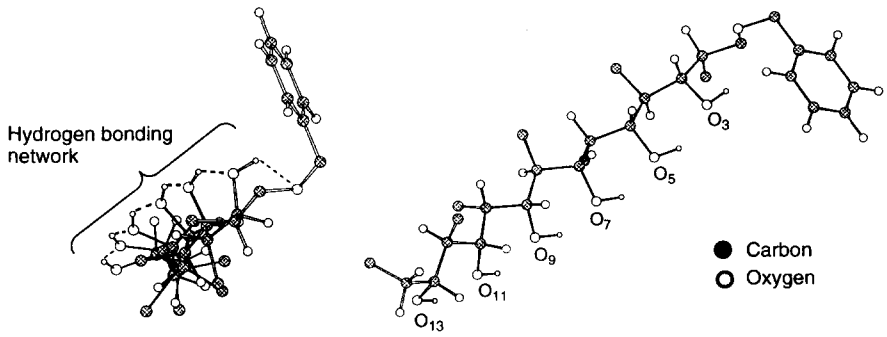


Fig 2: Global minimum conformer **7** of hexol **1** (only selected H shown for clarity)

The foregoing modelling results predict the existence of an extended intramolecular hydrogen bonding network, reinforcing the conformational constraint provided by the 1,3-*anti* methylation on the backbone. As shown in **Fig 3**, the hydroxyl protons of **1** are markedly downfield in chemical shift (δ range 4.47–6.07 ppm in C_6D_6) and appear as six distinct singlets.[5] Over the concentration range of 0.5 mM to 17.4 mM, these chemical shifts are invariant ($\Delta(\delta) \leq 0.03$ ppm), supporting the existence of well-defined intramolecular hydrogen bonding networks. These stabilising hydrogen bonds can be thought of as forming 6-membered rings along the length of the alkane backbone, thereby constraining the molecular conformation.

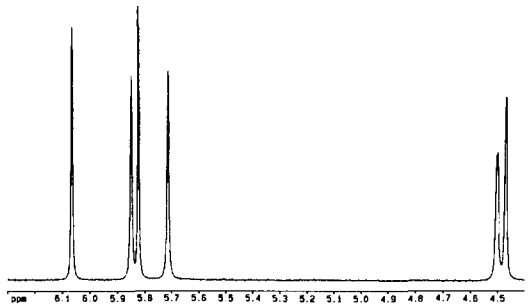


Fig 3: Part of the ^{1}H NMR spectrum of hexol **1** (6.3 to 4.4 ppm, C_6D_6 solution)

From the molecular modelling, the methyl groups of the main chain (excluding the ethyl terminus) were predicted to split into two distinct chemical shift groupings, due to their distinct chemical environments in **7**. A NOESY experiment (500 MHz, C_6D_6) permitted us to move through space between the backbone methyl groups, thereby allowing unambiguous assignment. The expected separation was observed: 1.15, 1.10, 1.04 ppm for the 1,5-*syn* methyl groups behind the plane (2-Me, 6-Me, and 10-Me), whereas those in front (4-Me, 8-Me and 12-Me) appeared at 0.70, 0.60 and 0.55 ppm. Moreover, the methyl groups exhibited quite distinct NOE patterns (**Fig 4**), as expected from the preferred conformation **7**. This is illustrated by considering the methyl groups attached to C_6 and C_8. From the modelling results, we expected the 8-Me to show the observed NOE contacts with H_7, H_8 and H_9 and with H_6 and H_{10}. Contrastingly, the 6-Me shows NOEs to H_4, H_6 and H_8 but there are no observable NOEs to either H_5 or H_7. In the global minimum conformer, H_5 and H_7 are locked in a *trans* arrangement (dihedral angles 165, 177°) with respect to the 6-Me, and are thereby constrained to the opposite face of the molecule. Whilst not positive evidence, this is supportive of the local conformation in this region of the molecule. Indeed, neither the 2-Me, 6-Me nor the 10-Me show cross-peaks to the methines of the adjacent hydroxyl bearing carbons.[9]

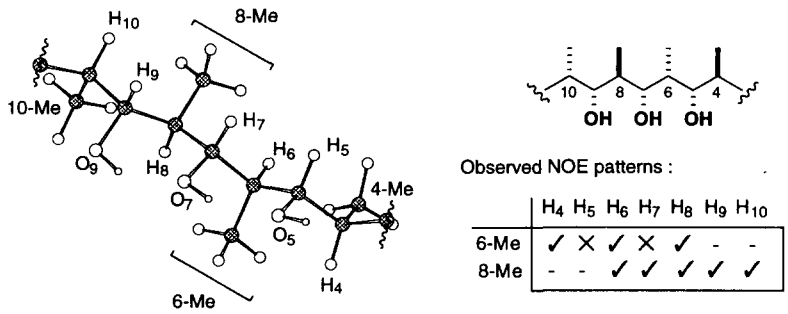


Fig 4: Molecular fragment of **1** with observed NOEs

We next turned to the diastereomeric hexol **2**, where the configurations at three of the six hydroxyl bearing carbons (at C_3, C_7 and C_{11}) have been inverted relative to **1**. This enabled us to establish that the internal hydrogen bonding pattern observed in **1** was highly specific. In contrast to **1**, molecular modelling of the hexol **2** did not provide any similar distinct global minimum. In the ^{1}H NMR spectrum (500 MHz, $CDCl_3$),[5,10] the hydroxyl protons in **2** are considerably relaxed such as to preclude observation of vicinal coupling constants, and there is no evidence for specific hydrogen bonding. In this case, the 1,3-*anti* related hydroxyl groups are

presumably no longer all in an appropriate spatial arrangement to cooperatively hydrogen bond, *i.e.* the conformational determinants in **2** are now non-reinforcing.

In summary, the avoidance of *syn*-pentane steric interactions can act in concert with internal hydrogen bonding, controlling the geometry of an otherwise fully flexible backbone in the hexol **1**, and forcing it to populate a single extended conformer with a helical twist. Further studies of the conformational properties of the diverse molecular backbones generated in our polyketide libraries are underway.

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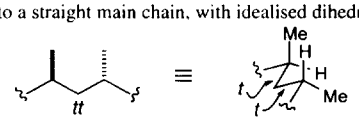
References and Notes

1. Paterson, I.; Scott, J. P. *Tetrahedron Lett.* **1997**, *38*, 7441.
2. For a review on conformational aspects of polypropionates, see: Hoffmann, R. W. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1124.
3. For leading references to other work on conformationally restricted, acyclic systems, see: (a) Göttlich, R.; Kahrs, B. C.; Krüger, J.; Hoffmann, R. W. *Chem. Commun.* **1997**, 247. (b) Hoffmann, R. W.; Schopfer, U.; Stahl, M. *Tetrahedron Lett.* **1997**, *38*, 4055. (c) Göttlich, R.; Fäcke, T.; Rolle, U.; Hoffmann, R. W. *J. Chem. Soc., Perkin Trans. II* **1996**, 2059.
4. Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440.
5. Diol **5** had ^{1}H NMR δ (500 MHz, $CDCl_3$) 7.38 - 7.27 (5H, m), 4.54 and 4.52 (2H, ABq, *J* = 12.0 Hz), 3.97 (1H, s), 3.81 (1H, dd, *J* = 1.4, 9.5 Hz), 3.74 (1H, s), 3.64 - 3.55 (3H, m), 1.97 - 1.90 (1H, m), 1.70 - 1.60 (2H, m), 1.46 - 1.37 (1H, m), 0.99 (3H, d, *J* = 6.7 Hz), 0.97 (3H, t, *J* = 7.3 Hz), 0.74 (3H, d, *J* = 6.9 Hz); ^{13}C NMR δ (100 MHz, $CDCl_3$) 137.6, 128.5, 127.8, 127.6, 79.6, 77.3, 75.6, 73.5, 40.2, 35.0, 27.1, 12.6, 9.3, 9.1; HRMS (CI, NH_3) found 267.1960, $C_{16}H_{27}O_3$ [M+1] requires 267.1960. Hexol **1** had ^{1}H NMR δ (500 MHz, C_6D_6) 7.35 - 7.15 (5H, m), 6.07 (1H, s), 5.85 (1H, s), 5.82 (1H, s), 5.72 (1H, s), 4.50 (1H, s), 4.48 (1H, s), 4.34 and 4.30 (2H, ABq, *J* = 12.0 Hz), 3.98 (1H, dd, *J* = 1.5, Obs Hz), 3.96 (1H, dd, *J* = 1.3, Obs Hz), 3.92 (1H, dd, *J* = 1.2, 9.4 Hz), 3.89 (1H, dd, J = 1.7, 9.3 Hz), 3.87 (1H, m), 3.77 - 3.75 (1H, m), 3.47 - 3.40 (2H, m), 1.89 - 1.71 (7H, m), 1.60 - 1.51 (1H, m), 1.22 (3H, t, *J* = 7.3 Hz), 1.15 (3H, d, *J* = 7.0 Hz), 1.10 (3H, d, *J* = 6.9 Hz), 1.04 (3H, d, *J* = 7.0 Hz), 0.70 (3H, d, *J* = 6.9 Hz), 0.60 (3H, d, *J* = 6.8 Hz), 0.55 (3H, d, *J* = 6.9 Hz); ^{13}C NMR δ (62.5 MHz, $CDCl_3$) 137.7, 128.5, 127.9, 127.6, 83.7, 83.1 - 83.0 (3C), 80.4, 77.5, 75.9, 73.6, 40.1, 38.0 (2C), 35.1 (3C), 27.3, 13.2, 13.1, 12.8, 9.4, 9.1, 4.3, 4.2; HRMS (+FAB) found 499.3672, $C_{28}H_{51}O_7$ [M+1] requires 499.3635; Anal. found C 67.64, H 9.98, $C_{28}H_{50}O_7$ requires C 67.44, H 10.11. Hexol **2** had ^{1}H NMR δ (500 MHz, CD_3OD) 7.37 - 7.20 (5H, m), 4.52 (2H, s), 4.05 - 3.95 (4H, m), 3.88 (1H, dd *J* = 1.2, 9.8 Hz), 3.70 (1H, dd, *J* = 4.5, 9.0 Hz), 3.56 (1H, dd, *J* = 6.4, 8.9 Hz), 3.51 - 3.48 (1H, m), 1.94 - 1.86 (1H, m), 1.79 - 1.56 (6H, m), 1.53 - 1.43 (1H, m), 0.98 (3H, t, *J* = 7.4 Hz), 0.92 (3H, d, *J* = 6.8 Hz), 0.92 (3H, d, *J* = 7.0 Hz), 0.81 - 0.73 (12H, m); ^{13}C NMR δ (62.5 MHz, CD_3OD) 137.0, 126.4, 125.9, 125.7, 74.3, 72.7, 71.4, 70.7, 70.2, 69.5, 69.1 (2C), 37.2, 36.1 (3C), 35.7, 35.4, 25.6, 11.5, 7.8, 7.3, 6.4 (3C), 6.2; HRMS (+FAB) found 499.3670, $C_{28}H_{51}O_7$ [M+1] requires 499.3635.
6. (a) Haasnoot, C. A. G.; de Leeuw, F. A. A. M.; Altona, C. *Tetrahedron* **1980**, *36*, 2783. (b) Haasnoot, C. A. G.; de Leeuw, F. A. A. M.; de Leeuw, H. P. M.; Altona, C. *Org. Magn. Reson.* **1981**, *15*, 43.
7. The local conformation *trans-trans* leads to a straight main chain, with idealised dihedral angles of 180°, as shown in **Fig 5**.

Fig 5



8. We found 11 conformers within 10.5 kJmol^{-1} of the global minimum, all of which had essentially an identical main chain conformation, differing only in the orientations of the unconstrained ethyl and benzyloxy termini.
9. The terminal ethyl and benzyloxy groups are essentially conformationally unrestricted, such that the 14-Me exhibits an NOE contact with H_{13} and the 2-Me contacts with both the C_1 methylene protons.
10. We could only obtain satisfactory NMR spectra for **2** in the hydrogen bonding solvent CD_3OD, precluding direct comparison with the studies on **1**.

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