Melt supramolecular assembly of oligomers with regularly spaced, alternating hydrogen bonding and hydrophobic sites

Bryan Greener* and John Rose

Smith & Nephew Group Research Centre, York Science Park, Heslington, York, UK YO10 5DF. E-mail: bryan.greener@smith-nephew.com

Received (in Liverpool, UK) 18th August 1999, Accepted 18th October 1999

The melt condensation of 2,5-dihydroxybenzoic acid with dodecanedioyl dichloride resulted in oligomers with regularly spaced, multiple hydrogen bonding sites; fibres were drawn from melts at 150 °C.

Non-covalent interactions dominate the mechanisms of life. Hydrogen bonds and hydrophobic effects are frequently invoked to describe complex biochemical processes.[1] Much recent endeavour has been directed at the modelling of these exquisite interactions,[2] in the hope that such principles can be applied to industrial syntheses. It is striking that biochemical processes require the complementary interplay of both hydrophobic and hydrophilic interactions. This observation has provided inspiration in the fields of self assembly[3] and supramolecular polymer chemistry.[4] Attempts to create polymers linked only by non-covalent interactions (multiple hydrogen bonds) have achieved varying degrees of success.[4]

Replacing a single covalent bond with a non-covalent interaction of equivalent strength requires the interaction of multiple adjacent hydrogen bonding sites,[5] and it has been demonstrated that even the ordering of donor and acceptor groups at these sites can have a significant effect upon the overall interaction achieved.[6] Multiple adjacent sites have been realised, to date, by employing a limited range of nitrogen based donor/acceptor moieties.[4] To overcome the entropic barrier to the assembly of multiple non-covalent interactions systems reported thus far have clustered the interactive groups at terminal sites only,[5] thus limiting the number of hydrogen bonds that can be accommodated between adjacent molecules. With the aim of increasing the number of non-covalent interactions between adjacent molecules, here we report the synthesis and preliminary characterisation of biocompatible oligomers capable of multiple, multisite hydrogen bonding and hydrophobic interactions.[7]

The direct melt reaction of the aspirin metabolite and moth silk component,[8] 2,5-dihydroxybenzoic acid (gentisic acid) **G** with 1 equiv. of lauroyl chloride **L** produced 3-carboxy-4-hydroxyphenyl laurate **GL** in > 99% purity as determined by ^{1}H NMR spectroscopy. The specificity of this reaction was proposed to be due to the strong nucleophilicity of **G** in the 5-hydroxy position compared to the intramolecularly hydrogen bonded 2-hydroxy position. Furthermore, melt reactions involving *n* equiv. of **G** and $(n-1)$ equiv. of dodecanedioyl dichloride **D** produced a series of oligomers of average composition $\mathbf{G}_n\mathbf{D}_{n-1}$ (n = 2, 3, 4). While $\mathbf{G_2D_1}$ was a discrete compound, reaction products $\mathbf{G_3D_2}$ and $\mathbf{G_4D_3}$ were distributed over a narrow oligomeric range, as elucidated by electrospray MS and ^{1}H NMR spectroscopy. The three $\mathbf{G}_n\mathbf{D}_{n-1}$ oligomers were > 95% **G** capped (through the 5-hydroxy) as shown by ^{1}H and ^{13}C NMR spectroscopy. Reaction of 1 equiv. **G** with 1 equiv. of **D** produced **GD**, an oligomeric distribution centred around three of each subunit with random end-caps (**G** capping through the 5-hydroxy). For purposes of comparison, equivalent compounds were synthesised in an identical manner with methyl-2,5-dihydroxybenzoate **MeG** in the place of **G**; all lacked an intermolecular hydrogen bond donor.

All of the aforementioned compounds were fully soluble in THF, while only the **MeG**-based compounds were soluble in $CHCl_3$. Remarkably, **GD** dissolved a 40-fold molar excess of $CHCl_3$, resulting in liquification; phase separation occurred in the presence of excess $CHCl_3$. Comparison of the ^{13}C NMR spectra of **GD** in THF-d_8 and $CDCl_3$ showed a 5 ppm down-field shifting of inner-chain **G** carbonyl carbons (from δ_c 165.0 to 170.0) and a 1 ppm down-field shifting of terminal **G** carbonyl carbons (from δ_c 170.5 to 171.5) on moving from THF-d_8 to $CDCl_3$. This shifting was consistent with the **G** carbonyl oxygen acting as an intermolecular hydrogen bond acceptor site in terminal and inner-chain positions.[9] Infrared spectroscopic study of the oligomers was hampered by the intramolecular hydrogen bonding already present, however, **G** carbonyl absorbances (1700 cm^{-1}) were broadened due to multiple overlapping bands in contrast to the sharp discrete absorbance in **MeG**-based oligomers.

The melt behaviour of $\mathbf{G}_n\mathbf{D}_{n-1}$ oligomers was in sharp contrast to that of $\mathbf{MeG}_n\mathbf{D}_{n-1}$ oligomers in the respect that transparent, flexible, self-adherent fibres could be pulled from $\mathbf{G}_n\mathbf{D}_{n-1}$ compounds in the melt (150 °C) while $\mathbf{MeG}_n\mathbf{D}_{n-1}$ showed no such tendancy. Viscometric analysis of the oligomers was performed, in duplicate, at 150 °C and the resulting measured viscosities are shown in Table 1.[10] In general, the viscosity of **G**-based oligomers was an order of magnitude greater than that of the corresponding **MeG**-based oligomers. The significantly higher viscosities observed for **GD** than for $\mathbf{G}_n\mathbf{D}_{n-1}$ were due to a significantly broader oligomeric distribution in the former oligomers. These differences in physical properties can be attributed only to intermolecular hydrogen bonding interactions present in $\mathbf{G}_n\mathbf{D}_{n-1}$ but not $\mathbf{MeG}_n\mathbf{D}_{n-1}$.

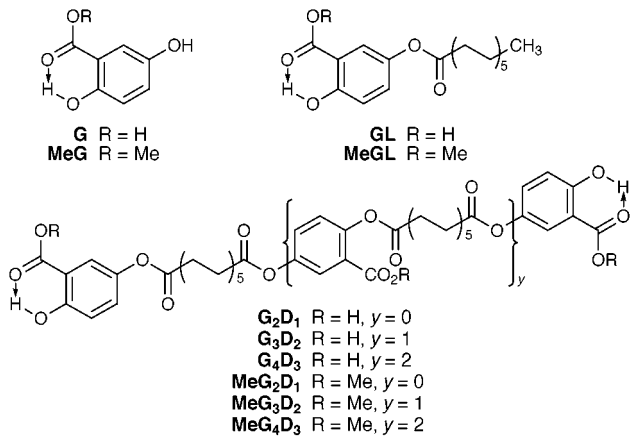

Table 1 Variation of viscosity in **G**- and **MeG**-based compounds

Oligomer	Viscosity/Pa s		Oligomer	Viscosity/Pa s	
MeGL	0.001	0.001	**GL**	0.007	0.009
$\mathbf{MeG_2D_1}$	0.007	0.010	$\mathbf{G_2D_1}$	0.148	0.066
$\mathbf{MeG_3D_2}$	0.022	0.017	$\mathbf{G_3D_2}$	0.346	0.319
$\mathbf{MeG_4D_3}$	0.030	0.017	$\mathbf{G_4D_3}$	0.820	0.771
MeGD	0.249	0.465	**GD**	2.909	3.399

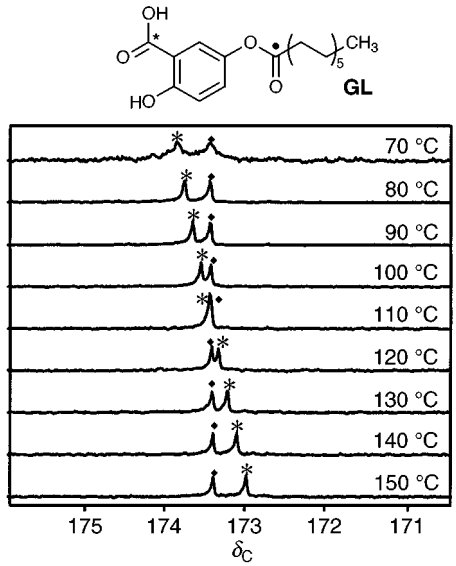

Fig. 1 ^{13}C NMR spectra (67 MHz) of neat **GL** recorded at various temperatures.

Further evidence of the intermolecular hydrogen bonding present in **GL**, in contrast to **MeGL**, was provided by a variable temperature ^{13}C NMR melt study. Neat samples of **GL** and **MeGL** were heated to temperatures in the range 70–150 °C. At each temperature the ^{13}C NMR spectrum of the sample was recorded. The result for **GL** is shown in Fig. 1. It can be seen that as the temperature was decreased the carboxylic carbonyl shifted to lower field, consistent with electronic donation to a hydrogen bond from the attached carbonyl oxygen.[9] No shifting was observed over this temperature range for **MeGL**.

The importance of hydrophobic interactions, between the alkyl chains of the oligomers, in producing the above physical effects was supported by the UV–VIS spectroscopic observations summarised in Fig. 2. It can be seen that λ_{max} did not vary widely for compounds with free 5-hydroxys, **G** and **MeG** (330–341 nm), or **MeGL** (315–318 nm), on going from THF solution to cast film (solid); 2-hydroxybenzoic acid (salicylic acid) **S** is also shown in Fig. 2 for comparison. The exception to

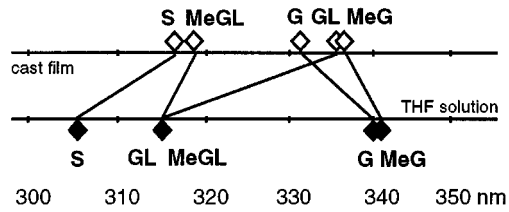

Fig. 2 Position of λ_{max} for **S**, **G**, **MeG**, **GL** and **MeGL** recorded as THF solutions and solid cast films on KBr.

this general rule was **GL**, which exhibited a 21 nm bathochromic shift on going from THF solution to cast film (solid), consistent with the effect of hydrogen bond formation in the solid state.[9] Extinction coefficients at these wavelengths were in the range 3700–7500 mol^{-1} dm^3 cm^{-1} for all compounds ($\pi\rightarrow\pi^*$ transition). In $\mathbf{G}_n\mathbf{D}_{n-1}$ and $\mathbf{MeG}_n\mathbf{D}_{n-1}$ oligomers a pair of absorbance bands were observed. The variation of these bands with formulation allowed us to deduce that the band at 313 nm was the result of a $\pi\rightarrow\pi^*$ transition in terminal **G** units (consistent with observations recorded in Fig. 2), while the band at 289 nm was the result of a $\pi\rightarrow\pi^*$ transition in inner chain **G** units.

We propose that the physical and spectroscopic observations reported herein can be accounted for by the hydrogen bonded aggregation of **G**-based subunits in a manner consistent with the previously reported crystal structure of **G**.[11] The hydrophobic compatibility of **D** with **D**, the hydrophilic, hydrogen bonded attraction of **G** with **G** and the mutual incompatibility of these two interactions promotes the hydrogen bonded aggregation of **G** moieties.

In conclusion, we have demonstrated the synthesis and preliminary characterisation of a new group of biocompatible supramolecular polymers. Further chemical and physical investigation of these systems is underway.

Notes and references

1 D. N. Silverman and S. Lindskog, *Acc. Chem. Res.*, 1988, **21**, 30.
2 B. Greener, M. H. Moore and P. H. Walton, *Chem. Commun.*, 1996, 27.
3 J. S. Moore, *Curr. Opin. Colloid Interface Sci.*, 1999, **4**, 108; N. Zimmerman, J. S. Moore and S. C. Zimmerman, *Chem. Ind.*, 1998, **15**, 604; R. B. Prince, T. Okada and J. S. Moore, *Angew. Chem., Int. Ed.*, 1999, **38**, 233.
4 R. P. Sijbesma, F. H. Beijer, L. Brunsveld, B. J. B. Folmer, J. H. K. K. Hirschberg, R. F. M. Lange, J. K. L. Lowe and E. W. Meijer, *Science*, 1997, **278**, 1601 and references cited therein.
5 B. J. B. Folmer, E. Cavini, R. P. Sijbesma and E. W. Meijer, *Chem. Commun.*, 1998, 1847; M. Kotera, J-M Lehn and J-P Vigneron, *J. Chem. Soc., Chem. Commun.*, 1994, 197.
6 T. J. Murray and S. C. Zimmerman, *J. Am. Chem. Soc.*, 1992, **114**, 4010.
7 Pat. Appl. 9917461.7
8 T. Ji, J. H. Hu, J. Wang, H. F. Guo, D. Z. Jin and J. T. Ju, *Sci. Chin., Ser. B*, 1993, **36**, 1046.
9 S. N. Vinogradov and R. H. Linnell, *Hydrogen Bonding*, Van Nostrand Reinhold, New York, 1971.
10 Samples were tested, in duplicate, on a Carrimed CSL500 constant stress rheometer, using a 4 cm diameter parallel plate and a 500 μm gap. Tests were carried out at 150 °C, except for $\mathbf{G_2D_1}$ which was tested at 170 °C as the material was solid at 150 °C.
11 M. Haisa, S. Kashino, S-I. Hanada, K. Tanaka, S. Okazaki and M. Shibagaki, *Acta Crystallogr., Sect. B*, 1982, **38**, 1480.

Communication 9/06756F