COMMUNICATION

ChemComm
www.rsc.org/chemcomm

Facile synthesis of aliphatic hyperbranched polyesters based on diethyl malonate and their irreversible molecular encapsulation†

Santimukul Santra and Anil Kumar*

Department of Chemistry, Indian Institute of Technology, Bombay, India. E-mail: anilkumar@iitb.ac.in; Fax: 91 22 25767152; Tel: 91 22 25767153

Received (in Cambridge, UK) 24th March 2004, Accepted 28th June 2004
First published as an Advance Article on the web 29th July 2004

Synthesis of diethyl malonate based wholly aliphatic hyperbranched polyesters having suitable polar matrix for irreversible molecular encapsulation is carried out for the first time.

The synthesis, characterization and applications of dendritic macromolecules are the most widely studied fields of research due to their unique chemical and physical properties.[1] These are mainly classified as dendrimers having well-defined structures and hyperbranched polymers having less controlled branched structure. Hyperbranched polymers are synthesized from AB_x ($x \geqslant 2$)-type monomers through a conventional polycondensation route. AB_2 monomers are the most common but AB_3, AB_4 and AB_6 monomers have also been reported.[2] These macromolecules having highly functionalized globular shape are used in the field of life sciences such as controlled drug delivery systems (DDS), gene therapy, organ transplantation and in other biomimetics.[3] The wholly aliphatic dendrimer, polyamidoamine (PAMAM)[4] is the most widely used polymer in several bio-applications. There are only a limited number of aliphatic hyperbranched polymers reported in the literature such as polyglycerol,[5–7] polyethers[8] from 3-ethyl-3-(hydroxymethyl) oxetane and polyesters[9] based on 2,2-bis(hydroxymethyl) propionic acid (bis-MPA). The encapsulation studies with guest molecules have been reported with polyglycerols and they are known to be biocompatible.[6,7] Frechet and co-workers[10] reported the fully aliphatic hyperbranched polyesters based on caprolactone derivative which was described to be biodegradable. Another bio-degradable poly(amino ester) reported by Park and co workers[11] showed efficient transfection and minimum toxicity. Apart from the above mentioned reports on aliphatic systems,[5–11] most of the reported hyperbranched polymers were mainly aromatic.[12] This is due to the difficulties involved in design, synthesis and purification of aliphatic monomers with proper functional connectivity. However, some of the advantages of the wholly aliphatic hyperbranched polymers are: better solubility, highly functional surface, globular shape and presence of polar cavity. Thus, there is a greater need for a facile and efficient synthesis of wholly aliphatic hyperbranched polyesters. It will be of great advantage if the synthesis can be achieved in very few efficient steps and has the potential for easy structural modifications.

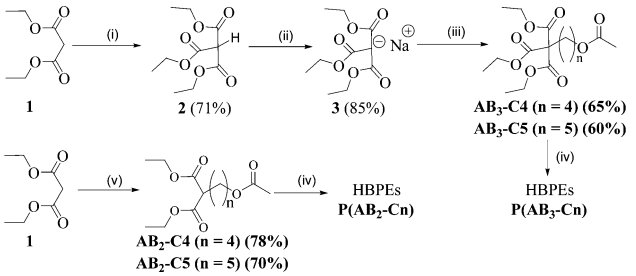
In this paper, we report the synthesis and characterization of aliphatic hyperbranched polyesters (HBPE) from AB_2 and AB_3 systems based on diethyl malonate. The salient features of the present synthetic route are that the monomers can be synthesized in one step from the commercially available diethyl malonate. Furthermore, the structural modifications in terms of the length of the aliphatic spacer (to change the internal cavity size) and the nature of the monomer, *i.e.*, AB_2 or AB_3 (to change the surface functionality) can be easily achieved. Therefore, the present design has the potential for the design and synthesis of a whole range of new aliphatic hyperbranched polyesters. Encapsulation studies were also carried out by using methyl orange as a guest molecule and the results are discussed.

† Electronic supplementary information (ESI) available: Experimental details along with the spectral data and UV/Vis spectra for encapsulation studies. See http://www.rsc.org/suppdata/cc/b4/b404447a/

DOI: 10.1039/b404447a

The synthetic strategy for the preparation of AB_3 systems is shown in Scheme 1. One of the acidic protons of diethyl malonate (**1**) was selectively removed by using Grignard reaction to get triethyl methanetricarboxylate (**2**).[13] The treatment with sodium ethoxide on **2** resulted in the sodium salt **3**, to which the aliphatic spacers were incorporated by reacting with 4-bromobutyl acetate (**4**) or 5-iodopentyl acetate (**5**)[14] to get colourless liquid monomers **AB3–C4** and **AB_3–C5** respectively. For the synthesis of AB_2 monomers (**AB_2–C4** and **AB_2–C5**), the synthetic procedure described by Arumugam *et al.*[15] was followed, but without using any catalyst, since the conventional sodium ethoxide method resulted in mainly dialkylation of diethyl malonate (Scheme 1). These monomers were then polymerized by the standard melt polymerization technique using zinc acetate as catalyst to get the corresponding polymers **P(AB_3–C4)**, **P(AB_3–C5), P(AB_2–C4)** and **P(AB_2–C5)**.

All the polymers were soluble in $CHCl_3$, DMF and DMSO when prepared at 190 °C for 8 h. However, when the polymerization was carried out further after 8 h under vacuum for 2 h, the polymers were found to be insoluble in $CHCl_3$ but were still soluble in DMF and DMSO. Yields and weight average molecular weight (M_w) obtained from SEC for the DMF soluble polymers are summarized in Table 1. The comparison of molecular weights of the AB_3 and AB_2 systems shows that the weight average molecular weights of the former ones were lower than that of the latter. This could be due to the crowded transition states (TS) in the case of AB_3 systems, where the ester carbonyl carbons were attached to the R_3C– group.[9] If one considers the AB_2 systems, less sterically crowded TS is expected since the ester carbonyl is attached to the R_2C– group. Hence the reaction would be more feasible and high molecular weight polymer is obtained for the AB_2 systems as expected. In order to study the effect of polymerization time at



Scheme 1 Synthesis of aliphatic HBPEs from AB_3 and AB_2 monomers.

Table 1 Properties of the polymers

Polymer	Yield (%)	T_{dec} (°C)[a]	M_w (PD)[b]
P(AB_3–C4)	45	245	32900 (1.1)
P(AB_3–C5)	48	260	36700 (1.6)
P(AB_2–C4)	52	250	74800 (1.7)
P(AB_2–C5)	54	276	122500 (2.1)

[a] Decomposition temperature at 10% weight loss in TGA studies; [b] Weight average molecular weight obtained from SEC analysis in DMF solvent; the polydispersity (PD) values are given in parenthesis.

190 °C on the weight average molecular weight (M_w), the samples were taken from the reaction mixture during the polymerization and were analyzed by SEC. It was observed that with increase in time, there was a gradual increase in molecular weight for the first 8 h when the polymerization was done at atmospheric pressure. However, a sharp increase in molecular weight was observed after 8 h when the polymerization was carried out under low pressure. When this low pressure polymerization was continued beyond 2 h, it resulted in the formation of insoluble materials. This insolubility could be because of the very high molecular weight polymer formation. Thermogravimetric analysis (TGA) indicated moderate thermal stability for these polymers. The decomposition temperatures at which 10% weight loss occurred were ranging from 245 °C to 276 °C.

For highly branched polyesters, calculation of the degree of branching is an important parameter. However, in the present case, these calculations were not possible because the NMR (both ^{1}H and ^{13}C) signals of the internal methylene units were not sensitive if these belong to the dendritic, terminal or linear units. However, in the case of hyperbranched polymers, the number of internal units approaches the number of terminal units at higher degree of polymerization.[16] In the present hyperbranched polyesters, one can calculate the number of terminal units from the methyl protons (-COOCH$_2$*CH$_3$*) and the number of internal units from the methylene protons (–CH$_2$COO*CH$_2$*CH$_2$–) in ^{1}H NMR spectroscopy. The number of terminal units was found to be comparable to that of internal units indicating highly branched structures for the polymers synthesized.

Encapsulation studies using methyl orange dye were carried out to explore the efficiency of the polar binding sites in the polymer matrix, which would be used for drug encapsulation. For these studies, the chloroform soluble hyperbranched polyester, **P(AB$_2$–C4)**, (M_w = 49 000, PD = 3.4) was synthesized by carrying out the polymerization at 190 °C for 8 h under atmospheric pressure. The chloroform solution of polyester was agitated briefly with different concentrations of dye dissolved in the aqueous phase. The observation of an absorbance maximum at 400 nm in the UV/Vis spectrum confirmed the presence of dye in the organic layer. In all cases a linear change in the color intensity of both the layers was observed below the saturation point. After the saturation point, there was no change in absorption with further increase of the dye concentration (Fig. 1). Methyl orange (dye) was quantitatively extracted into the organic layer and it was calculated that an average load of 0.61 molecules of the dye were encapsulated per polymer molecule. These calculations have been done quantitatively from UV/Vis experiments by assuming the same absorption coefficient for the dye in both the layers.[5] Irreversible encapsulation of the dye molecules was confirmed by recording UV/Vis spectra after sonication.

In summary, a series of diethyl malonate based aliphatic hyperbranched polyesters containing flexible aliphatic spacers were synthesized for the first time. High molecular weight polymers were obtained from AB_2 systems compared to the AB_3 systems due to the less crowded structures of the AB_2 monomers. The polymers showed moderate thermal stability in TGA studies. The presence of the binding sites in the polymer matrix was confirmed by the observation of the irreversible molecular encapsulation, which could be a promising factor in the field of drug delivery. Non-toxicity and biodegradation studies of the polymers using microbes collected from soil are currently in progress.

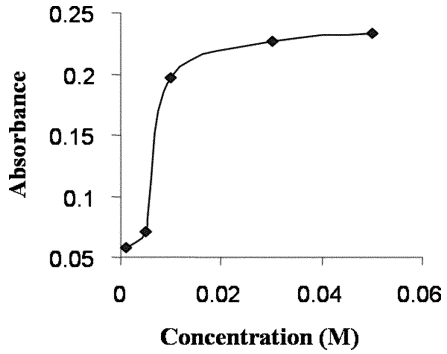


Fig. 1 Absorbance of dye molecules into the polymer matrix as a function of different dye concentrations.

We would like to thank the MHRD and DST India for financial help and the RSIC, Bombay for instrumental facilities. S.S. thanks the CSIR, India for a Senior Research Fellowship.

Notes and references

1 (*a*) G. R. Newkome, C. N. Moorefield, G. R. Baker and R. K. Behera, *Angew. Chem., Int. Ed.*, 1991, **30**, 1176; (*b*) B. I. Voit, *Acta Polym.*, 1995, **46**, 87.
2 (*a*) L. J. Mathias and T. W. Carothers, *J. Am. Chem. Soc.*, 1991, **113**, 4043; (*b*) J. F. Miravet and J. M. J. Frechet, *Macromolecules*, 1998, **31**, 3461; (*c*) J. M. J. Frechet, M. Henmi, I. Gitsov, S. Aoshima, M. Leduc and R. Grubbs, *Science*, 1995, **269**, 1080.
3 (*a*) A. U. Bielinska, C. Chen, J. Johnson and J. R. Baker, Jr., *Bioconjugate Chem.*, 1999, **10**, 843; (*b*) M. X. Tang, C. T. Redemann and F. C. Szoka, Jr., *Bioconjugate Chem.*, 1999, **7**, 703.
4 D. A. Tomalia, *Macromolecules*, 1986, **19**, 2466.
5 A. Sunder, M. Kramer, R. Hanselmann, R. Mulhaupt and H. Frey, *Angew. Chem.Int. Ed.*, 1999, **38**, 3552.
6 M. Kramer, J. Stumbe, H. Turk, S. Krause, A. Komp, L. Delineau, S. Prokhorova, H. Kautz and R. Haag, *Angew. Chem. Int. Ed.*, 2002, **41**, 4252.
7 A. Sunder, R. Mulhaupt and H. Frey, *Macromolecules*, 2000, **33**, 309.
8 H. Magnusson, E. Malmstrom and A. Hult, *Macromolecules*, 2001, **34**, 5786.
9 E. Malmstrom, M. Johansson and A. Hult, *Macromolecules*, 1995, **28**, 1698.
10 M. Liu, N. Vladimirov and J. M. J. Frechet, *Macromolecules*, 1999, **32**, 6881.
11 Y. Lim, S. Kim, Y. Lee, W. Lee, T. Yang, M. Lee, H. Suh and J. Park, *J. Am. Chem. Soc.*, 2001, **123**, 2460.
12 (*a*) A. Kumar and E. W. Meijer, *Chem. Commun.*, 1998, 1629; (*b*) M. Trollsas, B. Atthoff, H. Claesson and J. L. Hedrick, *Macromolecules*, 1998, **31**, 3439.
13 H. C. Padgett, I. G. Csendes and H. Rapoport, *J. Org. Chem.*, 1979, **44**, 3492.
14 A. Oku, T. Harada and K. Kita, *Tetrahedron Lett.*, 1982, **23**, 681.
15 S. Arumugam, D. McLeod and J. G. Verkade, *J. Org. Chem.*, 1998, **63**, 3677.
16 D. Holter, A. Burgath and H. Frey, *Acta Polymer*, 1997, **48**, 30.