Journal of Peptide Science
J. Peptide Sci. **11**: 247–249 (2005)
Published online 31 January 2005 in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/psc.642

JOURNAL OF PEPTIDE SCIENCE

Synthetic polymers containing α-amino acids: from polyamides to poly(ester amide)s‡

JORDI PUIGGALÍ and JUAN A. SUBIRANA*
Departament d'Enginyeria Química, Universitat Politècnica de Catalunya, 08028, Barcelona, Spain

Received 9 November 2004; Accepted 26 November 2004

Keywords: biodegradability; electron microscopy; glycine; polyamides; poly(ester amide)s; x-ray diffraction

INTRODUCTION

In the early 1980s our group decided to study polyamides which had a close structural relationship with proteins. The structure of polyglycine [1] and poly-β-alanine [2] were studied first by electron microscopy. It was discovered that the introduction of glycine as a co-monomer in nylons gave rise to novel structures [3], which were subsequently studied in great detail (reviewed in [4]). These studies were mainly carried out by electron microscopy and fibre diffraction.

In order to achieve a better understanding of the structural basis of the behaviour of glycine and related residues in polyamides it was decided to study the detailed structure of oligomers by single crystal x-ray diffraction. In order to learn the possibilities of such an approach one of us (JAS) spent a sabbatical period in 1988–89 in the laboratory of Murray Goodman. Subsequently, X. Vidal, a graduate student from Barcelona, spent several months in San Diego and synthesized a number of oligomers which showed unexpected features, as described in his thesis [5]. One of the structures obtained [6] is presented in Figure 1. It demonstrates the strong influence of glycine on the polyamide chain, which shows sharp bends. Polyamides usually have straight parallel chains.

Another important outcome of our relation with Murray's laboratory came from his suggestions that resulted in a research project which was carried out in collaboration with the group of E. Peggion in Padova. The aim of that project was the development of new biocompatible polyamides and was supported by the European Community within the BRITE-EURAM programme [7]. Our relationship with the University of Padova which started in this period has had a recent development in another joint European project on anthraquinone-amino acid drugs involving Murray's former associates (S. Mammi, M. Palumbo, G. Zagotto). In summary, although our direct collaboration with the San Diego laboratory was short, it had long-term effects. We are most grateful for the inspiration received from Murray. He visited our Department in Barcelona on several occasions.

Our endeavours in this field have continued. In recent years we carried out a systematic study of poly(ester amide)s containing α-amino acids that was focused on obtaining new biodegradable polymers [8–12]. In fact, these polymers may combine adequate mechanical properties, due to the presence of strong intermolecular hydrogen bond interactions between amide groups, with a high degradation rate due to the presence of labile ester groups. Furthermore, the presence of natural amino acids may enhance the susceptibility to enzymatic degradation.

This family of polymers can be synthesized with a high yield by interfacial polyamidation, as described in Scheme 1, and also by an alternative method based on a thermal polyesterification [11].

Thermal properties, such as glass transition and melting temperatures, were variable but always within a range characteristic for similar polyamides and polyesters. Evaluation of the mechanical parameters demonstrated that it is possible to obtain either a rigid or a flexible sample depending on the chemical constitution (i.e. the number of methylene groups or the size of the amino acid lateral group), with the Young's modulus in the 10^9–10^6 Pa range.

Degradation studies performed with this series of polymers demonstrated its potential interest and applicability. A great variability in the degradation rate was observed depending on the methylene content of the repeat unit and also on the type of amino acid involved. Thus, the possibility of combining different proportions of L- and D-amino acids gives rise to an excellent way of controlling biodegradation.

Polymers with lateral groups and a high methylene content are soluble in organic solvents, such as chloroform. In this way, it is possible to obtain microspheres that can be used as drug delivery systems.

In vitro biocompatibility assays with permanent cell lines were also carried out [9]. As cell attachment and proliferation on the polymer surfaces were observed, a cytotoxic response can be discarded.

* Correspondence to: Dr Juan A. Subirana, Departament d'Enginyeria Química, Universitat Politècnica de Catalunya, Av. Diàgonal 647, 08028, Barcelona, Spain; e-mail: juan.a.subirana@upc.edu

‡ Selected paper part of a special issue dedicated to the memory of Murray Goodman.

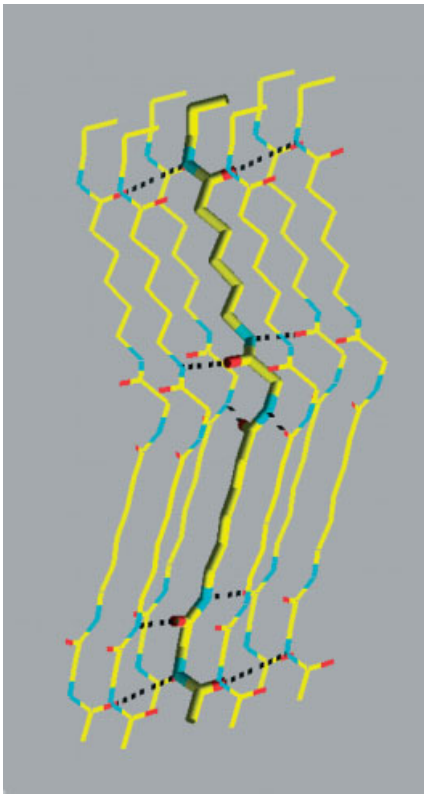
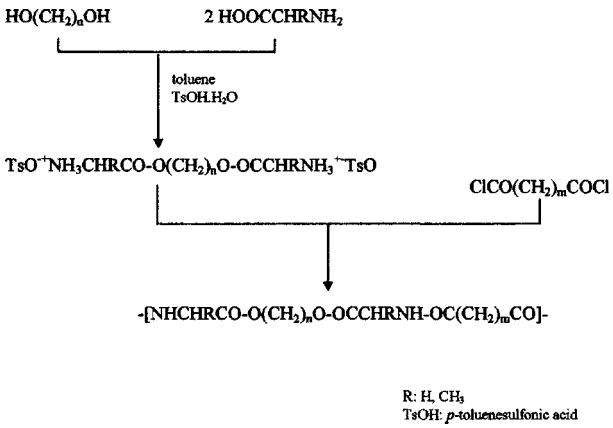


Figure 1 Demonstration of the strong influence of glycine co-monomers in polyamide chains [6]. They induce a large bend in the polymer chains, as obvious in the centre of the Figure. In the crystal, every chain forms hydrogen bonds (dotted lines) with six neighbours. The central chain is enhanced. Carbon atoms are shown in yellow, oxygen in red and nitrogen in blue. Hydrogen atoms are omitted.



Scheme 1

Derivatives of glycine and L-alanine are highly crystalline in contrast to the amorphous character of polymers constituted by amino acids with bulky side groups. Glycine containing poly(ester amide)s crystallized from the melt usually gives rise to spherulites which display the characteristic features of polyesters. Thus, a negative birefringence and a fibrillar texture are typically observed, whereas double-ringed spherulites can be obtained at very low supercoolings. It is worth noting that spherulites with the typical positive birefringence of polyamides can only be prepared under very restricted conditions.

Structural studies of glycine derivatives performed by means of x-ray and electron diffraction and transmission electron microscopy (Figure 2) revealed interesting features and provided new insights since structural data on poly(ester amide)s are scarce due to their recent development.

Diffraction data of glycine derivatives showed that different packing preferences of ester and amide groups compete, giving rise to distinct structures. It is interesting to note that the reported structures for aliphatic polyamides and polyesters, both with all-*trans* conformations, exhibit two main distinctive features for their *c*-chain axis projections: (a) values close to $a/3$ and $a/2$ describe the molecular shift between neighbouring chains, and (b) values close to 0° or 45° define the setting orientation angle. These

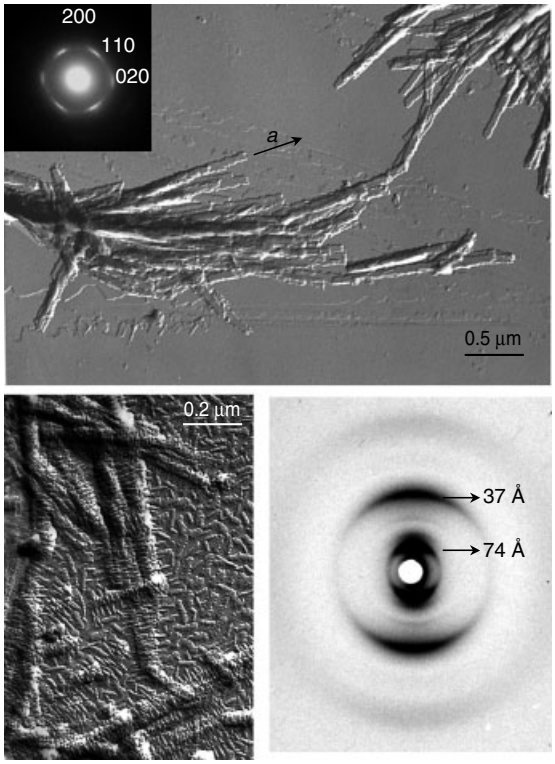


Figure 2 Electron micrographs and x-ray diffraction pattern of the poly(ester amide) derived from dodecanediol, glycine and adipic acid [13]. Correlation of electron diffraction patterns and brightfield micrographs indicates that hydrogen bonds run along a single direction that corresponds to the crystal growth direction. Polyethylene decoration suggests a regular crystal surface with folds parallel to the hydrogen bonding direction. Lamellar orders and subsidiary maxima are clearly visible in the pattern of a mat of sedimented crystals, which indicates a highly regular lamellar thickness and infers the number of chemical repeat units that exist in the lamellar core.

differences are a consequence of the minimization of the packing energy, i.e. the establishment of strong hydrogen bond interactions along the *a* crystallographic direction causes polyamides to adopt a setting angle near 0°.

The structure of the new poly(ester amide)s seems to be characterized by intermolecular hydrogen bonds along a single direction. The inversion centre symmetry of the molecular chains and their specific chemical sequence force the conformation of glycine residues to have no influence on the hydrogen bonding geometry. This feature contrasts with the network of hydrogen bonds that is observed in polyamides induced by the presence of glycine residues. Unusual hexagonal and triangular single crystal morphologies were found in some of these polyamides [4].

In a similar way to that described for conventional nylons, the structure of new poly(ester amide)s can be defined by a stacking of hydrogen bonded sheets. However, packing may be stabilized by different shifts between consecutive sheets. In this way, the projected unit cell becomes rectangular when this displacement is equal to $a/2$. The unit cell is composed of only two sheets of hydrogen bonded chains and resembles aliphatic polyesters with a slight change in the values of the a and b parameters. The electron diffraction pattern shown in Figure 2 represents a clear example. In some cases, a disorder in the stacking of sheets was deduced, since a streak was clearly visible in the electron diffraction patterns around the theoretical 100 reflection. In other cases [12], superstructures with unit cells composed of six hydrogen bonded layers are originated, due to the combination of different shifts among them.

In summary, the results obtained in the past years have demonstrated that the incorporation of α-amino acid units into a polyester or into a polyamide chain gives rise to unusual crystalline structures, and that new materials with a wide range of properties can be obtained.

Acknowledgements

This research has been supported by different grants. We want to mention the support from CICYT and FEDER for our last project (MAT2003-01004) and from the Generalitat de Catalunya, grant 2001SGR00250.

REFERENCES

1. Muñoz-Guerra S, Puiggalí J, Rodríguez-Galán A, Subirana JA. Crystals of polyglycine in the β-form. *J. Mol. Biol.* 1983; **167**: 223–225.
2. Muñoz-Guerra S, Fernández-Santín JM, Rodríguez-Galán A, Subirana JA. Structural studies on the polymorphism of nylon 3. *J. Polym. Sci., Polym. Phys. Ed.* 1985; **23**: 733–742.
3. Puiggalí J, Muñoz-Guerra S, Lotz B. Extended-chain and threefold helical forms of poly(glycyl-β-alanine). *Macromolecules* 1986; **19**: 1119–1124.
4. Subirana JA, Muñoz-Guerra S, Puiggalí J. Glycine containing polypeptides. In *Polymeric Materials Encyclopedia*, Salomone JC (ed.). CRC Press: Boca Raton, FL, 1996; 5422–5432.
5. Vidal X. *Síntesi i Caracterització de Poliureas i Poliamides Alifàtiques*. Ph.D. Thesis. Universitat Politècnica de Catalunya, 1993.
6. Tereshko V, Vidal X, Goodman M, Subirana JA. Structure of oligomers of glycine and ε-aminocaproic acid as a model of nylon 2/6. *Macromolecules* 1995; **28**: 264–268.
7. Fernández-Santín JM, Puiggalí J, Peraire C, Franco L, Aceituno JE, Tereshko V, Vidal X, Navarro E, Alemán C, Bella J *et al. Synthesis, Characterization and Development of New Biocompatible Polyamides with Controlled Biodegradability*. Final Report Brite-Euram Project N°: BE-3106-89. Commission of the European Communities, Directorate XII: Brussels, 1993.
8. Paredes N, Rodríguez-Galán A, Puiggalí J. Synthesis and characterization of a family of biodegradable poly(ester amide)s derived from glycine. *J. Polym. Sci., Polym. Chem. Ed.* 1998; **36**: 1271–1282.
9. Paredes N, Rodríguez-Galán A, Puiggalí J, Peraire C. Studies on the biodegradation and biocompatibility of a new poly(ester amide) derived from L-alanine. *J. Appl. Polym. Sci.* 1998; **69**: 1537–1549.
10. Rodríguez-Galán A, Pelford M, Aceituno JE, Puiggalí J. Comparative studies on the degradability of poly(ester amide)s derived from L- and L,D-alanine. *J. Appl. Polym. Sci.* 1999; **74**: 2312–2320.
11. Asín L, Armelin E, Montané J, Rodríguez-Galán A, Puiggalí J. Sequential poly(ester amide)s based on glycine, diols and dicarboxylic acids: thermal polyesterification versus interfacial polyamidation. Characterization of polymers containing stiff units. *J. Polym. Sci., Polym. Chem. Ed.* 2001; **39**: 4283–4293.
12. Paredes N, Casas MT, Puiggalí J, Lotz B. Structural data on the packing of poly(ester amide)s derived from glycine, hexanediol, and odd-numbered dicarboxylic acids. *J. Polym. Sci., Polym. Chem. Ed.* 1999; **37**: 2521–2533.
13. Paredes N. *Poliamidas y Poliesteramidas Derivadas de Aminoácidos. Síntesis, Estructura y Degradación*. Ph.D. Thesis. Universitat Politècnica de Catalunya, 1999.