

Diketopiperazine-Based Polymers from Common Amino Acids

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ABSTRACT: High-melting-point polymers with heterocyclic backbone units were synthesized from common amino acids. Acids were first converted to methyl ester salts and then were dimerized to form diketopiperazines, which were polymerized in solution. Aspartic acid, serine, lysine, glycine, and tyrosine were used as starting materials for the diketopiperazines. Aromatic and aliphatic comonomers were used. Thus, we demonstrate the technical feasibility of producing strong, durable resins from abundant domestic resources. These resins show great potential for high-performance polymers for use in films, fibers, and composites. © 2000 John Wiley & Sons, Inc. *J Appl Polym Sci* 78: 2213–2218, 2000

Key words: diketopiperazine; polymers from renewable resources; amino acids

INTRODUCTION

Strong, durable, high-performance plastics that can be produced in an economic and environmentally sound manner are always of interest. If these plastics can be produced from abundant domestic renewable resources, there are additional strategic and economic benefits, such as reducing dependence on foreign petrochemicals and increasing markets for agricultural products and byproducts.

For any plastic, the chemical nature of the monomers, the molecular weight, and the presence of cyclic units in the backbone are important factors in determining the mechanical properties of the polymers. Chain configuration is one of the most significant factors in determining polymer performance. High-temperature resins contain cyclic structures within their backbones. Symmetric chain configurations maximize hydrogen bonding and degree of crystallization. Kevlar® (a registered trademark of DuPont) is a high-cost,

high-performance resin with a cyclic backbone that packs tightly into a highly crystalline solid; nylon is a low-cost resin of similar chemical composition but has a linear backbone. A comparison of the properties of the aramid Kevlar® 49 with those of amide nylon demonstrates the importance of tightly packed cyclic structures. Kevlar® has a fiber tensile strength of 2758 MPa, whereas nylon has a strength of 986 MPa; Kevlar® has a modulus of 124 GPa, whereas nylon has a modulus of 5.5 GPa; and the crystal melting temperature of Kevlar® is 537°C, whereas that of nylon is 216°C.¹

It should be possible to make crystalline polymers with both the properties and costs between those of Kevlar® and nylon through the use of other symmetric cyclic compounds as monomers. Specifically, pairs of naturally occurring amino acids will form diketopiperazines (DKPs), which are highly polar, symmetrical rings that can contain functional side chains, depending on the original amino acids. These DKP monomers, also referred to as *dioxopiperazines* and *amino acid anhydrides*, can be condensed with other monomer units to produce crystalline polymers with properties between those of Kevlar® and nylon.

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DKPs are easy to produce. In the early 1900s, Fischer and Maillard reported two simple, reliable synthesis routes. Fischer converted the acid to a free-base methyl ester and cyclized it.^{2,3} Maillard had success with the controlled heating of amino acids in glycerol. Other synthesis schemes also exist, with significant differences in complexity and yields.^{4–6} In particular, the Kupryszewski–Sokolowska modification⁷ combines high yields with simplicity and mild processing conditions. The DKP monomers are so easily formed that much of the published DKP chemistry is aimed at preventing their spontaneous formation because DKP formation interferes with protein synthesis.⁸

The polymerization of DKPs has been reported in the literature. Iwakura et al.⁹ produced a heat-stable plastic that also contained phenyl rings and decomposed between 400 and 500 °C. Kobayashi et al.¹⁰ reported that melt-spun fibers formed from DKP–amine resins had a strength of 3.2 g/denier and were dyeable. Crescenzi et al.^{11,12} reported optically active polymer powders from lysine and adipic acid.

Amino acids, building blocks of proteins, are composed of a central carbon attached to four different groups; three of these [the hydrogen atom, the amino group, ($-\text{NH}_2$), and the carboxylic acid group ($-\text{COOH}$)] are common to all. The fourth group, R , which differs with each amino acid, may be aliphatic or aromatic and may contain sulfur or nitrogen. This work demonstrates the technical feasibility of producing high-performance plastics from the DKPs of these naturally occurring amino acids with both amine and acid comonomers. The targeted amino acids occur naturally in grains and legumes and their byproducts. Some, such as lysine, are already commercial commodities themselves, produced synthetically or with fermentation technology. Figure 1 shows the five DKPs synthesized in this study: the derivatives of aspartic acid (Asp), serine (Ser), lysine (Lys), glycine (Gly), and tyrosine (Tyr). As shown in the diagram, the R groups for these amino acids are $-\text{CH}_2\text{COOH}$, $-\text{CH}_2\text{OH}$, $-(\text{CH}_2)_4\text{NH}_2$, $-\text{H}$, and $-\text{CH}_2(4\text{-hydroxyphenyl})$, respectively. Asp, Ser, and Tyr DKPs were polymerized successfully. The polymer from the Gly DKP was a noncrystalline, viscous liquid, as would be expected from the lack of crosslinking.

A key step for high yields in DKP production from amino acids is inactivating any reactive R groups to reduce the competing reactions during the cyclization. In this work, functional groups were protected by the conversion of individual

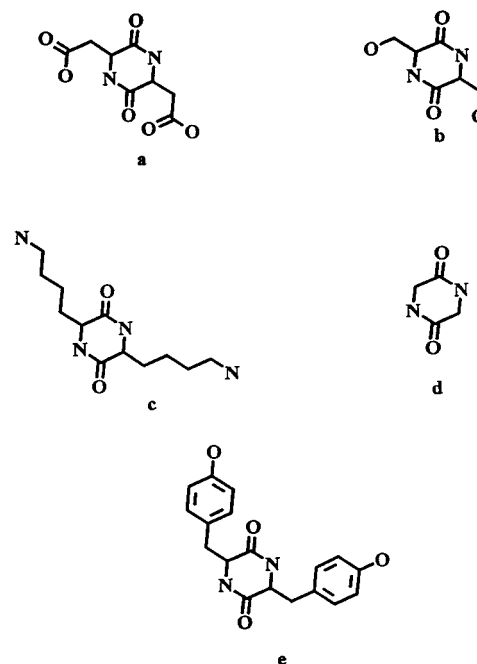


Figure 1 Synthesized DKP monomers. The starting amino acids are (a) Asp-Asp, (b) Ser-Ser, (c) Lys-Lys, (d) Gly-Gly, and (e) Tyr-Tyr.

amino acids into their methyl ester salts; the DKPs were then produced from the ester salts. These DKPs were condensed with suitable comonomers to form polymers with the desired properties. The polymerization method was simple: the monomers were dissolved and subjected to prolonged mild heating in an inert atmosphere. The DKPs were polymerized with other DKPs, with aliphatic and aromatic diamines, with aliphatic diols, and with aliphatic and aromatic diacid chlorides. The two most easily molded crystalline polymers were the Ser DKP copolymerized with a diacid and the Asp DKP copolymerized with a diamine. These were further characterized by differential scanning calorimetry (DSC). The aspartic acid-based polymer was successfully molded into bars with approximate dimensions of $2 \times 0.5 \times 6$ cm.

METHODS

Methyl Ester Salt Synthesis

The methyl ester salts of the amino acids (aspartic acid, lysine, serine, and tyrosine) were prepared with Kupryszewski and Sokolowska's modification of Fischer's chlorination method.⁷ The

Table I Experimental Monomers and Polymers Formed in This Study

DKP	Comonomer	Solvent	Remarks
Asp	Ethylene glycol	TEA	
Asp	Propylene glycol	TEA	
Asp	Octane diol	TEA	
Asp	1, 6-Hexane diamine	TEA, DMA	DMA product very moldable
Asp	Phenyl diamine	TEA	
Asp	Ser DKP	DMA	Black liquid with fibers
Gly	Gly DKP	Glycerol	Rubbery goo
Lys			
Ser	Adipic acid	DMA	Black, brittle glassy solid
Ser	Succinyl chloride	DMA	
Ser	Sebacyl chloride	DMA	
Ser	Terephthaloyl chloride	DMA	Moldable
Ser	Phenyl diacid chloride	DMA	
Ser	Asp DKP		See above
Tyr	Terephthaloyl chloride	DMA	

ultrapure amino acid (20 g) was stirred into 300 mL of analytical-grade methanol. Twenty-percent excess thionyl chloride was added to the iced suspension. The mixture rested at room temperature for 48 h and then was purified by vacuum evaporation of the solvents. The salt was then dissolved again in methanol to neutralize any excess hydrochloric acid. After a second vacuum evaporation, the salts were recrystallized by washing with diethyl ether, dissolution in methanol, and precipitation with ether. Results were verified by Fourier transform infrared (FTIR), NMR, and HPLC.

DKP Monomer Formation

The cyclization reactions were performed by the dissolution of the purified ester salts in a minimal amount of methanol and neutralization with two equivalents of triethylamine (TEA). The TEA salt was precipitated with ether, and the mixture was cooled in an ice bath for 1 h. After filtration to remove the salt and vacuum drying to remove trace solvents, the remaining free-base esters were heated at 100°C for 24 h. During that time, needle crystals and an orange-brown residue formed. The residue was removed by washing with methanol. The monomers were washed with methanol again and recrystallized from water with one equivalent of diethylether plus sufficient methanol to form the precipitate. Results were verified by the melting point, FTIR, NMR, and HPLC.

Polymer Synthesis

Table I shows the polymer syntheses performed. The monomers were dissolved in a minimal

amount of solvent: *N,N*-dimethylacetamide (DMA) for the Ser DKPs and Tyr DKPs and TEA for the Asp DKPs. These solutions were heated at mild temperatures (100–160°C) for 3–72 h in a low vacuum (22 inHg) or in atmospheric-pressure nitrogen. A variety of reaction times and temperatures were used for the production of these polymers. The reaction yields and product properties were not sensitive to time and temperature, as long as the time was long and the temperature was as low as possible and still above the vapor pressure of the solvent. No optimization of the reaction conditions was attempted.

RESULTS

Monomer Synthesis

DKPs of the ester salts of four amino acids were produced. The progress of the reaction was followed by FTIR, HPLC, and NMR. Typical FTIR results are shown in Figure 2. This spectrum is for the Asp DKP monomers. Major features are labeled 1–9, and the assignments are as follows:¹³ Methyl esters absorb strongly at feature 1, 1742 cm⁻¹, because of carbonyl stretching and at feature 8, 1174 cm⁻¹, because of C—O stretching. A weak absorption due to asymmetric O—CH₃ stretching occurs at 1062 cm⁻¹, band 9. The *cis*-amides within the DKP ring absorb strongly at feature 2, 1676 cm⁻¹, because of a C=O vibration, at feature 3, 1460 cm⁻¹, because of N—H bending, and at feature 5, 1330 cm⁻¹, because of C—N stretching. A broad band at 800 cm⁻¹ is caused by N—H wagging. Band 6, 1270 cm⁻¹ is

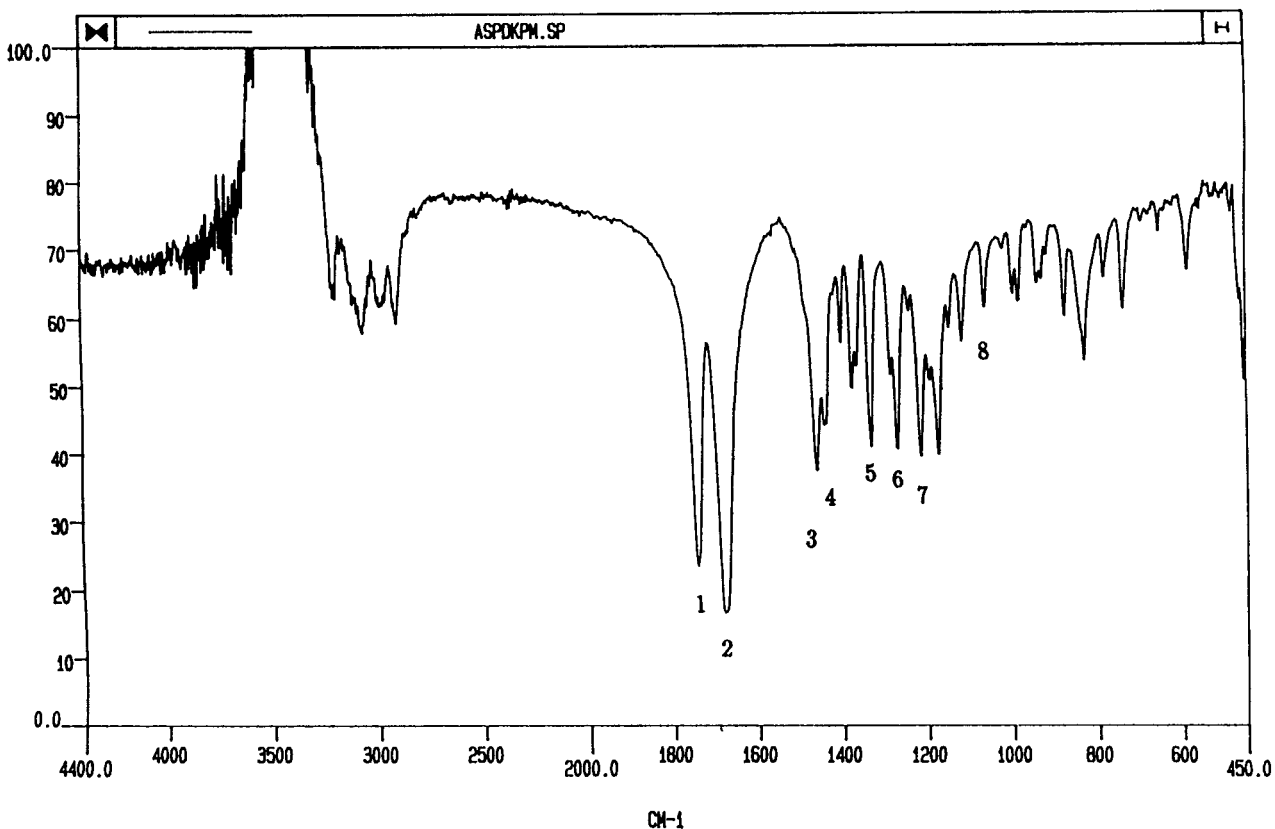


Figure 2 FTIR of DKP dimethyl ester.

associated with the C—O in the —CO—CHR—NHR— segment of the ring. Band 7 is associated with the C—O of the ester. Monosubstituted *trans*-amides absorb strongly around 1550 cm^{-1} because of N—H bending and C—N stretching. This is not observed, further demonstrated that the amides are in the cyclic structure. Band assignments are consistent with published DKP literature.^{11,12,14} An FTIR analysis of Ser and Tyr DKPs gave similar indications of cyclizations not seen in the starting materials.

Melting-point determinations gave the following results for the DKPs: Asp DKP, 244–245°C; Ser DKP, decomposition at 240°C before the melt was observed; Tyr DKP, 260°C; and Lys DKP, 237–241°C. The lack of a sharp melting point for the Lys DKP may indicate a need for further purification.

Polymer Synthesis

The aspartic acid-based polymers were selected for the production of test-specimen bars. DSC of the Asp DKP polymerized with hexamethylenediamine is shown in Figure 3. The peak at

227°C is associated with recrystallization during annealing, and those peaks near 384°C indicate a crystal melting temperature. Thermal decomposition occurs near 450°C.¹⁵ The Ser DKP polymerized with terephthaloyl chloride showed similar peaks at 252°C and near 375°C, respectively. These crystal melting temperatures are between those for nylon and Kevlar[®], indicative of mechanical properties between their mechanical properties.

DISCUSSION AND CONCLUSIONS

This work demonstrates the technical feasibility of constructing strong, durable, high-performance polymers from abundant domestic resources. Potential uses include films, fibers, and composites, all of which command sizable commercial markets. If these resins continue to demonstrate the properties that preliminary experimentation and polymer theory indicate, they have the potential to make a significant impact in the polymer industry.

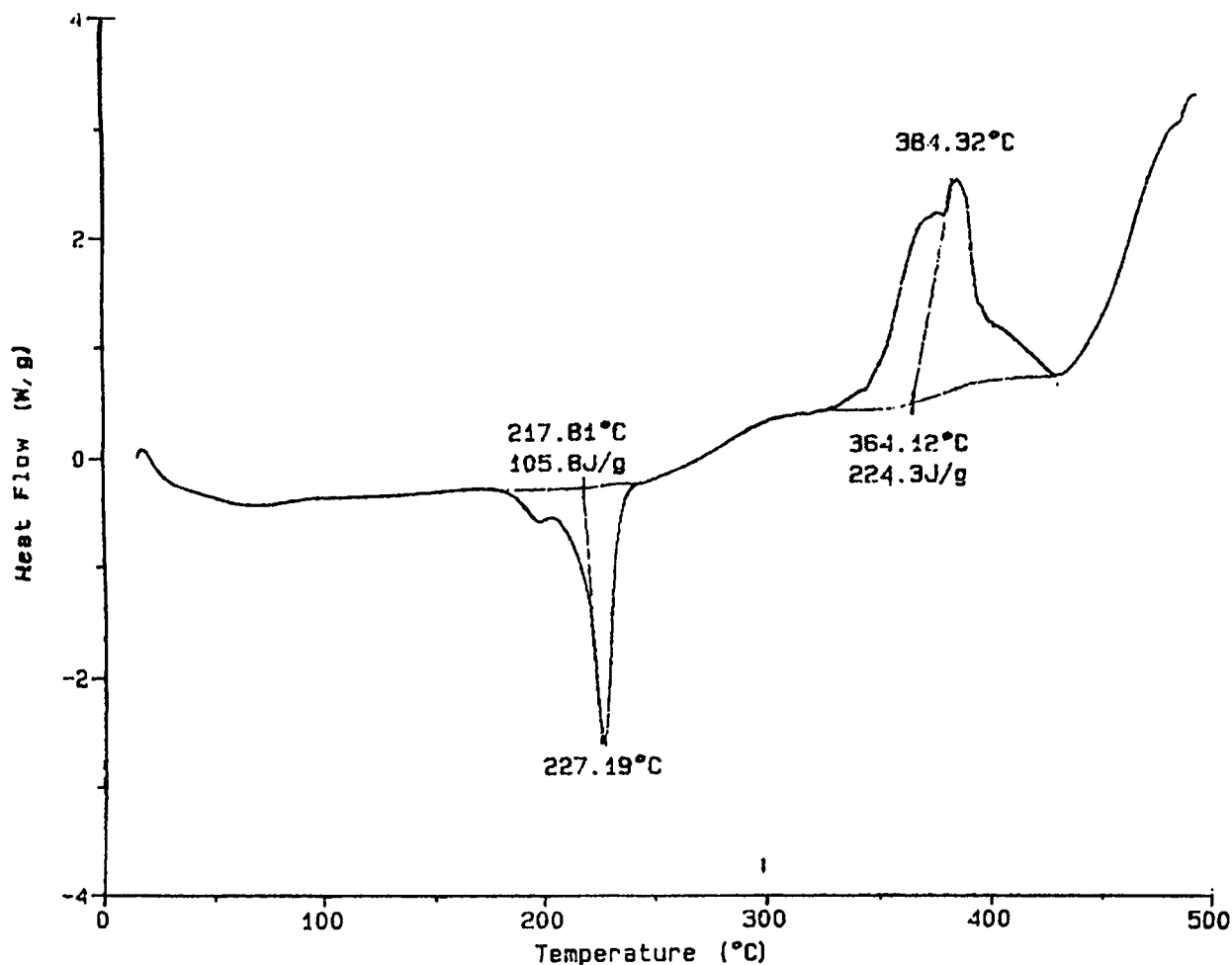


Figure 3 DSC of the polymer from aspartic acid. The transamidization polymerization was performed in DMA of Asp-Asp DKP.

The effect of configuration modifications is a logical next technical step; other comonomers and asymmetric DKP monomers are two such variations. Although each of the DKPs studied so far has been formed from two identical amino acids, it should be possible to dimerize a pair of nonidentical amino acids to create less symmetric DKPs with different functional groups at each end. For example, an Asp-Ser DKP would be a DKP cyclic platform and two pendent chains, a methylcarboxylic acid and a methylhydroxyl.

The advantages of DKP-based polymers are many. The amino acids occur widely in plants and in animal byproducts such as fishmeal. Therefore, petroleum resources can be preserved for other uses. The DKP monomers are easily formed; in fact, great care is taken in protein and peptide synthesis to avoid the chain termination of amino acid polymers with DKPs. The DKPs that do oc-

cur in nature and as breakdown products of artificial aspartame have not been found to be harmful. Indeed, therapeutic applications, such as antifungal agents and antihistamines, have been proposed. The chemistry is simple, and the reaction conditions are mild. Product quality is relatively insensitive to reaction conditions, although long times and low temperatures were always used. The optimization of reaction and curing conditions needs to be investigated.

Early researchers must have encountered difficulties with DKP-based polymers; otherwise, they surely would have commercialized the results. Whether these problems were economic or technical can only be a matter of speculation. There were some reports that the polymers would disintegrate because of their hygroscopic nature, but such problems were not observed in these specimens. One possible explanation is that these

disintegration problems were due to incomplete reaction and curing times and temperatures, which our patience and mild conditions eliminated. Another possible explanation is that in the earlier experiments, there may have been problems with the purity of the amino acid precursors. Obtaining the pure amino acid raw materials at a reasonable cost is not trivial. If these polymers continue to show the promise of these exploratory experiments and fill a market need, there will be an incentive to explore the cheaper purification of the necessary amino acids. Extant research for purification for other purposes via a combinations of methods such as pH control, electrical fields, and ultrafiltration membranes is promising for selective amino acid purification. Separation technology and production of supplemental amino acids, such as lysine, by fermentation methods have improved since the early DKP-based polymer syntheses were reported.¹⁶

DKP-based resins could make a significant impact on the utilization of agricultural resources and residues. The amino acids needed for these syntheses are widely available, not only in crops themselves, but also in fermentation byproducts, such as distillers' grain. Some, such as lysine, are already commercial commodities themselves, produced synthetically or with fermentation technology. The utilization of domestic crops as feedstock for plastics instead of foreign petrochemicals has both environmental and strategic advantages. Some proposed syntheses also use large quantities of agriculturally derived reagents.⁶

Films and fibers with properties between the properties of nylon and Kevlar[®] would have a wide range of industrial applications. Further study is needed to optimize reaction conditions before a complete economic analysis can be done. Yields of ester salts via the Kupryszewski-Sokolowska⁷ method have been reported as ranging from 70 to 97%, with 90% being typical. Polymerization yields have been reported to be 70%.¹¹ This would suggest that an overall yield of 60% based on the initial acids would be reasonable with current technology. Because 99% pure lysine is commercially available between \$2 and \$3, the portion of the cost of a Lys DKP polymer due to lysine feed would be about \$5 per pound. Nylon has an annual market of 10 million tons per year

and is worth about \$2 per pound. Intermediate engineering resins sell for \$5–20 per pound. This suggests that high-performance DKP-based polymers may be economically feasible as well.

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