# Piperazine Copolymers for Medical Implant Applications

STEPHEN D. BRUCK*

*Piperazine copolymers were investigated for possible use in medical implant applications with special reference to the replacement of the cornea of the eye. Initial work involved the study of the thermal stability of the polymers which is important in sterilization procedures; their stability toward long-wave ultraviolet and visible radiation; and blood coagulation tests.*

*The thermal stability of piperazine copolyamides was studied by both programmed and isothermal techniques. Experiments were carried out with the block copolymers of terephthaloyl* trans-*2,5-dimethylpiperazine/isophthaloyl* trans-*2,5-dimethylpiperazine; terephthaloyl* trans-*2,5-dimethylpiperazine/sebacyl* trans-*2,5-dimethylpiperazine; and isophthaloyl* trans-*2,5-dimethylpiperazine/sebacyl* trans-*2,5-dimethylpiperazine. In contrast to the previously studied homo polymers, the activation energies (range 185 to 256 kJ/mole), rates of volatilization and half-life values are influenced by the molecular weights of the block copolymers. In general, the data indicate a random degradation process during isothermal heating in a vacuum between 336°C and 440°C. The exception is the block copolymer of isophthaloyl* trans-*2,5-dimethylpiperazine/sebacyl* trans-*2,5-dimethylpiperazine which shows the completing effect of hydrolytic processes.*

*Film samples of the polymers that have been irradiated up to 160 h by a long wave ultraviolet lamp (having an energy peak close to 360 nm with virtually no radiation shorter than 300 nm) showed no changes in the ultraviolet and visible spectra and no gelation occurred. These results are important since polymer films that are to be considered for cornea replacement must exhibit good stability to long wave ultraviolet and visible radiation.*

*Initial data on blood coagulation tests indicate that the polymers considerably increase the coagulation times of human blood when glass is used as a standard.*

## INTRODUCTION AND BACKGROUND

ONE of the pioneering areas for the use of plastic materials is the field of eye research. Experimental polymers are needed for the replacement of scarred corneas, drainage tubes, substitute for the vitreous gel, and implants for the replacement of the entire eye. Pioneering work on cornea replacement has been carried out by Stone *et al*[1–5]. Stone evolved the concept of the 'incompletely covered foreign body' in connection with the plastic artificial cornea and post-enucleation implant. In such cases the polymeric material is partly exposed to the exterior environment which thus prevents the normal healing of epithelial cells. Hence, an incompletely covered foreign body places additional requirements on biomedical polymers.

Copolymers, and especially block copolymers, offer potentially distinct advantages for biomedical applications, especially eye research, since one of the blocks (chain macrosegments) could be so designed as to impart the necessary strength, while the other blocks could serve to control the hydrophobicity/hydrophylicity and permeability of the system. As was discussed above, sufficient hydrophylicity and permeability are necessary to facilitate nutrition and prevent dehydration of the cornea. Poly (methyl methacrylate), while in many respects desirable, apparently falls short of meeting these requirements[4].

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*Present Address: National Heart and Lung Institute, National Institute of Health, Bethesda, Md. 20014, U.S.A

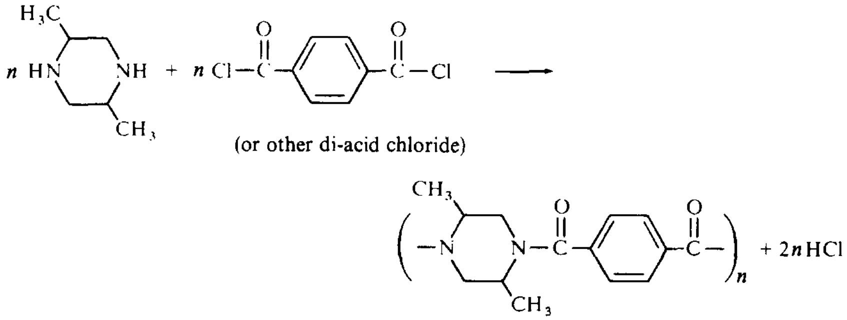
The physico-chemical properties of copolyamides based on piperazine have been under investigation by this author for some time[7–10]. Although these earlier investigations were not directed towards biomedical applications, the copolyamides exhibited several interesting properties which are of potential interest to biomedical applications in comparison to other linear homopolymers (nylons). Some of these properties are related to the absence of a hydrogen atom on the amide nitrogen, and to the relatively bulky piperazine ring that creates a steric barrier for the approach of water molecules.

## EXPERIMENTAL

### (A) *Preparative approach*

The preparation of piperazine polyamides has been studied by Morgan[11] and Morgan and Kwolek[12] using a low temperature polycondensation technique. This method, carried out at a low temperature, minimizes degradation and permits the preparation of high molecular weight products without the need for a catalyst. Block copolymers of terephthaloyl *trans*-2,5-dimethylpiperazine/isophthaloyl *trans*-2,5-dimethylpiperazine; terephthaloyl-*trans*-2,5-dimethylpiperazine/sebacyl *trans*-2,5-dimethylpiperazine; and isophthaloyl *trans*-2,5-dimethylpiperazine/sebacyl *trans*-2,5-dimethylpiperazine were prepared. In addition, the random copolymer of terephthaloyl *trans*-2,5-dimethylpiperazine/isophthaloyl *trans*-2,5-dimethylpiperazine (prepared in a previous investigation) was also available for comparison.

The copolymers are prepared from the disubstituted piperazine and the appropriate di-acid chloride according to the following general scheme:



The following abbreviations will be used in this paper:
*t*-2,5-DiMePip-T: terephthaloyl *trans*-2,5-dimethyl piperazine
*t*-2,5-DiMePip-I: isophthaloyl *trans*-2,5-dimethyl piperazine
*t*-2,5-DiMePip-10: sebacyl *trans*-2,5-dimethyl piperazine

### (B) *Fabrication of films*

Clear polymer films were prepared by casting from solution. The block copolymers are soluble in formic acid, whereas the random copolymers and the homopolymers are soluble in mixtures of chloroform and methyl alcohol. The thickness of the films was controlled by a micrometer-equipped 'doctor' knife. Before use, the polymer films were carefully purified by soaking in distilled water and then dried in a vacuum.

### (C) *Molecular weights*

The inherent viscosities were determined in *m*-cresol at 30 ± 0·05°C with Cannon-Fenske viscometers. The viscosities varied between 1·2 and 2·2; these values correspond to number average molecular weights of approximately 13 000–30 000[9].

## RESULTS AND DISCUSSION

### (A) *Thermal stability of the copolymers*

The thermal stability of the polymers is an important parameter to be considered. Sterilization procedures of polymers which will be in contact with blood and tissue are best carried out by steam[13]. Polymers having low softening temperatures cannot, of course, be used in this process. This places a limitation on polymers with otherwise potential biomedical applications.

The melting temperatures of the copolymers described in this report are above 400°C as indicated by thermograms obtained by differential scanning calorimetry (Perkin-Elmer Model DSC-1B) and DTA measurements (duPont Thermograph Model 920). The copolymers did not exhibit glass transition ($T_g$) temperatures which presumably occur in the range of the melting temperatures. Hence, steam sterilization procedures could be used.

Programmed and isothermal degradation studies were carried out with powdered 3–7 mg samples using a Cahm RG electrobalance[7–10] with a modified hangdown tube-thermocouple assembly shown in *Figure 1*. A. chromel–alumel thermocouple was positioned just below the sample capsule. The thermocouple wires were welded to both end of tungsten leads (equal length and diameter) which were fused to the inner member of a pyrex standard tapered joint. The use of tungsten was necessary to circumvent the problem of vacuum sealing the chromel–alumel thermocouples to glass. The output of the thermocouple was recorded on a millivolt recorder in series with an electronic cold junction compensator.

*Thermal stability under programmed heating rates*—The thermal stability of the following block copolymers with number average molecular weights of 13000–14000 was investigated under programmed rates of heating of 4°C/min both in air and in a vacuum:

(1) *t*-2,5-DiMePip-T/*t*-2,5-DiMePip-I, 50/50 mole %
(2) *t*-2,5-DiMePip-T/*t*-2,5-DiMePip-10, 50/50 mole %
(3) *t*-2,5-DiMePip-I/*t*-2,5-DiMePip-10, 50/50 mole %

The results are illustrated by *Figure 2* (air) and *Figure 3* (vacuum). It can be seen that these copolymers have the following order of thermal stability in air:

*t*-2,5-DiMePip-I/*t*-2,5-DiMePip-10 >
*t*-2,5-DiMePip-T/*t*-2,5-DiMePip-I >
*t*-2,5-DiMePip-T/*t*-2,5-DiMePip-10

while in a vacuum it is:

*t*-2,5-DiMePip-T/*t*-2,5-DiMePip-I >
*t*-2,5-DiMePip-I/*t*-2,5-DiMePip-10 >
*t*-2,5-DiMePip-T/*t*-2,5-DiMePip-10.

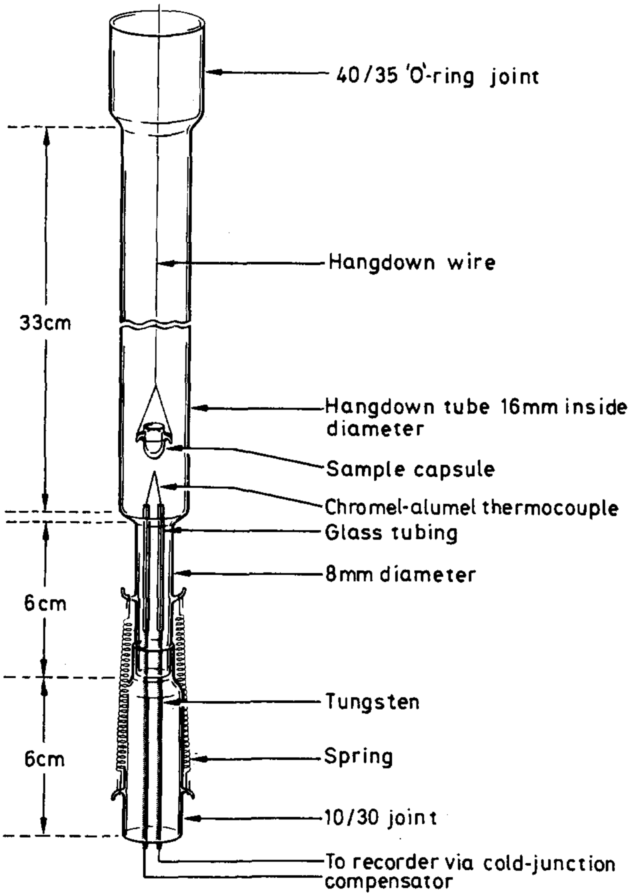


*Figure 1*—Hangdown tube-thermocouple arrangement

*Thermal stability under isothermal conditions in vacuum*—The rate of thermal degradation were obtained from volatilization–time curves with the aid of an electronic computer. The number average molecular weights of the block copolymers varied between 13 000–14 000 and could be divided into two groups: (1) high molecular weight samples ($\bar{M}_n = 20\,000–30\,000$), and (2) medium molecular weight samples ($\bar{M}_n = 13\,000–14\,000$). *Figures 4* and *5* show, respectively, the rates of volatilization of high molecular weight samples of 70/30 and 50/50 mole % block copolymer of *t*-2,5-DiMePip-T/*t*-2,5-DiMePip-I. *Figures 6* to *8* illustrate the rates of volatilization of medium molecular weight samples of 50/50 mole % block copolymers of *t*-2,5-DiMePip-T/*t*-2,5-DiMePip-I; *t*-2,5-DiMePip-T/*t*-2,5-DiMePip-10; and *t*-2,5-DiMePip-I/*t*-2,5-DiMePip-10, respectively. The data indicate that, at comparable temperatures, the high molecular weight samples show considerably lower rates of volatilization than those of medium molecular weight. This situation is especially clear when the two 50/50 mole % composition block copolymers of *t*-2,5-DiMePip-T/*t*-2,5-DiMePip-I are considered. At the

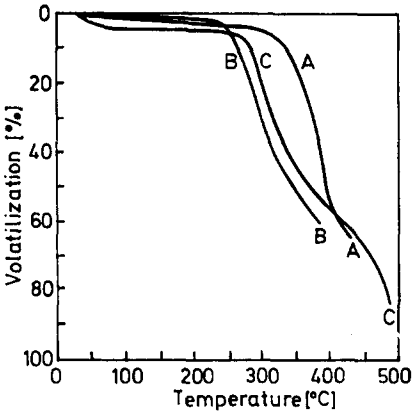


*Figure 2*—Thermal degradation in air under programmed thermogravimetry of 4°C/min of 50/50 mole % piperazine block copolymers

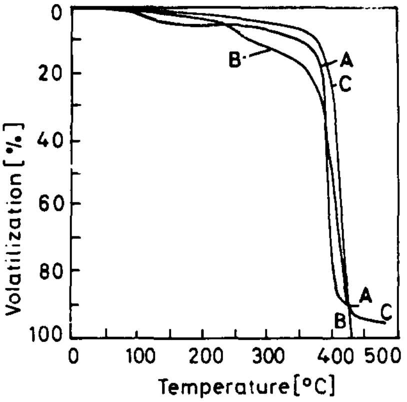


*Figure 3*—Thermal degradation in a vacuum under programmed thermogravimetry of 4°C/min of 50/50 mole % piperazine block copolymers

A, *t*-2,5-DiMePip-I/*t*-2,5-DiMePip-10; B, *t*-2,5-DiMePip-T/*t*-2,5-DiMePip-10; C, *t*-2,5-DiMePip-T/*t*-2,5-DiMePip-I

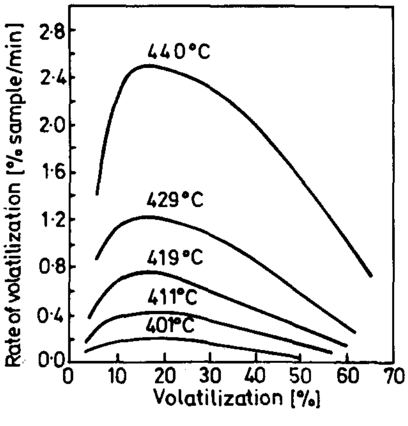


*Figure 4*—Rates of thermal degradation of 70/30 mole % block copolymer ($\bar{M}_n > 20000$) of *t*-2,5-DiMePip-T/*t*-2,5-DiMePip-I (Bruck, S. D. and Levi, A. A. *J. Macromol. Sci.* 1967, **A1** (6), 1095

temperature of 410°C, the high molecular weight sample exhibits a maximum rate of volatilization of 0·51% sample per minute; whereas at 412°C the medium molecular weight material shows a maximum rate of 4·06% sample per minute. It is apparent that the stability of the block copolymers is influenced by their molecular weights in contrast to the homopolymers discussed in earlier publications[7–9]. The results also indicate that with the exception of the medium molecular weight 50/50 mole % block copolymers of *t*-2,5-DiMePip-I/*t*-2,5-DiMePip-10, the maxima of the rate curves appear between 25 and 30% conversion. On the other hand, the maxima in the case

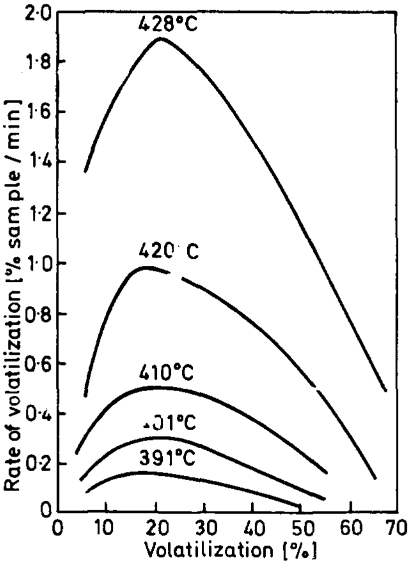


*Figure 5*—Rates of thermal degradation of 50/50 mole % block copolymer ($\bar{M}_n > 20{,}000$) of *t*-2,5-DiMePip-T/*t*-2,5-DiMePip-I (Bruck, S. D. and Levi, A. A. *J. Macromol. Sci.* 1967, A1 (6), 1095

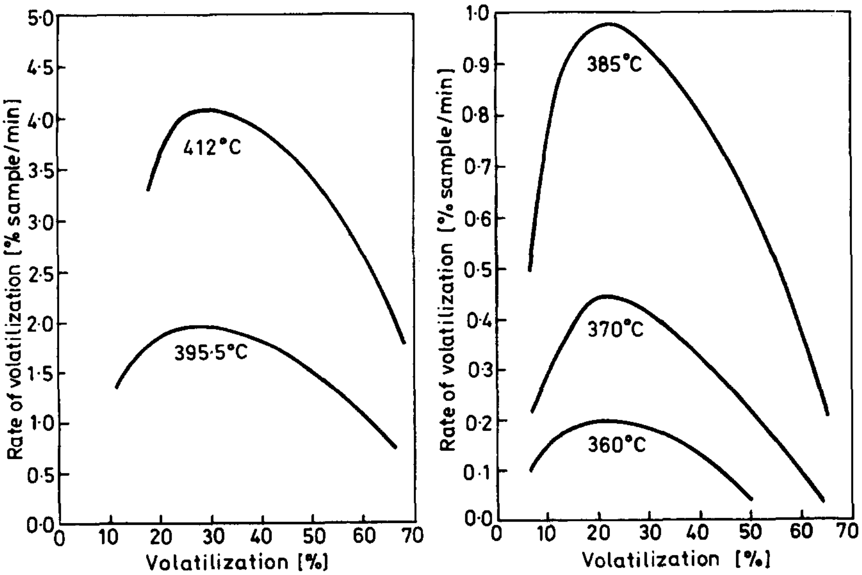


*Figure 6*—Rates of thermal degradation of 50/50 mole % block copolymer of *t*-2,5-DiMePip-T/*t*-2,5-DiMePip-I in a vacuum

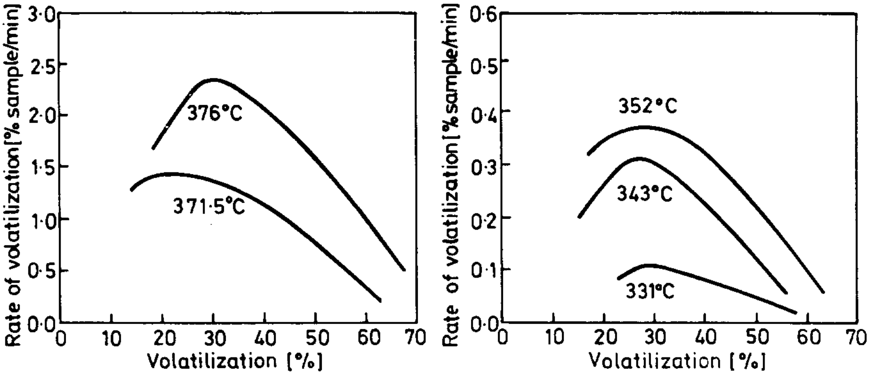


*Figure 7*—Rates of thermal degradation of 50/50 mole % block copolymer of *t*-2,5-DiMePip-T/*t*-2,5-DiMePip-10 in a vacuum

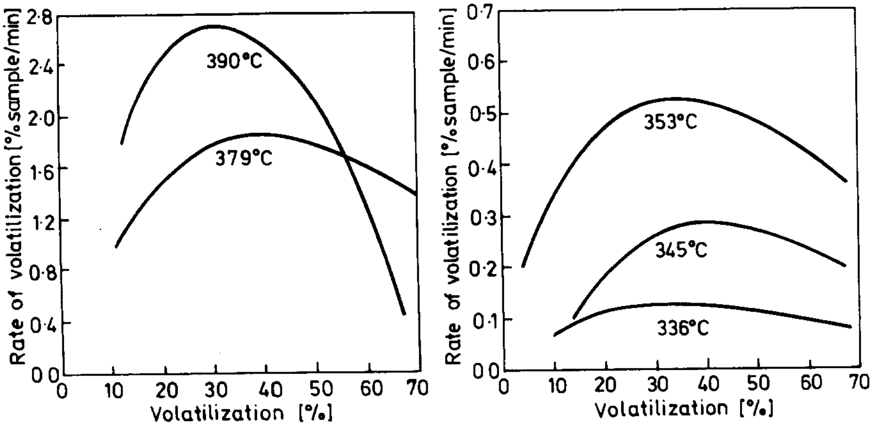


*Figure 8*—Rates of thermal degradation of 50/50 mole % block copolymer of *t*-2,5-DiMePip-I/*t*-2,5-DiMePip-10 in a vacuum

of the medium molecular weight 50/50 mole % *t*-2,5-DiMePip-I/*t*-2,5-DiMePip-10 appears between 30 and 40% conversion.

The Arrhenius plot for the thermal degradation of the block copolymers are illustrated by *Figure 9* and the pertinent data are summarized in *Table 1*. The highest activation energies are exhibited by the high molecular weight samples of the block copolymers, while the lowest activation energy (185 kJ/mole) is shown by the medium molecular weight 50/50 mole % *t*-2,5-DiMePip-I/*t*-2,5-DiMePip-10. This latter polymer also shows a shift in the maximum rates of volatilization to higher conversions, as mentioned above. In the case of purely random type degradations the maxima appear at about 26% conversion[14]; and the observed shift to 30–40% conversion coupled with a lowered activation energy indicates the influence of non-random processes, such as hydrolytic scission[15, 16].

The half-life ($T_g$) values of the block copolymers correspond to 50% volatilization of the sample during isothermal conditions[17]. According to

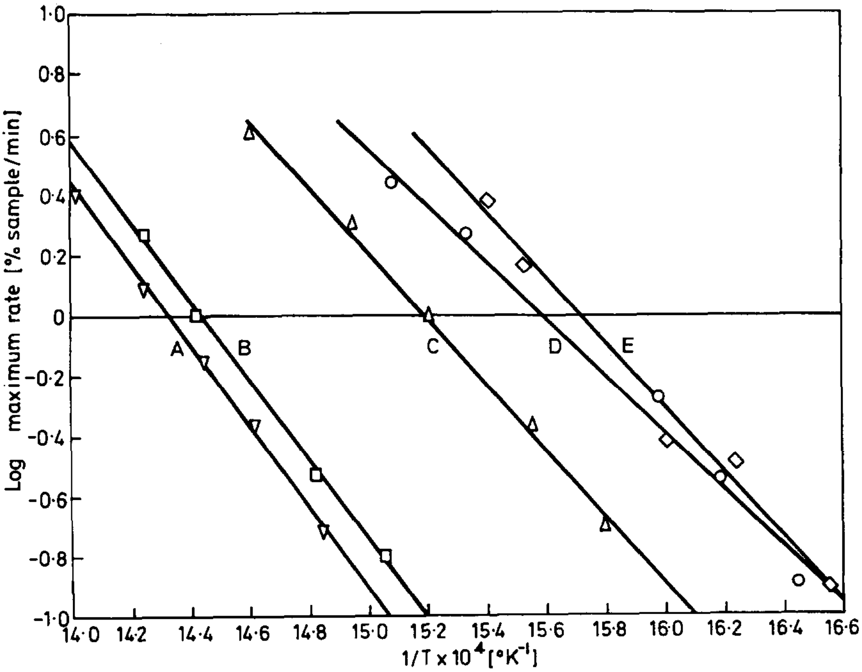


*Figure 9*—Arrhenius plots for the thermal degradation in vacuum of high (20 000–30 000) and medium (13 000–14 000) $\bar{M}_n$ piperazine block copolymers

High $\bar{M}_n$ A, 70/30 mole % *t*-2,5-DiMePip-T/*t*-2,5-DiMePip-I
B, 50/50 mole % *t*-2,5-DiMePip-T/*t*-2,5-DiMePip-I
Medium $\bar{M}_n$ C, 50/50 mole % *t*-2,5-DiMePip-T/*t*-2,5-DiMePip-I
D, 50/50 mole % *t*-2,5-DiMePip-I/*t*-2,5-DiMePip-10
E, 50/50 mole % *t*-2,5-DiMePip-T/*t*-2,5-DiMePip-10

the $T_h$ values, the polymers can be arranged in the following order of relative thermal stability under isothermal conditions in a vacuum:

70/30 mole % high M.W. *t*-2,5-DiMePip-T/*t*-2,5-DiMePip-I >
50/50 mole % high M.W. *t*-2,5-DiMePip-T/*t*-2,5-DiMePip-I >
50/50 mole % medium M.W. *t*-2,5-DiMePip-I/*t*-2,5-DiMePip-10 >
50/50 mole % medium M.W. *t*-2,5-DiMePip-T/*t*-2,5-DiMePip-10.

(B) *Volatile degradation products*

The results of the mass spectrometric analyses are summarized in *Table 2*. The main volatile degradation products consist of carbon monoxide, carbon dioxide, methane, hydrocarbons, ammonia, nitrogen and water. The latter product most likely represents adsorbed moisture in the polymer. The presence of large quantities of carbon monoxide is unlike the situation with aliphatic polyamides, where only trace amounts of this degradation product are produced[15, 16]. This appearance of carbon dioxide has been attributed to hydrolytic processes involving the amide groups[15, 16]. There is a greatly reduced production of ammonia and increased evolution of nitrogen in the case of the medium molecular weight polymers. It is interesting to note that

*Table 1.* Rates, activation energies and half-life ($T_h$) values for high (20 000–30 000) and medium (13 000–14 000) $\bar{M}_n$ block copolymers of *t*-2,5-DiMePip

| *Polymer* | *Temp* (°*C*) | *Max rate* (% *sample/min*) | $\Delta E$ (*kJ/mole*) | *S* $(sec^{-1})$ | $T_h$ (°*C*) |
|---|---|---|---|---|---|
| T/I, 70/30* | 440 | 2·50 | 256 | $1{\cdot}9 \times 10^{17}$ | 436 |
| High $\bar{M}_n$ | 429 | 1·22 | | | |
| | 419 | 0·76 | | | |
| | 411 | 0·42 | | | |
| | 401 | 0·20 | | | |
| T/I, 50/50* | 428 | 1·88 | 253 | $1{\cdot}5 \times 10^{17}$ | 427 |
| High $\bar{M}_n$ | 420 | 0·90 | | | |
| | 410 | 0·51 | | | |
| | 401 | 0·29 | | | |
| | 391 | 0·16 | | | |
| T/I, 50/50 | 412 | 4·06 | 214 | $4{\cdot}7 \times 10^{16}$ | 393 |
| Medium $\bar{M}_n$ | 395·5 | 1·96 | | | |
| | 385 | 0·98 | | | |
| | 370 | 0·42 | | | |
| | 360 | 0·20 | | | |
| T/10, 50/50 | 376 | 2·37 | 206 | $7{\cdot}2 \times 10^{16}$ | 370 |
| Medium $\bar{M}_n$ | 371·5 | 1·44 | | | |
| | 352 | 0·38 | | | |
| | 343 | 0·32 | | | |
| | 331 | 0·12 | | | |
| I/10, 50/50 | 390 | 2·70 | 185 | $8{\cdot}1 \times 10^{14}$ | 373 |
| Medium $\bar{M}_n$ | 379 | 1·86 | | | |
| | 353 | 0·53 | | | |
| | 345 | 0·29 | | | |
| | 336 | 0·13 | | | |

*from Bruck, S. D. and Levi, A. A. *J. Macromol. Sci.* 1967, A1 (6), 1095

the medium molecular weight 50/50 mole % *t*-2,5-DiMePip-I/*t*-2,5-DiMePip-10 showed the largest quantity of carbon dioxide (28·5 mole %) evolved during vacuum pyrolysis. Furthermore, this polymer also showed a shift in the maximum rates of volatilization to higher conversions in comparison to the other block copolymers, as discussed above. Such a shift is characteristic for polyamides in which non-random processes, such as hydrolytic scissions, also operate and is accompanied by a lowering of the activation energy as well as the appearance of increased quantities of carbon dioxide. This view is supported by the data of the present study inasmuch as the medium molecular weight 50/50 mole % *t*-2,5-DiMePip-I/*t*-2,5-DiMePip-10 block copolymers shows the lowest activation energy (185 kJ/mole), a shift in the maximum rates of volatilization to higher conversion, and the production of large amounts of carbon dioxide. Hence, this polymer seems to be the most vulnerable to hydrolytic processes in comparison to the other samples studied.

### (C) *Stability of the polymer films toward long-wave ultraviolet radiation*

Polymer films that are to be considered for cornea replacement must exhibit good stability to long-wave ultraviolet and visible radiation. Any

*Table 2.* Mass spectrometric analysis of major degradation products volatile at room temperature of *t*-2,5-DiMePip block copolymers during vacuum pyrolysis (475°C, 1 h, ~ $10^{-5}$ mmHg)

| *Component* | *70/30 T/I** ($\bar{M}_n$ = *20000 to 30000*) (*mole %*) | *50/50 T/I** ($\bar{M}_n$ = *20000 to 30000*) (*mole %*) | *50/50 T/I* ($\bar{M}_n$ = *13000 to 14000*) (*mole %*) | *50/50 T/10* ($\bar{M}_n$ = *13000 to 14000*) (*mole %*) | *50/50 I/10* ($\bar{M}_n$ = *13000*) *to 14000*) (*mole %*) |
|---|---|---|---|---|---|
| Carbon monoxide | 33·7 | 37·9 | 22·2 | 9·7 | 7·2 |
| Carbon dioxide | 8·5 | 14·2 | 17·6 | 21·9 | 28·5 |
| Water | 14·5 | 11·8 | 25·7 | 43·2(?) | 20·5 |
| Ammonia | 16·4 | 14·0 | 1·6 | 0·2 | 0·1 |
| Nitrogen | 0·4 | 0·1 | 8·0 | 6·1 | 10·5 |
| Hydrogen cyanide | — | — | 0·9 | 0·7 | 0·1 |
| Hydrogen | — | 0·7 | 2·7 | 1·0 | 2·1 |
| Methane | 13·3 | 8·1 | 10·8 | 2·9 | 8·2 |
| Other aliphatic satd. and unsatd. hydrocarbons | 5·5 | 4·2 | 5·5 | 9·6 | 8·5 |
| 2,5-Dimethyl pyrazine | 1·9 | 2·1 | 2·2 | 0·6 | 1·7 |
| 2-Methyl pyrazine | 0·9 | 0·8 | 0·6 | 1·0 | 0·5 |
| Pyrazine | — | — | 0·4 | 0·5 | 0·3 |
| Benzene | 1·7 | 1·9 | 0·2 | 0·2 | 0·2 |

*from Bruck, S. D. and Levi, A. A. *Macromol. Sci.* 1967, **A1** (6), 1095 photo-degradation that results in the clouding of the film would seriously limit the usefulness of the polymers in eye research.

Approximately 0·5 mil thick polymer films were irradiated (dry) at 25° ± 2°C by a Black Raymaster (George W. Gates and Co., Franklin Square, Long Island, N.Y.) long wave ultraviolet lamp having an energy peak close to 360 nm with virtually no radiation shorter than 300 nm. The average intensity was 0·55 mJ $cm^{-2}$ $s^{-1}$ (0·55 mW $cm^{-2}$) and was monitored by a YSI-Kettering Model 65 Radiometer. No change was observed in the ultraviolet and visible absorption spectrum of the films even after 160 h of irradiation. No gelation occurred. Soaking the film samples first in an isotonic solution of sodium chloride and then irradiating them, likewise produced no change in the ultraviolet and visible absorption spectra. On the other hand, in an earlier publication it was shown[9] that the piperazine polymers do degrade if irradiated by very intense (31 000 $\mu W/cm^2$) short wave ultraviolet radiation (222·4 to 366·0 nm). However, the eye would normally not be exposed to such intense short-wave radiation ranges.

### (D) *Blood coagulation tests*

Although, the polymers described in this paper are aimed primarily at the replacement of the cornea of the eye where the problem of blood coagulation is of lesser importance than in other implant applications, some initial tests were carried out on random copolymers. The modified Lee White coagulation tests (in which the test tubes were coated with the polymer) indicate that the 20/80 and the 75/25 mole % random copolymers of *t*-2,5-DiMePip-T/*t*-2,5-DiMePip-I significantly prolonged the clotting times of human blood in comparison with glass as the standard.

Further work is needed, including the study of the permeability of the polymer films toward oxygen, water vapours and ions, and the clinical evaluation of the polymer films in animals.

*The work was carried out with the technical assistance of Mr Ashok Thadani, graduate research assistant in the Chemical Engineering Department, The Catholic University of America, Washington, D.C. The mass spectrometric analyses were done by Mr Ernest Hughes and Mr Julian Ives of the National Bureau of Standards, Gaithersburg, Md.*

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*Chemical Engineering Department*
*The Catholic University of America*
*Washington, D.C., 20017*

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