PII: S0032-3861(97)00358-3

Polymer Vol. 39 No. 4, pp. 883–890, 1998
© 1997 Elsevier Science Ltd
Printed in Great Britain. All rights reserved
0032-3861/97/$17.00+0.00

In vitro degradation of poly(methyl glyoxylate) in water

C. H. Brachais[a], J. Huguet[a], C. Bunel[a],* and L. Brachais[b]
[a]Laboratoire de Matériaux Macromoléculaires, Institut National des Sciences Appliquées de Rouen, Place E. Blondel, BP 08, 76131 Mont-Saint-Aignan Cédex, France
[b]Polymères Biopolymères Membranes, UMR 6522 CNRS, Université de Rouen, Faculté des Sciences, 76821 Mont-Saint-Aignan Cédex, France

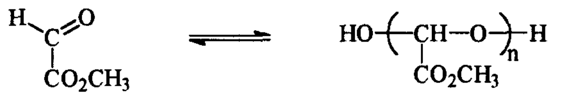
(Received 21 February 1995; revised 21 April 1997)

Degradation of poly(methyl glyoxylate) (PMG) was investigated *in vitro* in aqueous medium. Various techniques were used to control hydrolytic degradation effects, including weighing (weight loss and water uptake), differential scanning calorimetry (d.s.c.), potentiometry and ^{1}H nuclear magnetic resonance (n.m.r.). The final degradation products was identified by ^{1}H n.m.r., using various models such as methylglyoxylate, glyoxylic acid and 2,2-dimethoxy-methylacetate in pure water or acidic medium. Although glyoxilic acid was the final metabolite resulting from degradation, in closed aqueous medium, various equilibria occurred between degradation compounds. Concerning the degradation mechanism, ester groups are first hydrolysed leading to carboxylic functions followed by chain scissions, by cleavage of acetal bonds, and fast depolymerization. © 1997 Elsevier Science Ltd.

(Keywords: poly(methyl glyoxylate); methyl glyoxylate; glyoxylic acid)

INTRODUCTION

In a previous paper[1], we described the synthesis and characterization of a series of new bioresorbable poly-(methyl glyoxylate) (PMG) with various reactive extremities. PMG is obtained by ionic polymerization of methyl glyoxylate (MG) according to the following scheme[2–4]:



$$\mathrm{H{-}C({=}O){-}CO_2CH_3} \rightleftharpoons \mathrm{HO{-}\!\left(CH(CO_2CH_3){-}O\right)_n\!{-}H}$$

MG PMG

Polymerization-depolymerization equilibrium, due to low ceiling temperature[5–7], requires an effective end-capping of hydroxy extremities. In this work we used hexamethylene diisocyanate (HMDI) as reagent, in excess with regard to hydroxy functions. After precipitation into methanol, polymer extremities are the following[1]:

The interest of these kinds of polymers, whose degradation by-products are metabolites, is growing very fast in the field of ecology or biomedical applications for both surgery and drug release. In the case of PMG, the final expected metabolite is glyoxylic acid[8]. In a preliminary study PMG was observed to degrade when implanted into rats[9] and in this paper, we describe the development of *in vitro* experiments designed to elucidate the mechanism of hydrolytic degradation of PMG.

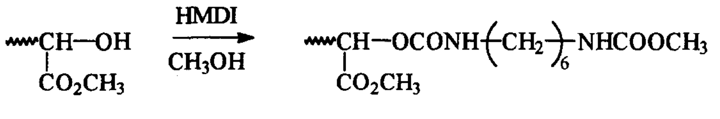
Different techniques (water uptake, weight loss, differential scanning calorimetry (d.s.c.), potentiometry and ^{1}H nuclear magnetic resonance (n.m.r.) were used to follow and identify degradation compounds in a degradation medium which was chosen to be water in vapour or liquid phase.

EXPERIMENTAL

Materials

PMG ($\overline{M_n} = 20\,000$) was obtained by anionic polymerization of methyl glyoxylate (MG) in dichloromethane, at −20°C using triethylamine as initiator[1].

2,2 – dimethoxy-methylacetate and methyl glyoxylate were kindly supplied by Société Française Hoechst. Glyoxylic acid was purchased from Aldrich.



$$\sim\mathrm{CH(CO_2CH_3){-}OH} \xrightarrow[\mathrm{CH_3OH}]{\mathrm{HMDI}} \sim\mathrm{CH(CO_2CH_3){-}OCONH{-}\!\left(CH_2\right)_6\!{-}NHCOOCH_3}$$

---

* To whom correspondence should be addressed.

Water uptake

For weighing experiments, the polymer was cast into thin films in aluminium capsules. Samples were weighed initially (m_0) and *versus* time to obtain swollen weights (m_s). Water uptake was calculated by:

$$\%H_2O = \frac{m_s - m_0}{m_0} \times 100$$

Weight loss

The above-mentioned samples where then dried under vacuum over P_2O_5 for 48 h and reweighed to obtain dry weights (m_d). Weight loss was determined by comparing the remaining dry weight m_d at a given time with the initial weight m_0,

$$\%\text{Weight Loss} = \frac{m_0 - m_d}{m_0} \times 100$$

Thermal properties

The polymer was used as a powder and the samples were degraded under moisture at 30°C. For each degradation time, two samples were recovered. They were first visually examined and then further analysed. Glass transition temperature (T_g) values were determined at midpoint before and after drying.

N.m.r. studies

N.m.r. spectra were recorded on Bruker spectrometers. An AC200 was used for the monomer degradation studies at room temperature while the polymer degradation experiments were performed on an AM400WB at 303 K. For each spectrum, 32 scans were acquired with a spectral width of 10 ppm (2000 or 4000 Hz according to the field of the magnet). Fourier transforms were performed by Brucker Aspect 3000 and Aspect station 1 computers.

RESULTS AND DISCUSSION

Water uptake

Water uptake *versus* degradation time is shown in *Figure 1*.

During the first 9 days, water absorption of the samples lightly increases (8.5%). Then the rate of absorption increases significantly to reach 80% in 12 days. Afterwards, no weighing is possible because the degraded samples were entirely liquid. Concerning the physical aspect of the samples, a whitening is progressively observed for 3 days, then the polymer becomes transparent and completely soft in 8 days and finally liquid.

Weight loss

Concurrently, we measured the weight loss of the polymer in the same experimental conditions. These measures show up the water soluble compounds proceeding from chain degradations (*Figure 2*).

During the first 3 days, the weight of the samples remained unchanged in spite of aspect change as above-mentioned. The onset of weight loss curve was detected after 9 days and then an important increase is observed.

Comparison between *Figures 1 and 2*, shows that water uptake during the first 3 days, is only representative of water diffusion in the polymer without degradation. On the other hand, after 9 days, a true degradation of the polymer occurs, expressed by an increase in weight loss.

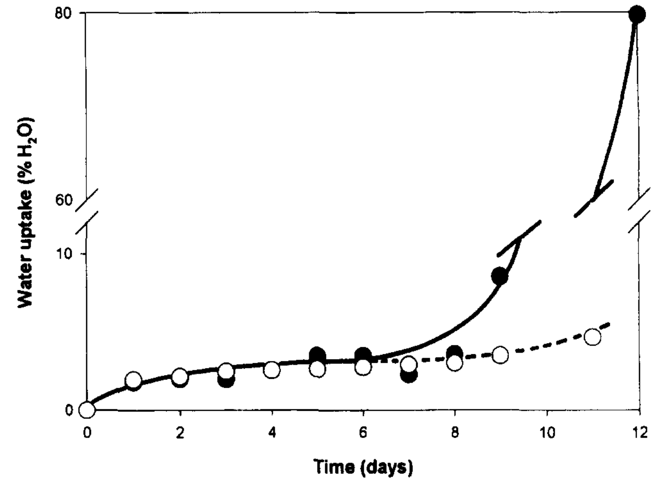


Figure 1 Water uptake *versus* degradation time: experimental values (•); theoretical values computed from Gordon–Taylor relation (○)

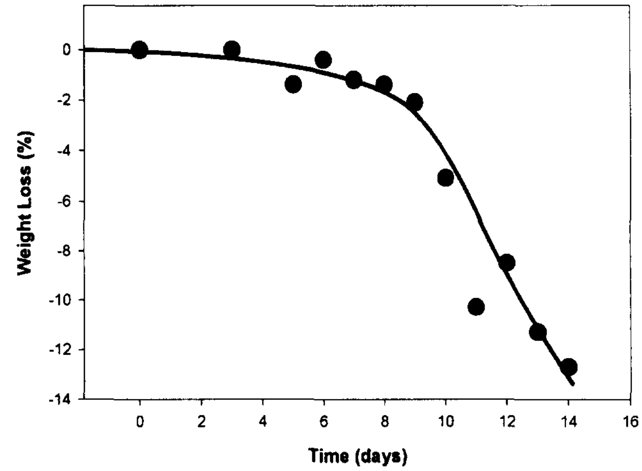


Figure 2 Weight loss *versus* degradation time

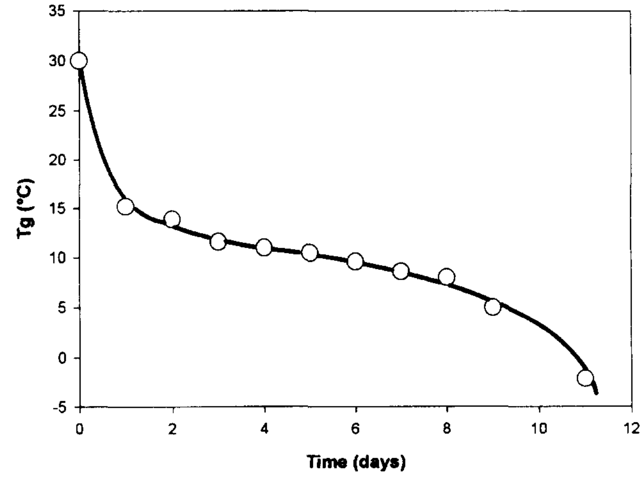


Figure 3 T_g *versus* degradation time of swollen polymer

Thermal properties

The variations of glass transition temperature T_g *versus* time (*Figure 3*) clearly shows the plasticizing effect of

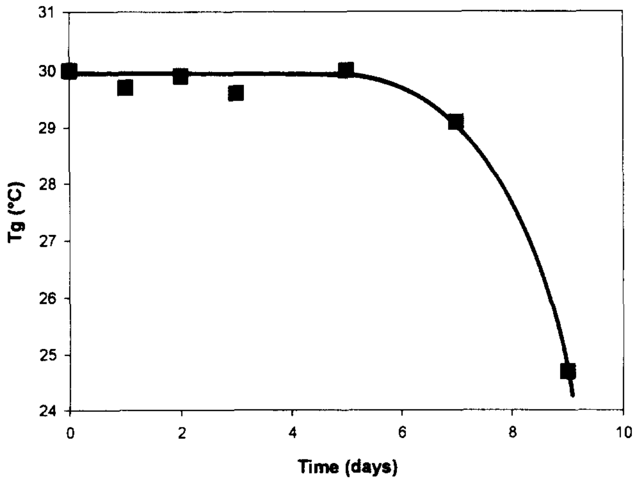


Figure 4 T_g *versus* degradation time of dry polymer

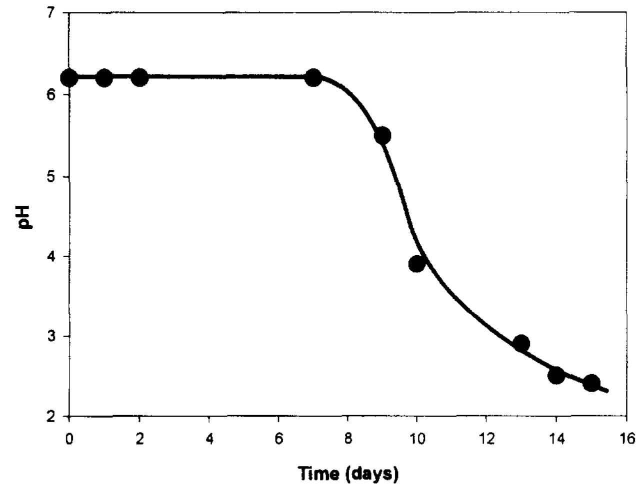


Figure 5 pH of aqueous medium *versus* degradation time

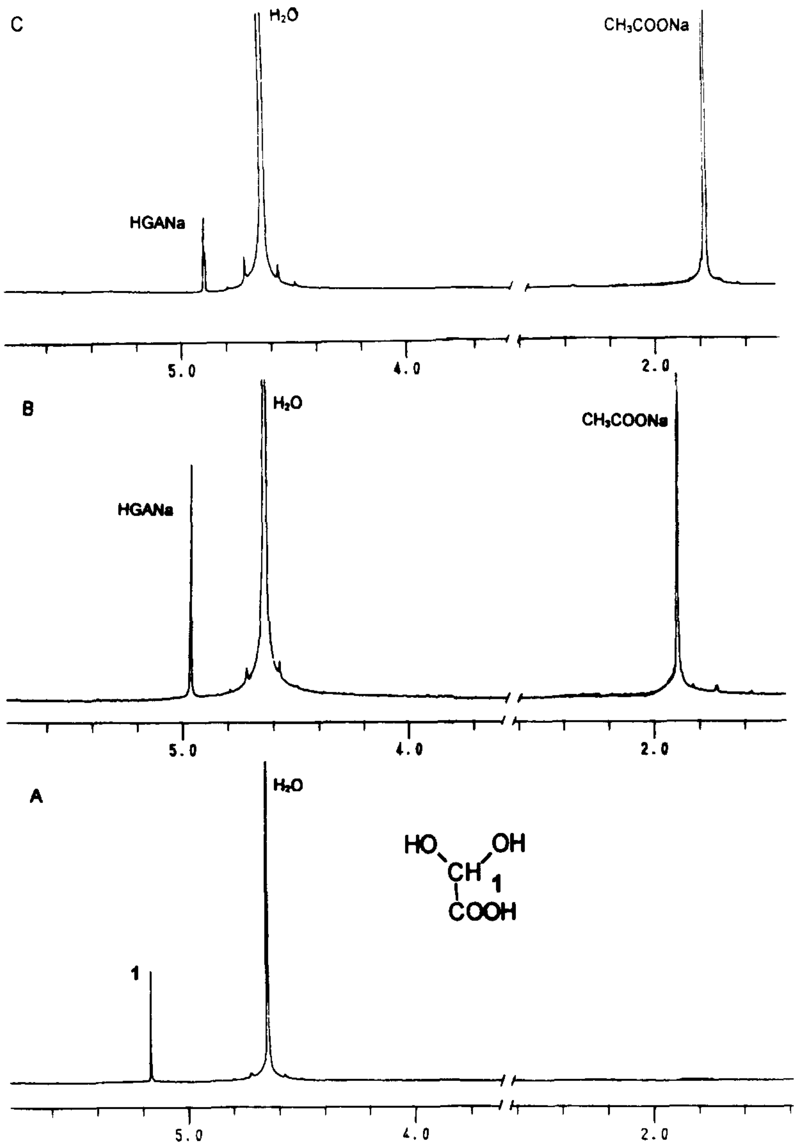
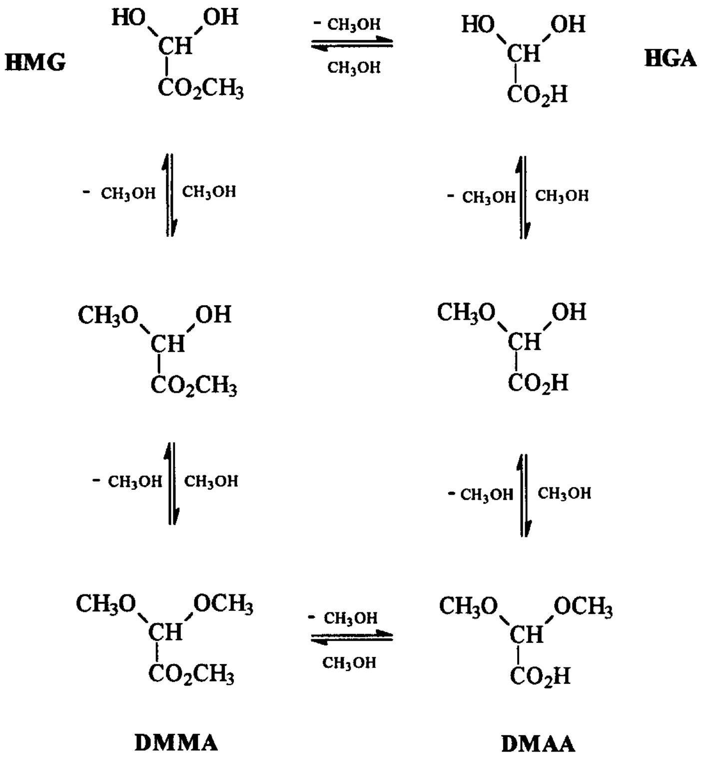


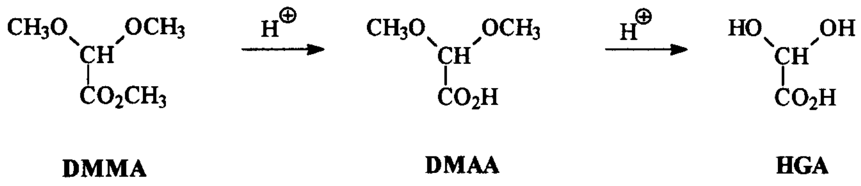
Figure 6 ^{1}H n.m.r. spectrum of glyoxylic acid hydrate (HGA)

absorbed water in the polymer. This observation is strengthened by the measurement of T_g on dried samples (*Figure 4*). In that case, no variation of T_g is observed until degradation occurs. After 8 days a dramatic drop in T_g values was observed in each case. No T_g could be precisely measured after 11 days due to degradation phenomenum.

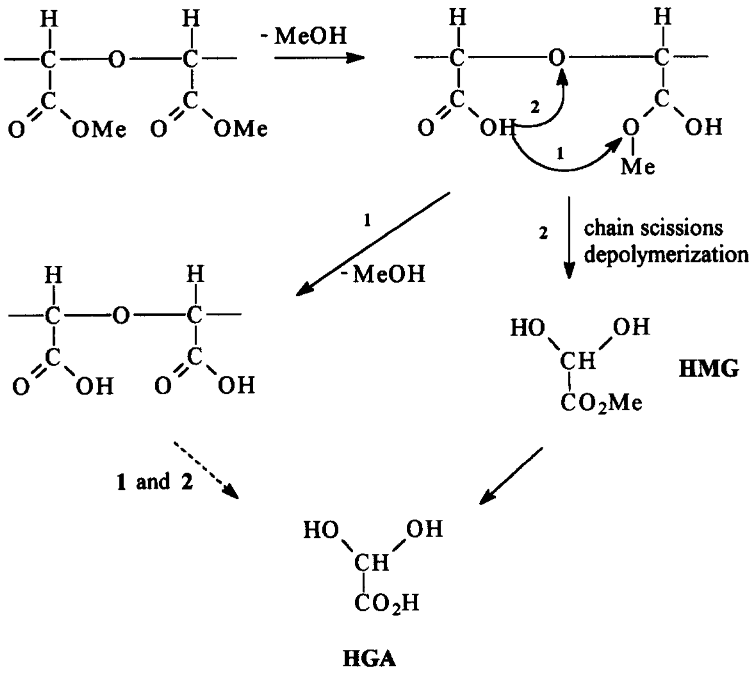
It is noteworthy that plasticizing effect of water on PMG chains is very important since decreasing T_g is about 15°C in



Scheme 1



Scheme 2



Scheme 3

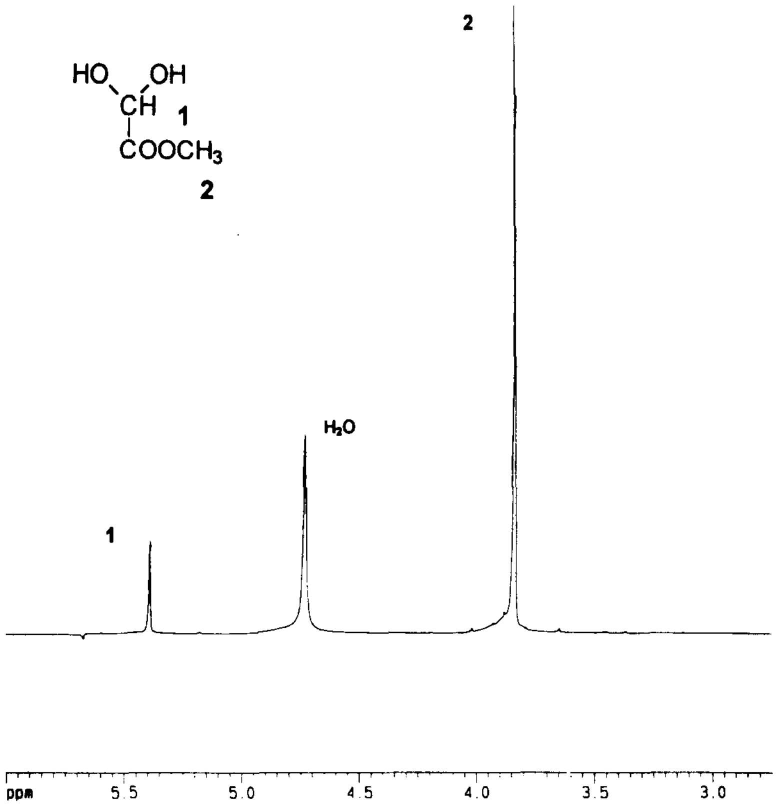


Figure 7 ^1H n.m.r. spectrum of methyl glyoxylate hydrate (HMG)

24 h (*Figure 3*). This value can be related to a water uptake of 2%. By using the well-known Fox–Flory relation, we can calculate a theoretical value of T_g according to:

$$\frac{1}{T_g} = \frac{1-w}{T_g^p} + \frac{w}{T_g^w}$$

where $T_g^p = 303$ K (30°C for PMG), $T_g^w = 138$ K (evaluated for pure water to -135°C by Angell[10]) and $w = 0.02$. In that case, we obtain 23°C instead of 15°C. Literature also reports examples of polymeric systems (PVA/H_2O or cellulose/H_2O) for which the experimental T_g value is much more lower than the calculated one[11,12].

From the Gordon–Taylor relation,

$$T_g = \frac{(1-w)T_g^p + K_w T_g^w}{(1-w) + K_w}$$

a value of $K = 4.9$ is obtained with the experimental $T_g = 288$ K (15°C). From this value of K, we computed theoretical water uptake corresponding to experimental T_g values. The result, reported in *Figure 1*, is only in agreement with experimental observations up to 8 days, that is to say when only diffusion of water is considered. As soon as degradation occurs, a great divergence is observed since Gordon–Taylor relation is not valid.

pH variations

In order to observe acidic groups due to PMG hydrolysis, degradation of PMG powder was followed by potentiometry directly in water. This degradation is a heterogeneous reaction since powder is totally insoluble in water. In *Figure 5* we report pH variations of the degradation medium *versus* time.

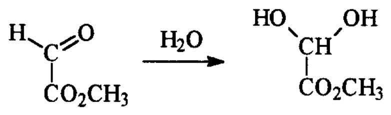
These results are also in agreement with previous studies, since degradation phenomenum begins after 8 days. Then, an important drop in pH appears, corresponding either to free carboxylic groups (release of glyoxylic acid in the solution by chain cleavages) or to poly(glyoxylic acid) chains in the solution. After 10 days, the whole of the powder is in solution.

n.m.r. degradation study

In aqueous dilute medium, chain scissions must lead to elementary units because of fast depolymerization. Thus, according to repeating unit structure of the polymer (acetal and ester functions), we can *a priori* assume the presence of several small molecules (*Scheme 1*) where aldehydes are in their hydrates form in water.

A comprehensive n.m.r. study of these by-products is dealt with in another paper[13]. In regard to our purpose, only hydrate of glyoxylic acid (HGA) and hydrate of methyl glyoxylate (HMG) spectra will be considered (*Figures 6 and 7*) with those of 2,2-dimethoxy-methylacetate (DMMA) *versus* time (*Figure 8*) in acidic medium, to enhance degradation.

- HMG spectrum was obtained by dissolution of 100 mg of freshly distilled MG in 20 ml of water. The solubilization of MG immediatly leads to hydrate compound:



$$\mathrm{HC(=O)CO_2CH_3} \xrightarrow{H_2O} \mathrm{(HO)_2CH\,CO_2CH_3}$$

MG **HMG**

The degradation of HMG (5.7×10^{-2} M) was evaluated by potentiometry at 30°C. From pH values we calculate COOH concentration (*Figure 9*) by using the following relation:

$$[\mathrm{COOH}] = \frac{[\mathrm{H}^+]^2}{K_a} + [\mathrm{H}^+]$$

where $K_a = 7.08 \times 10^{-4}$ ($pK_a = 3.15$) was determined by titration of glyoxylic acid with NaOH.

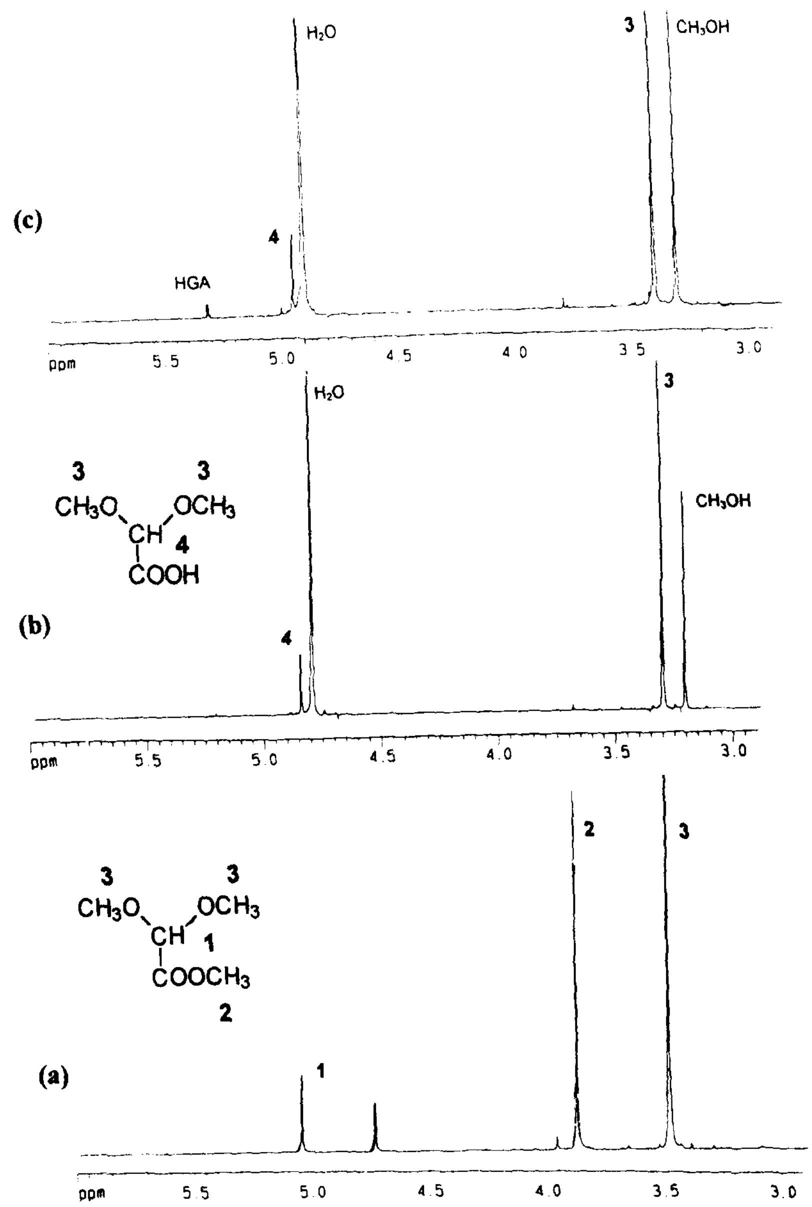


Figure 8 ^{1}H n.m.r. spectrum of 2,2-dimethoxy-methylacetate *versus* time in acidic medium: $t = 0$ (a); 1 day (b); 3 days (c)

One can observe a fast increase of acidity after 2 days, attesting methyl ester hydrolysis.

- For all compounds, chemical shifts greatly depend on concentration, degradation progress or pH of the medium and can make assigments more difficult. For example, CH chemical shift of HMG is observed in the range 5.14–5.40 ppm, according to experimental conditions, and is very close to the CH chemical shift of HGA (5.16–5.30 ppm). Nevertheless, in the presence of increasing concentration of CH_3CO_2Na, HGA leads progressively to its salt form (HGANa) and CH chemical shift varies now progressively up to 4.89 ppm when sodium acetate is in excess with respect to HGA concentration (*Figure 7*). Thus, the use of CH_3CO_2Na allows the CH differentiation between HMG and HGA at the very beginning of the degradation.
- In the case of DMMA, *Figure 8* shows clearly, after 1 day, the entire disappearance of methyl ester peak and the presence of methanol. This observation corresponds to ester hydrolysis and 2,2-dimethoxy acetic acid (DMAA) formation. It is only after 3 days that glyoxylic acid is observed from acetal hydrolysis according to *Scheme 2*.

If we assume that DMMA is a model of PMG, ester hydrolysis can be expected before chain degradation by cleavage of acetal bonds.

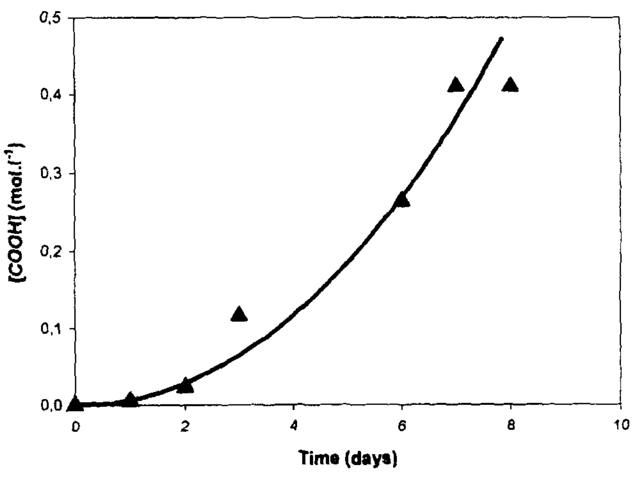


Figure 9 Glyoxylic acid concentration *versus* degradation time

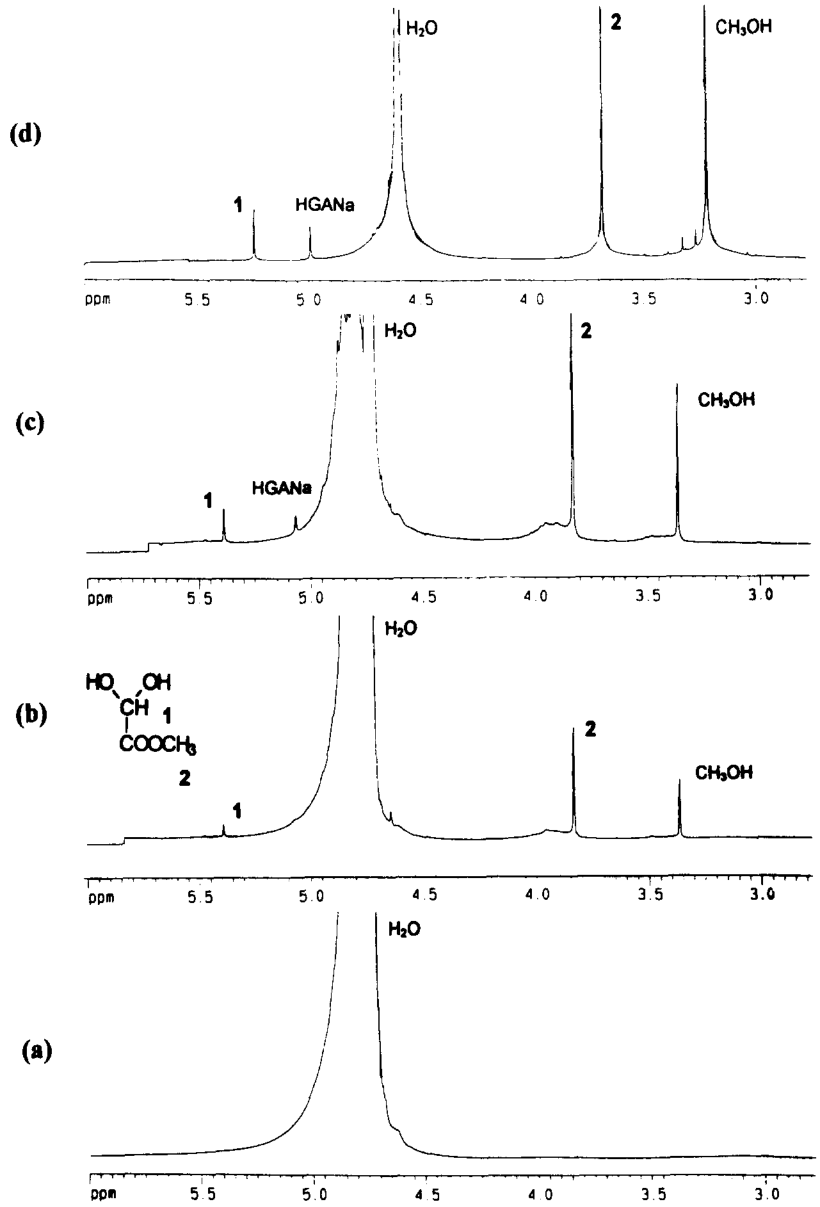


Figure 10 ^{1}H n.m.r. spectra of poly(methyl glyoxylate) *versus* degradation time in water with sodium acetate as internal standard: $t = 0$ (a); 2 days (b); 9 days (c); 28 days (d)

- In *Figure 10*, we reported n.m.r. spectra of PMG (104 mg in 0.5 ml of D_2O with 3.1 mg of CH_3CO_2Na as internal standard, at 30°C). PMG is insoluble in D_2O and only small soluble molecules are observed. Degradation spectra of PMG can now be easily assigned with the help of previous n.m.r. compounds. At $t = 2$ days, the peaks are assigned to MeOH and HMG. After 9 days, an additional peak appears at 5.06 ppm which is assigned to CH of glyoxylic acid (HGANa form). At $t = 28$ days, the same peaks are observed with an increase of methanol and glyoxylic acid.

Thus, the presence of methanol at the beginning of the degradation gives evidence of ester hydrolysis. Nevertheless, potentiometry study (*Figure 9*) and n.m.r. spectra show that there is very little carboxylic function in the medium. On the other hand, methyl glyoxylate appears concurrently with methanol. If we remember that, in our conditions, ester hydrolysis is faster than acetal cleavage, *Scheme 3* suggests the most probable mechanism which bring to the fore an anchimeric effect of carboxylic group.

Hydrolysis of soluble HMG, released in the medium, leads to increasing concentration of HGA and therefore an autoacceleration of the degradation can occur.

CONCLUSION

The degradation process of poly(methyl glyoxylate) in water can be depicted by three steps. The first one is diffusion of water into polymer matrix and plasticization. Then, a random hydrolysis of methyl ester functions is observed which is responsible of methanol release and appearance of carboxylic functions on the polymer backbone. Finally, these latest functions generate chain scissions and a fast depolymerization occurs with an important release of methyl glyoxylate, which is the repeating unit of the polymer. It should be noted that an autoacceleration is observed when glyoxylic acid appears that is to say when acidity of the medium increase by methyl glyoxylate hydrolysis.

REFERENCES

1. Brachais, C. H., Huguet, J. and Bunel, C., *Polymer*, 1997, **38**, 4959.

2. Crutchfield, M. M. and Upton, C. J., Monsanto Co., US Patent No. 4140676, 1979.
3. Crutchfield, M. M., Papanu, V. D. and Warren, C. B., Monsanto Co., US Patent No. 4144226, 1979.
4. Crutchfield, M. M., Papanu, V. D. and Warren, C. B., Monsanto Co., US Patent No. 4146495, 1979.
5. Muller, E., Thesis, Université P. et M. Curie, Paris VI, 1992.
6. Vairon, J. P., Muller, E. and Bunel, C., *Makromol. Chem., Macromol. Symp.*, 1994, **85**, 307.
7. Vairon, J. P., Muller, E. and Bunel, C., *J. Macromol. Sci., Macromol. reports*, 1994, **A31**(6&7), 821.
8. Gledhill, W. E. and Saeger, V. W., *J. Ind. Microbio.*, 1987, **2**, 97.
9. Brachais, C. H., Thesis, University of Rouen, 1995.
10. Angell, T., *J. Chim. Phys.*, 1980, **84**, 268.
11. Kolov, Y. M., Kynin, A. T., Nikolaev, A. F. and Grebennikov, S. F., *Zhur. Prikld. Khim.*, 1989, **62**, 1673.
12. LeHuy, M. and Rault, J., *Polymer*, 1993, **35**, 136.
13. Brachais, C. H., Huguet, J., Bunel, C. and Brachais, L., *Polymer* to be published.