Partial Depolymerization and Solubilization of Poly[(*R*)-3-hydroxybutanoate] (PHB) and Its Copolymer with (*R*)-3-Hydroxyvalerate (*BIOPOL*®) by Treatment with Li-Amides/LiCl in Tetrahydrofuran at Low Temperature [1]

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Dieter Seebach*, Albert K. Beck, Urs Brändli, Dieter Müller, Michael Przybylski,** and **Klaus Schneider****

Abstract. The biopolymers PHB and PHB/PHV (mol. weight $> 7 \cdot 10^5$ g·mol^{-1}) from fermentations of certain lot numbers or PHB samples which had previously been precipitated from dichloroethane solution can be dissolved by treatment with excess lithium-diisopropylamide in LiCl-containing tetrahydrofuran. The samples recovered from these solutions in good yields have molecular weights of 1000–5000 g·mol^{-1}.

A) Introduction

Polyhydroxybutyrate [2] (PHB) is a member of a class of biopolymers referred to as PHAs (polyhydroxyacids) which are produced by microorganisms. PHB and the copolymer containing up to 30% hydroxyvalerate units (PHB/PHV, *BIOPOL*®) are products made on an industrial scale [3] by fermentation of *Hydrogenomonas eutropha* (*Alicaligenes eutrophus*) [4]. Gene-technological methods have been applied to transfer the ability to produce PHB to other organisms [5] [6]. The high biocompatibility and the biodegradability of PHB and its congeners render these polymers attractive materials and have spurred expectations and speculations about future uses, as indicated by the title of a recent *Science* Research News Article, 'In Search of the Plastic Potato' [6]. The molecular weight of PHB from *A. eutrophus* is *ca.* 10^6. Lower-molecular-weight oligomers of hydroxybutyrate could be useful, for instance as plasticizers for the high-molecular-weight material or for retard formulations in drug delivery. Besides degradation by depolymerases [7], mixtures of oligomers have been obtained previously by methanolysis [8] of PHB [9]. We have observed a surprising partial degradation of PHB (**1** in *Scheme 1*) which was mentioned in a recent review article [10] and which is described in full detail herein.

B) Results

PHB of molecular weight of *ca.* $7.5 \cdot 10^5$ (by light scattering; $\bar{M}_w$) [11] was obtained from *ICI Biological Products* [12] as a sample of lot number MBL 100/80, a colourless, light fluffy material. It was dried, mixed with 3 equiv. LiCl and suspended in THF under an Ar atmosphere. The vigorously stirred mixture was cooled to temperatures between −75 and −105°, and combined with a cold solution of 3 equiv. lithium diisopropylamide (LDA), 2,2,6,6-tetramethylpiperidide (LTMP), or hexamethyldisilazide (LHMDS) in the same solvent *(Table 1)*. The polymer dissolved and the mixture turned yellow. Quenching of this solution with aq. NH_4Cl caused a precipitate to be formed and the yellow colour to disappear. Evaporation of volatiles gave an aq. slurry from which samples of oligomeric hydroxybutyrates were extracted with $CHCl_3$ in yields ranging from 10 to 75%. PHB samples from other lot numbers, which were more dense, had to be precipitated by pouring a 1,2-dichloroethane solution into aq. MeOH to give the fluffy material (*cf.* runs number *2* and *4* in *Table 2*). The copolymer PHB/PHV (lot No. *MBL 100/12*, 22% PHV content) could likewise be dissolved in THF with a Li-amide base in the presence of LiCl. In both cases, in the absence of LiCl, an excess of up to 10 equiv. LDA had to be employed in order to achieve solution, conditions which were not further investigated.

The materials recovered from the THF solutions were investigated by gel-permeation chromatography (GPC), by osmometric methods ($\bar{M}_n$ molecular weights), by differential scanning calorimetry (DSC), by ^{1}H-NMR [13a], and by plasma-desorption mass spectroscopy (PDMS [13b,c], see *Figs. 1–4* and *Tables 1* and *2*. Varying values for the molecular weight of a given sample were obtained by the different methods, but they all ranged from 1000 to 5000. We are not in a position to evaluate the reasons for these discrepancies at this stage, but we can safely make the following statements:

i) except after prolonged periods of time, PHB (**1**) is not fully degraded to crotonate (**2** in *Scheme 1*) by excess $LiNR_2$ in a LiCl-containing solution at low temperature.

ii) Oligomers **3a** containing 10–50 hydroxybutyrate units with crotonate end groups are recovered from the THF solutions.

iii) The molecular-weight distribution in the mass spectrum of degraded PHB/PHV *(Fig. 4)* suggests that the hydroxyvalerate units are incorporated statistically in the bio-copolymer.

C) Discussion

Before hydrolysis, the THF solutions obtained from PHB and Li-amide bases must contain polylithiated species which are associated with LiCl, excess $LiNR_2$ and HNR_2 see **4** in *Scheme 2*. It is the relatively large stability of these species towards elimination to crotonate (**5** in *Scheme 2*) [14] and their solubility in the non-polar solvent THF, which are remarkable. The stability may be due to a highly complex structure containing intramolecular aggregations of Li-enolate moieties and intermolecular aggregations with the LiX species present (X = Cl or NR_2) [10], as well as complexation with the secondary amine, the by-product of deprotonation [10] [15]. The solubilization in THF of polylithiated compounds by adding Li salts has also been observed with peptides [10] [16].

* *Correspondence:* Prof. Dr. D. Seebach
Laboratorium für Organische Chemie der
Eidgenössischen Technischen Hochschule
ETH-Zentrum, Universitätstrasse 16
CH-8092 Zürich

**Fakultät für Chemie
Universität Konstanz
Universitätsstrasse 10
Postfach 5560
D-7750 Konstanz

Table 1. *Degradation of PHB* (lot *MBL 100/80*, 1-gm scale batches) with *$LiNR_2$ in THF with Different Reaction Times and at Different Temperatures*. The reaction mixtures were quenched by injecting excess sat. aq. NH_4Cl into the stirred cold soln.; the molecular weights ($\bar{M}_n$) were determined by vapor-pressure osmometry (see *Experimental* and accompanying text). In all runs, 3 equiv. LiCl and $LiNR_2$ per hydroxybutanoate unit were employed. Abbreviations for the bases, see text. Differential scanning calorimetry (DSC) of some samples with $\bar{M}_n$ 2100 – 3000 gave m.p. (max. peak temp.) between 128 and 140°, ranges of melting from 115 to 155°, and enthalpies of melting from 5700–7300 [$J \cdot mol^{-1}$], see also *Fig. 2*. Esterification of the sample of $\bar{M}_n$ = 2737 with CH_2N_2 and ^{1}H-NMR-spectroscopic analysis of the $C-CH_3/O-CH_3$ ratio leads to a molecular weight of 2450[a]).

Base $LiNR_2$	Reaction time [min]	Temperature [°C]	Yield of oligomer [%]	$\bar{M}_n$ [$g \cdot mol^{-1}$]
LDA	1	–78	63	2935
LDA	5	–78	62	2737
LDA	8	–105	64	3649
LDA	10	–78	40	2739[b])
LDA	15	–78	56	2355
LHMDS	15	–78	73	3060
LTMP	15	–78	30	4148
LDA	15	–105	63	3540
LDA	25	–78	48	2470
LDA	30	–105	58	4644
LDA	60	–78	39	2541
LDA	120	–78	23	2577
LDA	900	–78	no oligomers isolated[c])	

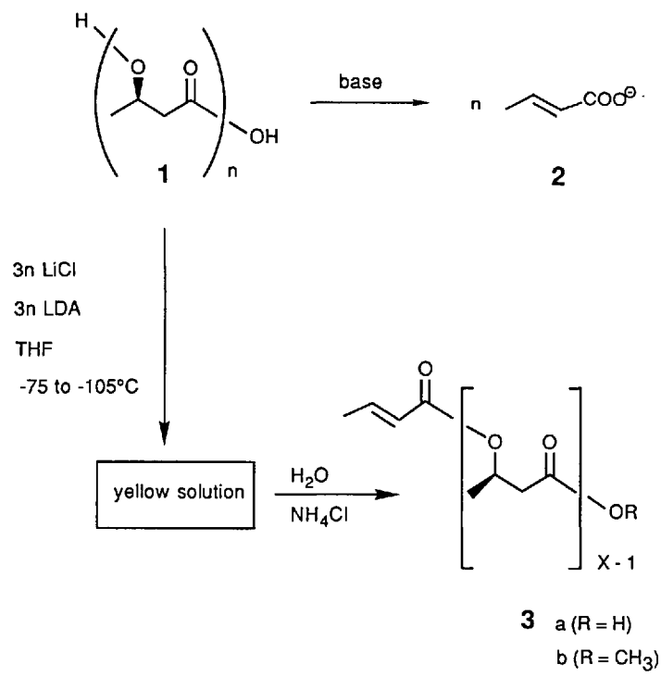
[a]) The crotonate C=C–CH_3 signal appears at 1.85 ppm (*dd*, J = 7.5,1) ($CDCl_3$, 200 MHz, *Varian-Gemini* spectrometer) [13a].
[b]) The yield in this run is somewhat smaller because the sample was isolated by taking an aliquot out of the reaction mixture, transferring it to another flask (–78°) and quenching.
[c]) Quenching after 15 h causes no more precipitation of oligomers. According to NMR analysis of the acid fractions from the workup procedure, crotonic acid and its non-conjugated isomer, but-3-enoic acid are the products of this 'total' degradation.

Table 2. *Preparative Degradation of PHB and PHB/22% PHV on a 10-g Scale with Samples from Different Lots, Using LDA or LHMDS in THF at –78°*. For details, see heading of *Table 1* and procedure.

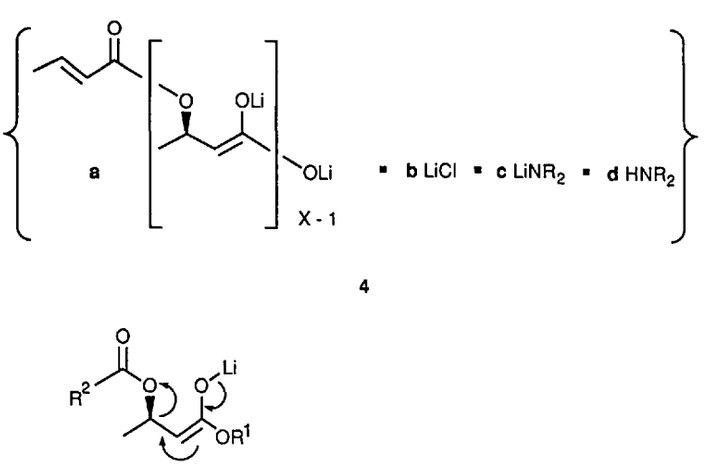
Run No.	Lot	Base $LiNR_2$	Yield [%]
1	*PHB-MBL 100/80*	LHMDS	75[a])
2	*PHB-MBL 100/393* (as received)	LHMDS	7
3	*PHB-MBL 100/393* (as received)	LDA	19
4	*PHB-MBL 100/393* (precipitated[b]))	LHMDS	51
5	*PHB/PHV-MBL 100/12*	LDA	26[c])
6	*PHB/PHV-MBL 100/12*	LHMDS	58

[a]) GPC and DSC see *Figs. 1* and *2*. b) By addition of $ClCH_2CH_2Cl$ solution to $MeOH/H_2O$, see accompanying text and *Experimental*. c) PDM, see *Fig. 3 (B)*.

Scheme 1



Scheme 2



The fact that the success of the partial depolymerization described here depends upon the source and pretreatment of the PHB samples (see *Table 2*) suggests that the molecular-weight range of the oligomers may not only be the result of special structural features in **4**, but may also be caused by the presence of substructures in the PHB starting material (*cf.* the helical, crystalline domains of PHAs) [17]. Since there is access to open-chain [18] [19] and cyclic [18] [20] oligomers [7] [21] of 3-hydroxybutanoic acid with defined chain lengths or ring size, we are now testing these possibilities.

We thank Dr. *A. Ragg* and *A. Webb* of the *MBL Division*, Billingham, England, for numerous helpful discussions and for carrying out some molecular-weight determinations of degraded PHB and PHB/PHV samples. Dr. *S. Bantle* and *Y. Duchesne* of the *Sandoz AG*, Basel, were generous enough to supply the GPC chromatograms and DSC curves for *Figs. 1* and *2*. The late Prof. *P. Pino* and *M. Colussi*, Institut für Polymere, ETH Zürich, have been very helpful in introducing us to the techniques typical of polymer chemistry. *T. Aeschbach*'s technical assistance in the large-scale degradation experiments and *R. Breitschuh*'s experiments concerning acidic degradation are gratefully acknowledged. *B. Lamatsch* contributed the statistical calculations shown in *Fig. 4*. Support by the *Deutsche Forschungsgemeinschaft* is also greatfully acknowledged. The *Sandoz AG*, Basel, continues to generously support our work financially. Free samples of diisopropylamine were received from *BASF Aktiengesellschaft*, Ludwigshafen, and hexamethyldisilazane from *Bayer AG*, Leverkusen. Finally, we would like to thank Dr. *F. Sternfeld* for polishing the English of our manuscript.

Experimental

The molecular weights listed in *Table 1* were determined by vapour-pressure osmometry using a *Corona Wescan 232 A/100* 'Molecular Weight Apparatus' in $CHCl_3$ at 25°. For calibration benzil ($\bar{M}_r$ = 210.2 $g \cdot mol^{-1}$) was used. The concentrations of the sample solns. measured were in the range 5–10 $mg \cdot ml^{-1}$.

$(i\text{-}Pr)_2NH$, hexamethyldisilazane (HMDS), and tetramethylpiperidine (TMP) were distilled from CaH_2 or NaH prior to use. For small-scale reactions, THF was distilled from $LiAlH_4$ or K under Ar; for large-scale work, it was purchased from *Fluka* (*p.a.* grade)

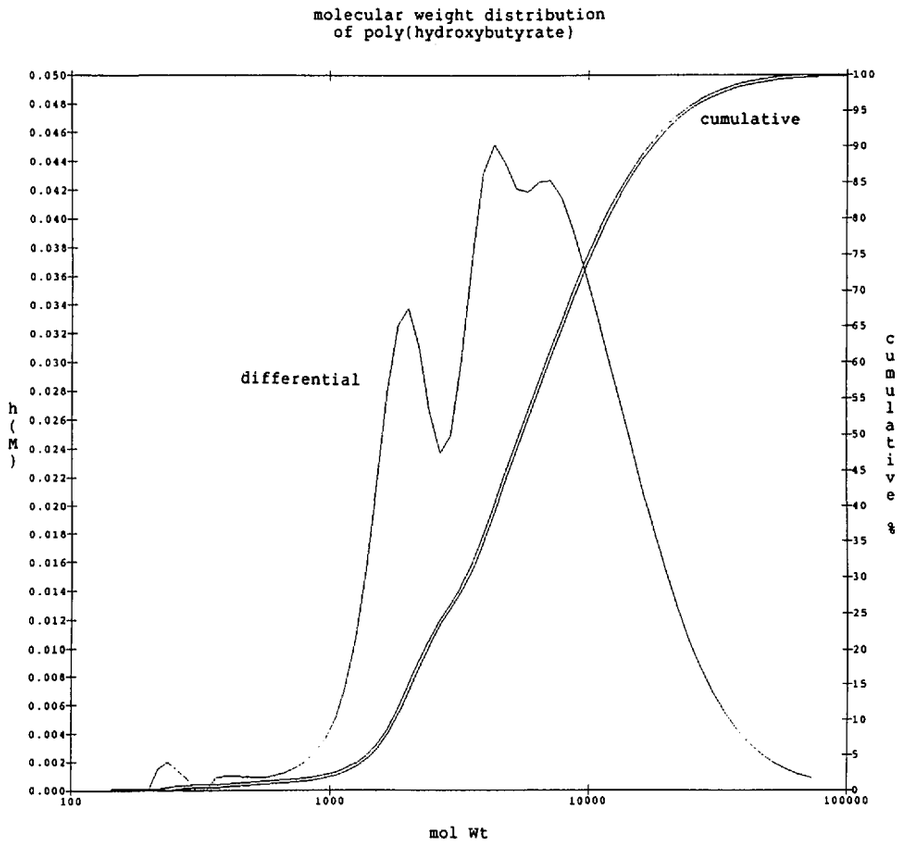


Fig. 1. *Gel permeation chromatogram (GPC) of the sample obtained in run number* 1 *(Table 2)*. Determination of molecular-weight distribution was performed using a *GPC-System* of *Waters*, Division of Millipore, *Waters 840* in CH_2Cl_2. The system was calibrated with narrow poly(styrene). The columns, poly(styrene)-cross-linked with divinylbenzene from *Polymer Laboratories*, UK, cover a molecular weight range from 100 to 500000. Calibration against poly(styrene) standards leads to a weight average molecular weight $\bar{M}_w$ of 7760 and a number average molecular weight $\bar{M}_n$ of 3370. The distribution curve consists of three overlapping peaks at approximately 3000, 4000, and 7000 g·mol^{-1}.

Reprecipitation of PHB

PHB lot No. *MBL 100/393* (50 g) was taken up in 1,2-dichloroethane (250 ml) to afford a nearly clear, brownish soln. This was heated under reflux and CH_2Cl_2 (750 ml) was added over 10 min. After cooling to r.t., the soln. was filtered through a 3-cm pad of *Celite* (diameter 6.5 cm) under suction. The *Celite* was washed with CH_2Cl_2 (100 ml). The resulting, almost colourless, clear soln. was concentrated to a volume of 500 ml and then poured into a vigorously stirred mixture of MeOH (1500 ml) and H_2O (600 ml) [24]. The fluffy white material which precipitated was filtered off and dried under high vacuum over P_2O_5 to constant weight (48.5 g).

Partial Depolymerization of PHB and PHB/PHV.

Small scale (PHB)

THF (100 ml) was syringed into a 2-necked flask containing PHB (1 g, 12.6 mmol) and LiCl (1.48 g, 34.8 mmol) under Ar. The mixture was stirred for 1 h to enable the PHB to swell up and then cooled to −78°. A cold (−78°) soln. of LDA (3 equiv.) in THF (13 ml), generated from DIPA (5.3 ml, 37.2 mmol) and BuLi (26 ml, 40.9 mmol), was added *via* syringe to give a clear, yellow soln.

After different periods of time (see *Table 1*), the reaction was quenched by addition of sat. aq. NH_4Cl soln. (10 ml) *via* syringe to give a precipitate. The mixture was allowed to warm up to r.t. and the THF evaporated. The residue was taken up in $CHCl_3$ and the org. layer washed with sat. $NaHCO_3$ soln. (2 × 150 ml), 1N HCl (2 × 150 ml), and brine (2 × 150 ml), dried ($MgSO_4$), and concentrated. Pentane or Et_2O was then added to precipate the degraded PHB.

For the reaction of PHB with LHMDS and LTMP, one half and one third of the above quantities were used, respectively.

Large scale (PHB)

A mixture of PHB (10 g, 126 mmol) and LiCl (16 g, 348 mmol) in THF (1 l) in a 2-l three-necked flask was stirred at r.t. for 2 h and then cooled to −75° (internal temp.) [25]. LHMDS (3 equiv.) was generated from HMDS (75 ml, 360 mmol) and BuLi (240 ml, 362 mmol) in THF (100 ml) and added as cold (−75°, internal temp.) solid/liquid mixture *via* a *Teflon* canula (diameter 2.5 mm) [26]. A further 20 ml THF was used to rinse the flask used for generation of the amide base, and this was also added to the reaction vessel.

and used directly. BuLi used was titrated either with *sec*-BuOH [22] or diphenylacetic acid [23]. LiCl was dried at 100° under high vacuum for 10–12 h.

PHB and PHB/22 % PHV samples were dried at r.t. under high vacuum for 24 h.

The molecular weight of a sample of PHB (lot No. *MBL 100/80*) was determined by light-scattering diffractometry using a *Sofica* apparatus and found to be $7.5 \cdot 10^5$ g·mol^{-1}.

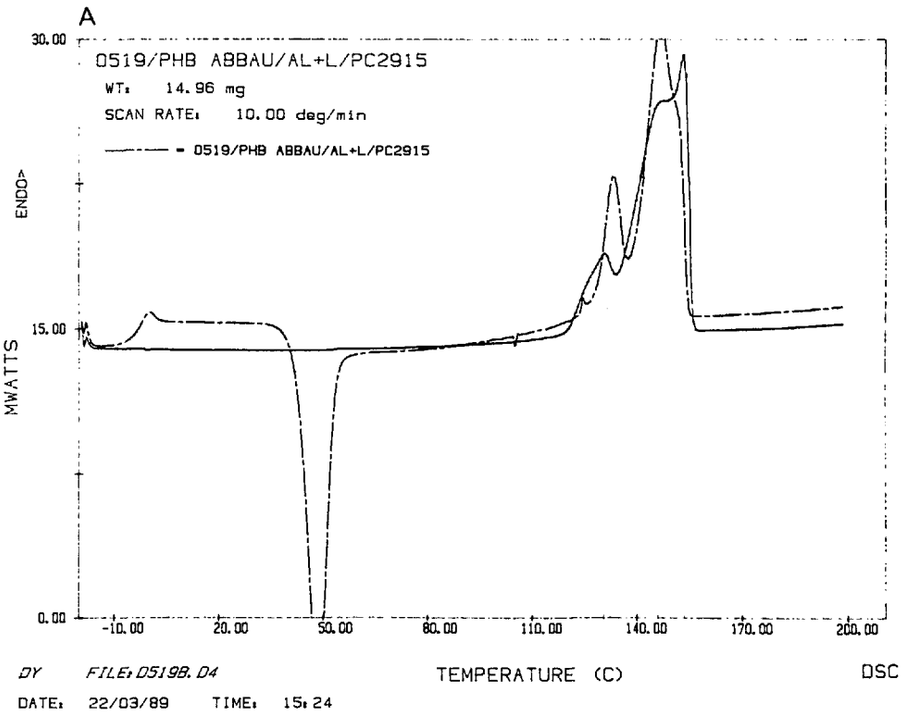


Fig. 2A. *Differential scanning calorimetry (DSC) of the sample of run number* 1. Entire scanning curve. A *Perkin Elmer* instrument, *DSC 4*, was used for the thermoanalysis of the sample. The instrument is calibrated with In and baseline compensated. After a first heating run to 200°, the sample was quenchcooled to −20° and then reheated with a scan of 10 deg·min^{-1}. The weight of the sample was 14.96 mg. Three distinct m.p. between 130° and 155° are seen in the first run. After quenchcooling, a glass transition is observed at −3.8° (midpoint), a recrystallization at 48° and subsequent melting at 130–155°.

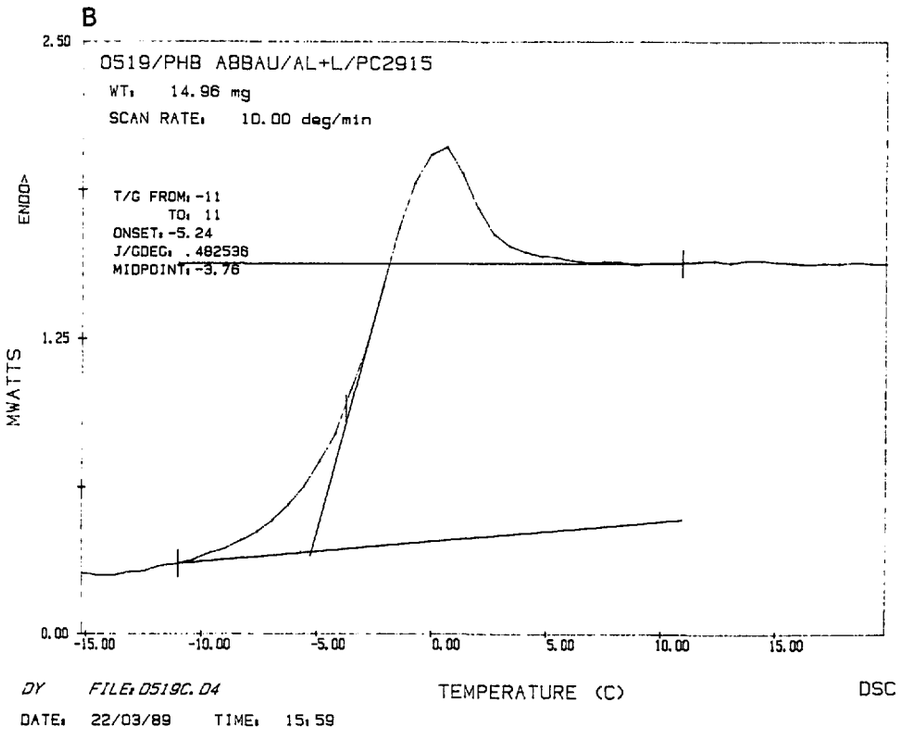


Fig. 2B. *Differential scanning calorimetry (DSC) of the sample of run number 1.* Enlargement of part near the glass transition.

The resulting mixture was difficult to stir and was removed briefly from the cooling bath and shaken by hand to afford a pale yellow, turbid soln. This was then stirred for 15 min at which time the internal temp. was −68°. Sat. NH_4Cl soln. (100 ml) was added by syringe, whereupon the temp. of the mixture became −38°, and a white solid precipitated. The mixture was then stirred at r.t. for 1½ h. The THF was evaporated and the residue taken up in $CHCl_3$ (800 ml) and washed with half-sat. $NaHCO_3$ soln. (600 ml) [24]. The aq. phase was re-extracted with $CHCl_3$ (200 ml), and the combined org. layers were washed with sat. $NaHCO_3$ soln. (2 × 300 ml). During this washing procedure, a gelatinous substance formed at the $CHCl_3/H_2O$ interface which was removed by filtering the mixture through *Celite*. The org. portion of the filtrate was washed with H_2O (500 ml), dried ($MgSO_4$), and evaporated to furnish 9.3 g of a beige-coloured solid. This was stirred with Et_2O (100 ml) at r.t. for 2 h and the solid then collected on a frit. Drying under high vacuum afforded 7.5 g of a white powder.

For runs *2* and *3* (*Table 2*) substantial amounts of solid could be filtered off from the aq. phase after the first extraction with $CHCl_3$. This material was presumably non-degraded PHB.

Run *3* was carried out using the above general procedure but with diisopropylamine (DIPA) instead of HMDS as the amine component.

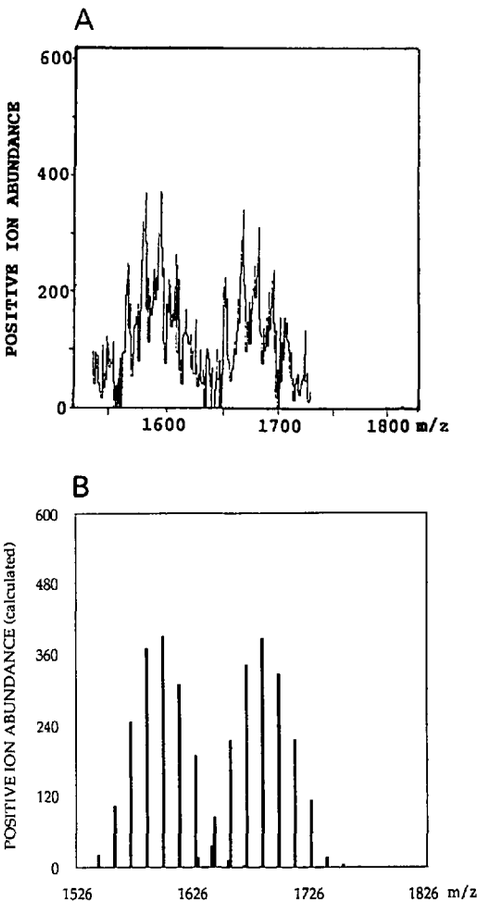


Fig. 4. *Comparison of measured and calculated molecular-weight distribution in degraded PHB/22% PHV.* (*A*) PDMS signals between 1550 and 1750 Daltons (*B*) Ratio of masses calculated for a fragment containing 18 and 19 β-hydroxy-acid units, with the assumption that the valerate moieties are statistically distributed.

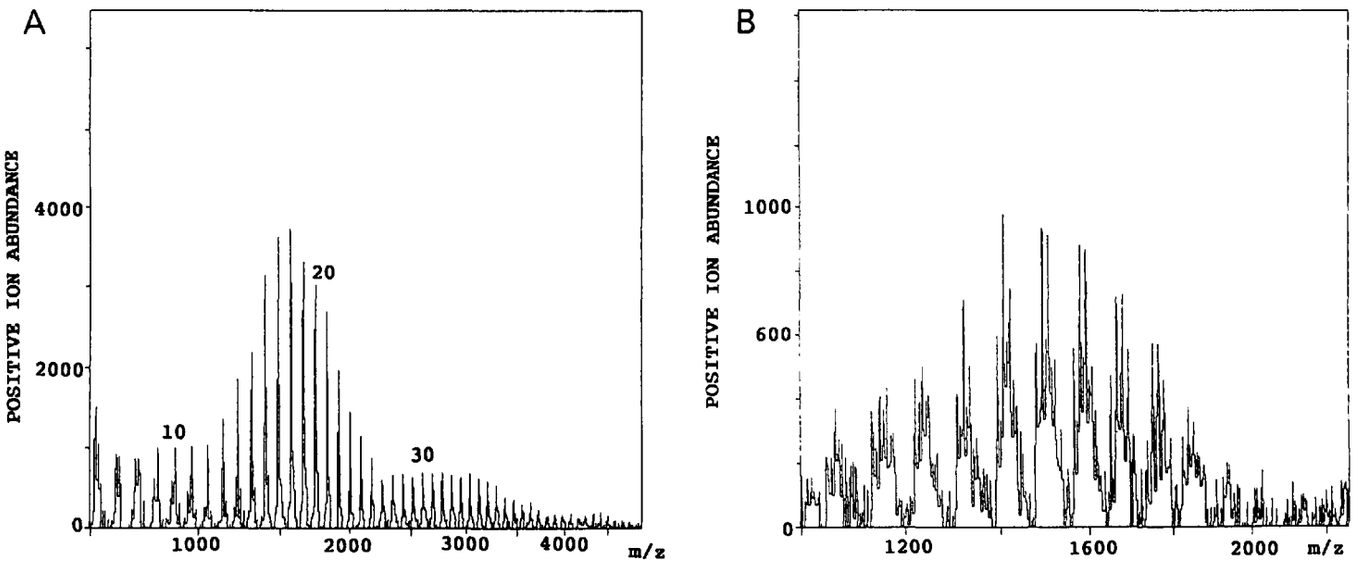


Fig. 3. *Plasma desorption mass spectra (PDMS) of partially degraded PHB* (A) *and PHB/22% PHV* (B). 5–30 μg in $CHCl_3$ electrosprayed on nitrocellulose. Spectra obtained on *BIO-ION 20 k* instrument, 15 kV accelerating voltage, start counts *A*) $3 \cdot 10^6$, *B*) $10 \cdot 10^6$. No peaks were detected in the same molecular-weight range, when the non-degraded polymer was applied. The PHB sample was from run *4* of *Table 1*, the PHB/22% PHV sample from run *5* of *Table 2*. Number of PHB residues are indicated (*A*), for PHB/22% PHV residues (*B*) see *Fig. 4*.

Large scale (PHB/22% PHV)

The transformations were carried out according to the general procedure described above for PHB.

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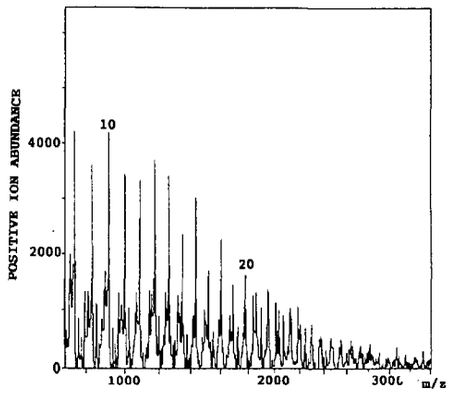

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It is interesting to note that the mass peak intensities alternate. Such alternations of properties with chain lengths are quite common: m.p. of hydrocarbons (see textbooks of organic chemistry), cyclizations to medium-size rings [V. Prelog, *J. Chem. Soc.* **1950**, 420], second order asymmetric transformations [K. Weinges, B. Stemmle, *Recent Developments in the Chemistry of Natural Carbon Compounds* **1976**, *7*, 89].

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[14] There is no indication in the NMR spectra of the recovered samples that the polyester chain was cleaved by nucleophilic attack of lithium amide on the ester carbonyl group (no $RCO-N(CHMe_2)_2$ signals, when LDA was used!).

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Nomenclature of Organic Polycycles out of the Computer – How to Escape the Jungle of the Secondary Bridges

Gerta Rücker and **Christoph Rücker***

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Abstract. A computer program is described which generates *IUPAC* names (*von Baeyer* names) and the corresponding numbering schemes for polycyclic hydrocarbons of any size and complexity. The program thoroughly uses constitutional symmetry which may be present. Parts of *IUPAC* rule *A-32* had to be formulated more precisely than codified hitherto. The names and the elapsed CPU times are given for some polycycles.

In spite of some dispute over the need for a systematic nomenclature as such, international organisations like *IUPAC*, major chemical journals and documentation services like *Beilstein* and *Chemical Abstracts Service* adhere to the rule that substances should be given structure-related systematic names [1] [2]. However, the chemists' skills in naming their products seem not to keep pace with their skills in

* *Correspondence:* Dr. Ch. Rücker
Institut für Organische Chemie und Biochemie
Universität Freiburg
Albertstr. 21, D–7800 Freiburg