Pergamon

Tetrahedron Vol. 51, No. 47, pp. 12929-12938, 1995

0040-4020/95 $9.50+0.00

0040-4020(95)00738-5

Isolation,Synthesis and Reactivity of a Key Macrobislactone ; 1,4,7-Trioxa-cyclotridecane-8-13-dione

Falmai Binns* and Alan Taylor

Baxenden Chemicals, Paragon Works, Baxenden, Nr. Accrington, Lancs BB5 2SN

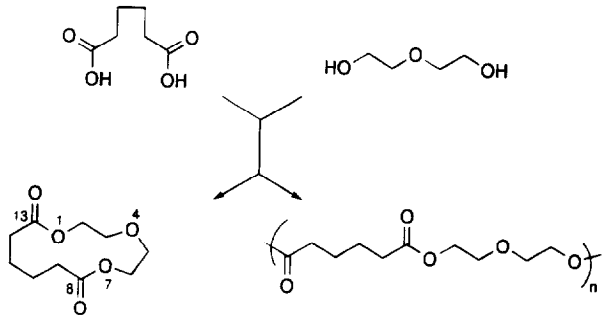
Dedicated to honour Professor Hans Suschitzky on the occasion of his 80th birthday

Abstract : Macrobislactone **1** , 1,4,7-trioxa-cyclotridecane-8-13-dione , believed to be the cause of the fogging of car windscreens by an oily film, has been formally synthesised from diethylene glycol and adipic acid and its content in commercial polyester formulations has been estimated. Study of its ring-opening potential towards both anionic and enzymatic reagents reveal surprizing stability in polyester formulations, coupled with anomalous high susceptibility in the pure state to the lipase *Candida antarctica*, immobilized as Novozyme™. Assay of macrobislactone **1** in a range of polyesters suggest that there is significantly more of this key lactone present than trends would predict. Reasons for this behaviour are advanced following modelling studies and from thermodynamic considerations.

INTRODUCTION

Flexible polyurethane foams are now commonplace components of car manufacture,for applications in headliners, door panels and fascias. Volatiles from polymers such as urethanes are believed to contribute to the phenomenon of 'fogging' , when an oily film accumulates on car windscreens. In the case of urethanes made from polyesters, analysis indicated that much of the deposit could be due to a C_{13} macrolactone formed from adipic acid and diethylene glycol. The implication was that the mainstream polycondensation between adipic acid and diethylene glycol, the bulk starting materials for polyester manufacture,was accompanied by a trace of cyclic ester formation, where the components linked 'nose - to - tail', rather than in the conventional linear fashion (Scheme 1). Since the 13-membered macrobislactone **1** produced possesses no hydroxyl functionality it is impervious to reaction with isocyanate, the reagent for chain extension of linear polyester to polyurethane. As a consequence the lactone **1** would be transferred intact into the urethane formulation, as a minor component (estimated to be in the region of 1% w/w) and in warm weather it would be sufficiently volatile to leach from the foam, giving rise to the observed effect .

Current research within the company was targeted at eliminating the 'fogging component ' from polyesters. as a quality improvement exercise. Clearly to evaluate the success or otherwise of endeavours in this direction. a sample of authentic material was required, in order to develop a quantitative monitoring method for macrolactone content of the polyester. Surprizingly, literature survey revealed no mention of the macrolactone postulated , although the corresponding analogue derived from butanediol/adipic acid had been prepared by Dale[1] in 1965, and also had been identified as a component of groundwater contamination[2].



1

Scheme 1

RESULTS AND DISCUSSION

Rather than developing a modern high dilution technique for synthesis of the novel macrolactone, we decided to match its method of manufacture, and simply adopt the depolymerisation methodology, first developed by Carothers[3] and later used by Dale[1]. Hence high temperature polymerization of adipic acid and diethylene glycol was followed by catalytic depolymerization at high temperature, with continuous removal of the volatile products under reduced pressure This strategy worked satisfactorily to provide the required material in acceptable (19%) yield, and we were able to fully characterize and therefore authenticate structural parameters. With a reference sample to hand, development of a GC method for quantitative assessment allowed ratification that the conventional polyester derived from adipic acid/ diethylene glycol did indeed contain a component with a similar elution characteristic. Further, stripping of the polyester, using high vacuum technique at a temperature tailored to the now known boiling point of the macrolactone, produced material which proved deficient , by GC monitoring , of a component at this characteristic elution, *and further showed no tendency to 'fog' after conversion to the urethane foam,* supporting the contention that

macrobislactone 1 was the cause of the nuisance effect. Subsequently, GC/MS accurate mass measurements demonstrated unequivocably that the byproduct identified in the polyester, was 1,4,7-trioxa-cyclotridecane-8-13-dione[4]; m.p. 80-81^0 C, (M + 18) 234.1351, $C_{10}H_{16}O_5$ = 234.1341. Reports of independent isolation of the latter from commercial polyurethane later appeared in the press[5].

Similarly synthesis of the butanediol/adipic acid analogue permitted assay of the latter derivative in the corresponding polyester. Study of oligomers in this system, by the more refined FAB mass spectrometric technique, revealed the occurrence of a range of cyclic compounds, generated as multiples of the base repeat unit $[(CH_2)_4OCO(CH_2)_4CO.O]_x$ (formula weight = 200), giving rise to (M + 1) signals at regular intervals [Figure1], measured at mass no. 201, 401,601,801, 1001, and 1201, corresponding to the 1-mer, 2-mer, 3-mer, 4-mer and 5-mer species, respectively, *cf.* previous workers report of analogous derivatives[6].

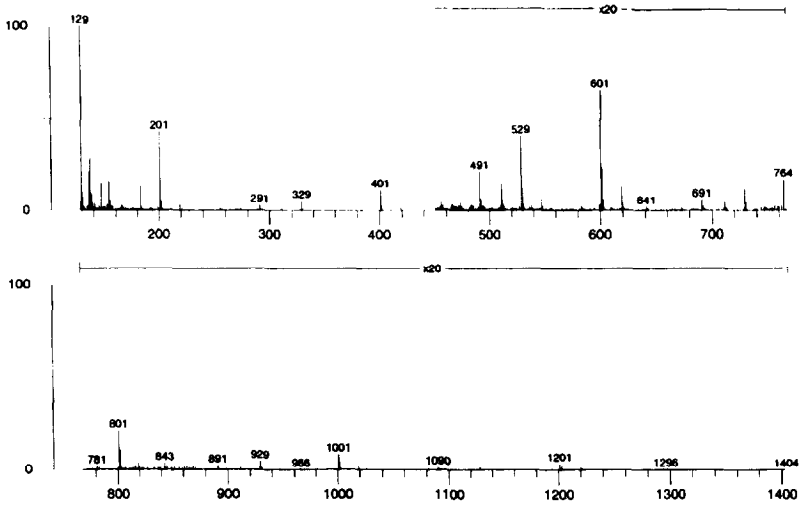


Figure 1. FAB mass spectrum of oligomers of the polybutylene adipate system

Following on successful quantification of the cyclic ester content of the commercial polyester, derived from diethylene glycol and adipic acid, attention was transferred to the crucial problem *i.e.* that of removal of this contaminant from the urethane precursor by some scavenging technique which would be preferable to an expensive high vacuum distillation approach. A programme of feasibility testing of a range of common anionic ring-opening reagents was carried out on the polyester itself to no avail. To confirm that the reagents under test were capable of ring-opening the macrolactone, a back check was carried out whereby their effectiveness in a *solvent-free* system, i.e. on neat , molten cyclic ester, at 90° C was conducted. Though the majority were ineffective, demonstrating the ring stability of the macrolactone, sodium methoxide did prove efficacious[7], giving rise to an array of oligomers as shown in the GPC trace [Figure 2]. The separate components were not

resolved , nor formally identified. but we believe them to be the 1- to 6-mer species from our experience with similar systems[3]. No kinetic measurements were carried out to determine relative rates to standard substrates. Significantly the unreactivity of the cyclic ester , when present in trace amount in polyester, contrasted to the facility of ring-opening when the substrate was presented neat to the reagent. This could be interpreted as an indication that the cyclic ester/ polyester mix was at thermodynamic equilibrium. If this premise were true it would suggest the unlikelihood of success with any chemical scavenging agent.

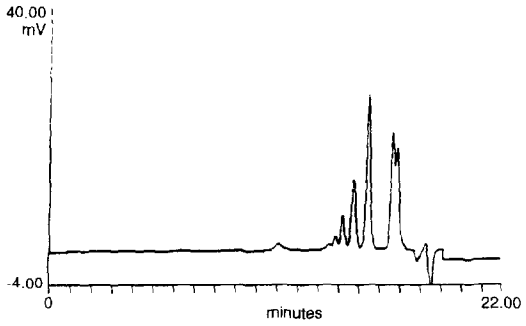


Figure 2. GPC trace of oligomers produced by ring- opening of lactone 1 with methoxide ion.

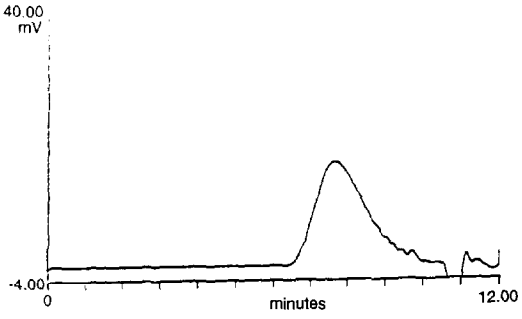


Figure 3. GPC trace of oligomers produced by ring-opening of lactone **1** enzymatically.

As an alternative strategy in tune with our interest in enzymatic polymerization[8,9], ring- opening of the key macrolactone seemed possible by use of the latter technique. The pioneering work of Knani *et al.*[10] had demonstrated the feasibility of enzymatic ring opening of caprolactone. We thus examined the ease with which a readily available commercial immobilized lipase formulation of *Candida antarctica* , Novozyme™, would facilitate ring opening of the latter substrate. The enzyme formulation proved to be remarkably efficient in promoting polymerization on neat substrate, conversion to high molecular mass material occurring within a very short time span , hours instead of the days reported by the previous workers.

Subsequent tests on the recognition potential of Novozyme™ for the novel synthetic macrobislactone **1** using crystalline starting material. with diisopropyl ether merely as a slurrying agent gave surprizingly, extremely fast reaction at 40^0 C., the crystals being converted to a array of oligomers as revealed by GPC (1-6mer range) in a few hours.followed by rapid transformation to polyester [Figure3], a mimic of commercial polydiethyleneglycol adipate [PEGA]. The relative speed of transformation was significantly faster

than that achieved using methoxide ion, despite the much lower temperature of reaction. Again attempts to use the enzyme to remove the trace macrolactone contaminant in the polyester failed, reinforcing the view that the system was in a state of thermodynamic equilibrium

Though the reactivity of the methoxide ion with the macrobislactone seemed in line with that reported previously for caprolactone, *viz.* slower than the latter substrate, as might be expected by consideration of the relative ring strain of the two species, the extraordinarily high reactivity of the macrolactone to Novozyme™ as compared to the reactivity of caprolactone to the latter reagent appeared paradoxical. Subsequently, similar reverse trends in activity to that predicted from ring strain calculations were reported[11] when a range of analogous macrolactones were subjected to enzymatic ring-opening. High reactivity of the enzymatic catalysts towards the larger macrolactone systems was cited to stem from molecular recognition benefits between the catalyst and the substrate, which lower the activation energy of their interaction.

Table 1. Percentage incorporation of macrobislactone in a range of polyglycol adipates

Glycol constituent	Macrobislactone content %	Ring size of macrobislactone [no. of atoms]
Butane-1,4-diol	0.38	12
Diethylene glycol	1.10	13
Hexane-1,6-diol	0.65	14
PEG 200	<0.01	19

Studies[12] on a range of commercial polyesters, *viz.* those derived from reaction of adipic acid with butane-1,4-diol, diethylene glycol, hexane-1,6-diol and polyethylene glycol of molecular weight 200 [PEG 200] with respect to their macrobislactone content showed that the 13 - membered macrolactone **1** was present in significantly higher relative quantity [see Table 1] than might have been predicted , since in these larger macrolactones no appreciable difference in ring strain would be predicted by examination of heats of combustion of the corresponding cycloalkanes[13-15].

The seemingly anomalous stability of macrobislactone **1** in polyester formulations may stem from the presence of an annular ethereal oxygen atom, derived from the diethylene glycol precursor ; models suggest the possibility of transannular interactions. Indeed energy minimization of molecular models indicate proximity

between a hydrogen atom on C_5 and the lone pair on the oxygen of the ether linkage at ring position 1, and/or, between a hydrogen atom on C_{12} and a lone pair on the oxygen atom of the ester linkage at ring position 7 [Figure 4]. This has recently been corroborated by X-ray study which shows a similar ring conformation to that depicted below. Despite the apparent symmetry of the molecule NMR spectra point to differentiation between hydrogens on C_2 / C_6 and between those on C_3 C_5 ,as they both appear as doublets of triplets.

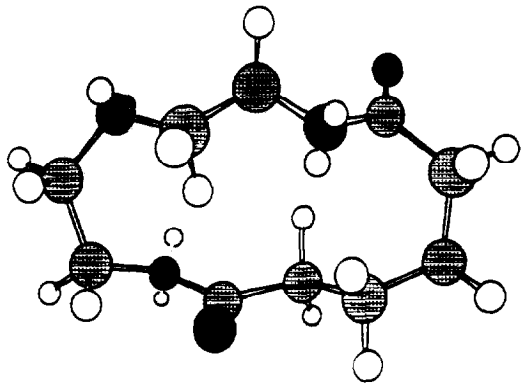


Figure 4. Energy minimized molecular model of macrobislactone 1

Thermodynamic factors may also contribute to the unexpected stability of the key 13-membered macrolactone, and hence to the difficulty in scavenging out trace quantity of the latter. Macrolactones are generally recognized[13-15] to owe their stability to the interplay of entropy [ΔS] and enthalpy factors [ΔH], the equation : -

$$\Delta H - T\Delta S = \Delta G \qquad [1]$$

being the controlling relationship. Where the Gibbs free energy term ΔG is less than zero the macrolactone will be inherently stable. The latter criterion is satisfied in macrocycles of ring size 16 units upwards, which may be considered virtually strain free, *i.e.* the enthalpy factor (ΔH) aproaches zero, and the entropy factor ($T\Delta S$) is large and positive, a reflection of the fact that the chain ends have little statistical likelihood of meeting up, once severed. For smaller rings, entropy/ enthalpy factors have a more complex relationship ; macrolactones of ring size 3-4 are inherently unstable, on enthalpy grounds, enthalpy values for these moieties being large and negative, an indication of the strain inherent in such restricted species, whereas entropy factors are around zero. Conversely in the ring size range (5-7) enthalpy values approach zero, coinciding with the

value of entropy factors. Passing to the ring size range (8-15), enthalpy values remain near the zero mark, but entropy factors now climb to positive values .

Further work is in train to investigate a range of macrobislactones to assess the possibility of transannular interaction by modelling, NMR/NOE and X-ray crystallographic techniques.

CONCLUSION

Synthesis of the novel macrobislactone 1,4,7-trioxa-cyclotridecane-8-13-dione **1**, has enabled the 'fogging component' of urethane foam, involved in the production of an oily film on car windscreens, to be formally identified. Ring opening of 1,4,7-trioxa-cyclotridecane-8-13-dione has been demonstrated as facile using immobilized *Candida antarctica*, at 40 ^{0} C to give a preliminary array of oligomers, the latter rapidly converting to a polyester. Similar transformation, but curtailed to oligomeric species only has been effected, but under more rigorous conditions , with sodium methoxide at 90 ^{0} C on molten material. Difficulty in effecting scavenging out of trace quantity of this key macrolactone in polyesters by enzymatic or anionic ring-opening techniques is believed to be due to the fact that these systems are in a state of thermodynamic equilibrium, and also to the fact that the key macrolactone **1** possesses exceptional stability. Range studies on a series of polyester systems have revealed that the abundance of the 13-membered macrolactone **1** is unexpectedly high, compared to closely analogous systems. This anomaly is correlated back to the possibility of transannular interaction conferring unexpected stability ; the latter phenomenon being suggested by modelling studies which tie in with NMR findings. The relevance of interplay of entropy and enthalpy factors to the stability of the key macrolactone is discussed.

EXPERIMENTAL

General. Gel permeation chromatography (GPC) was performed using Waters 510 series chromatographic equipment. The columns, manufactured by Polymer Laboratories had dimensions 300 x 7.5mm, and were packed with PL gel , a highly crosslinked spherical polystyrene/divinylbenzene material of particle size 5μm and pore sizes 50 and 100 Angstrom units. The detector was a Waters model 410 differential refractometer and estimates of molecular weight average were made by a Compaq 486 66μHz DX4 computer from a calibration against commercial polystyrene standards. All molecular weights are expressed in Daltons. Infrared spectra were conducted on a Perkin Elmer Fourier Transfer Infrared Spectrophotometer, model number 16 PC .

NMR analyses were kindly performed at the Universities of Central Lancashire, Salford and Manchester. Conventional mass spectrometric analysis was carried out at the University of Salford, and fast atom bombardment (FAB) mass spectrometric measurements were done courtesy of the University of Manchester. Flash column chromatography utilized silica gel 60 (40-63μm) from Merck, and thin layer chromatography was performed using precoated glass plates (Merck silica gel 60F 254); visualization was by means of iodine vapour. Alumina for column purification purpose was purchased as aluminium oxide active *neutral*, Brockmann grade 1, from BDH in laboratory reagent grade. Analytical gas chromatographic data was acquired using a Hewlett Packard gas chromatogram, model number 5890, using 10m. Chrompack columns, 0.25mm. i.d., coated with CP-SIL19CB, film thickness 0.2μm. Molecular modelling was carried out using a MM2 programme on a CSC systems using an Apple Mac computer at Manchester University. Microanalytical measurements were performed courtesy of Manchester University.

Adipic acid, butane-1,4-diol, diethylene glycol,hexane-1,6-diol, caprolactone, dibutyl tin laurate and diisopropyl ether were obtained commercially, with a stated minimum purity of 99%. Sodium methoxide, 0.5M solution in methanol, was purchased in analytical grade from Aldrich Chemicals. Ethyl acetate,methanol and petroleum ether (60-80^0 C) were used in analytical reagent grade. The immobilized *Candida antarctica lipase* was provided by Novo Nordisk in Denmark as the formulation Novozyme™.

Preparation of 1,4,7-trioxa-cyclotridecane-8-13-dione (I) and analogues by depolymerization[1,3] . Adipic acid (14.75 g, 0.10mol.) and diethylene glycol (10.91 g, 0.10mol.) were heated in a reaction flask under reflux for 3 h., at 190^0 C under atmospheric pressure. The flask contents were distilled under reduced pressure of 5 mbar, at bath temperature 190^0 C for a further 3 h. Dibutyl tin laurate (0.5 g, 0.2%w/w) was added, and a short path distillation rig fitted to the reaction flask. Distillation under reduced pressure of 5 mbar was effected by rapid heating of the reaction flask using a flame producing a mobile liquid, b.p. 160^0 C, which quickly solidified to pale yellow crystals. Redistillation gave a purer product b.p. 200^0 C, at a reduced pressure of 4 mbar, in 19% yield. The product was dissolved in ethyl acetate and passed down a short alumina column. Flash column chromatography, using ethyl acetate:petroleum ether in ratio 1:2 as eluant, gave colourless crystalline needles : m.p. 80-81^0 C : 200 mHz NMR ($CDCl_3$): δ 1.70-76 (m ,4H, CH_2), 2.35-41 (m ,4H, $OCOCH_2$), 3.70-74 (dt , J = 7Hz, J = 1.4Hz, 4H, OCH_2), 4.24-28 (dt , *J* = 4Hz, J =1.4Hz, 4H, OCH_2) : IR (nujol mull) ν_{max} 1738 (C=O stretch), 1149 (ether C-O stretch) : m/z (CI) [M+18] : Found 234.1351, $C_{10}H_{16}O_5$ requires 234.1341 amu. : Microanalysis ; calculated for $C_{10}H_{16}O_5$, C 55.6, H 7.4. Found C 55.4, H 7.4.

1,6-Dioxa-cyclododecane-2,7-dione[3]: m.p.92-3^0 C : 250 mHz NMR ($CDCl_3$): δ 1.70-75 (m ,4H, CH_2), 1.78-82 (m ,4H, CH_2), 2.30-34 (m ,4H, $OCOCH_2$), 4.24-28 (m, 4H, OCH_2) and 1,6-dioxa-tetradecane-2,7-dione[3]: m.p 68-70^0 C : 300 mHz NMR ($CDCl_3$): δ 1.42- 1.48 (m ,4H, CH_2), 1.60-1.75 (m, 8H, CH_2), 2.30-

2.39 (m ,4H. CH_2), 4.07-4.14 (t, J =5Hz, J = 6.5Hz. 4H. OCH_2) were synthesised using a similar technique to that described above.

Enzymatic, solvent-free ring-opening of ε-Caprolactone. ε-Caprolactone (15.1g ,132 mmole) , a catalytic amount of methanol (0.11mls) and Novozyme™ (200mgs) were stirred magnetically together at 40^0 C for 18 h.. Product analysis by GPC revealed a polymer with M_n 3556 , M_w 6933.

Anionic, solvent-free ring-opening of macrolactone 1 with methoxide ion. The macrobislactone 1 (2.0g , 9.26 mmole) and a magnetic follower were transferred to a vial which was fitted with a serum cap. The headspace was flushed continuously with argon, and the vial was placed in a bath at 90^0 C. The crystals melted out and a 1ml. aliquot (0.5mmoles) of sodium methoxide solution in methanol was added using a syringe. After 24 h., GPC analysis showed the product to be an array of oligomers, see Figure 3, M_n 155, M_w 260.

Enzymatic, solvent-free ring-opening of macrolactone 1. To the macrobislactone 1 (3.2g ,16.2 mmole) and a magnetic follower in a cell reactor diisopropyl ether (32mls) was added , followed by a catalytic amount of methanol (0.015mls). The reactor was heated in an oil bath at 40^{0}C. Novozyme™ (140mgs) was then added, and the flask contents stirred gently in the open vessel. for 19 h. After this time the product had been formed as an oil and analysis showed a short chain polymer, with M_n 2159 , M_w 3817 (see Figure 4). Analysis for residual macrolactone 1 showed only 0.5% .

Acknowledgement

The authors would like to express their gratitude to Dr. R.T. Brown of the University of Manchester for both the energy minimization modelling studies, and for help with the preparation of this manuscript. David Layton, John Davidson and Carol Dewhurst of the analytical department of Baxenden Chemicals are thanked for their contribution. The authors are indebted to Dr. Mike Stuckey for NMR data and to Dr. John Leonard for mass spectrometry analysis, both measurements carried out at the University of Salford.

REFERENCES

1. Dale, J. *J. Chem. Soc.* **1965**, 72-78.
2. Tomson , M.B. *et al. Water Research* **1981, *15*,**1109-16.
3. Carothers, W.H. *et al. J. Amer. Chem. Soc*, **1935**, *57*, 929-34.
4. Binns, F. *Baxenden Chemicals internal report* **1992.**
5. Soler, J ; Monso J. M ; Duocastella L. *Polyurethanes World Congress* **1993**, 552-557.
6. Wood, B. R ; Hodge, P ; Semlyen, J. A. *Polymer* **1993**, *34 (14),* 3052-3058.
7. Nomura R.; Ueno A.; Endo, T. *Macromolecules*, **1994**, *27*, 620-1.
8. Binns, F ; Taylor, A ; Roberts, S. M ; Williams, C. *J. Chem. Soc. Perkin Trans. 1* **1993**, 899-904.
9. *UK Pat. Applic.* GB 2272904; *Int. Pat. Applic.* PCT GB93/ 02461, Baxenden Chemicals.
10. Knani, D ; Gutman, A ; Kohn, D.H. *J. of Polymer Science :Part A Polymer Chemistry* **1993**, *31, 1221-1232.*
11. Uyama, H ; Kazuhiro T ; Kobayashi, S. *Bull. Chem. Soc. Jpn.* **1995**, *68,* 56-61.
12. Taylor, A. *Vita International Urethanes Seminar* Bollington U.K. **1995.**
13. Ivin, K. *Makromol. Chem., Macromol. Symp.* **1991** *42/3,* 1-14.
14. Brunelle, D.J. *et al. Contempory Topics in Polymer Science* **1992** *7* , 5-19.
15. Ward, R.S. *Bifunctional Compounds*; Davies, S.J.; Compton, R.G.; Evans, J., Eds., Oxford University Press, Oxford, 1994; pp. 77-8.

(*Received in UK* 11 *August* 1995; *accepted* 8 *September* 1995)