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Ring strain and polymerizability of cyclic esters

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Ring strain is one of the most important factors affecting the polymerizability of a cyclic monomer. In this work, the ring strains in γ-butyrolactone, δ-valerolactone and ϵ-caprolactone were inferred on the basis of infrared and Raman spectroscopy data. The thermodynamic factors influencing the ability to polymerize of these three lactones and other cyclic diesters in the glycolide series were studied using molecular modelling methods. The ring strain was observed to increase with increasing ring size for the three lactones studied increasing the thermodynamic scope for these monomers to polymerize. For the glycolide series, ring strain and polymerizability decreased with increasing substitution on the α-carbon. © 1998 Elsevier Science Ltd. All rights reserved.

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INTRODUCTION

The development of new biodegradable polyesters for use in biomedical applications such as absorbable sutures and controlled drug delivery systems is an area of considerable interest at the present time[1,2]. Of fundamental importance are the development of a clear understanding of the factors affecting the chemistry of the ring-opening polymerization of cyclic esters and the influence of polymer microstructure on properties, for both academic and technical reasons.

A detailed understanding of the factors affecting the ring-opening polymerization of cyclic esters is the starting point for developing polymer properties relevant to the intended application. The main factors to consider are ring size, ring strain, the nature and extent of substitution on the ring, functionality within the ring and the polymerization conditions used, including the nature of the initiator. Of these factors ring strain is particularly important. The major contributions to ring strain are bond angle distortion (angular strain), bond stretching or compression, repulsion between eclipsed hydrogen atoms (conformational strain, bond torsion) and non-bonding interactions between substituents attached to different parts of the ring (transannular strain)[3,4].

Strain energy calculations furnish valuable information about the relative ring strain in organic compounds, even when the absolute magnitudes obtained are uncertain because of assumptions made in the method and process of computation. Conventional strain energies are apparent in alicyclic compounds when the observed standard molar enthalpies of formation in the gaseous state are compared with values for strain-free structures calculated using modern bond-energy schemes[5]. Such strain energies have been reported for cycloalkanes, cyclic ethers, cyclic thioethers and cyclic imines, and, for all of these, minimum strain-energies are observed for the six-membered ring compounds[6]. For simple lactones, the standard molar enthalpies of combustion which have been reported are for two five-membered rings: γ-butyrolactone and γ-valerolactone, and one six-membered ring lactone: δ-valerolactone[7]. However, if the necessary group equivalents or the heat of formation of the compound of interest are unknown, another approach is required. The ring strains in the cyclic esters studied here can be compared in terms of their internal energies as calculated from molecular modelling and also in terms of the frequencies of their respective O–C(=O) and O–CH_2 ring stretching bands from Fourier transform infrared spectroscopy (*FT*i.r.), Fourier transform Raman spectroscopy (*FT*-Raman) and molecular modelling.

The polymerizability of a cyclic monomer is generally expressed by the extent to which the free energy of the polymerizing system changes as it converts into polymer[8]. Molecular modelling was used to calculate the difference in internal energy between the polymer and the monomer in each case and thus obtain an estimate of polymerizability.

EXPERIMENTAL

Materials

The structures of the cyclic esters studied in this work are illustrated in *Figure 1*.

γ-Butyrolactone, γ-valerolactone, δ-valerolactone and ϵ-caprolactone were supplied by Fluka and were each purified by vacuum distillation from calcium hydride. Glycolide, L-lactide and tetramethyl glycolide were synthesized and purified by recrystallization.

Spectroscopy

All *FT*i.r. analyses were performed on a Perkin–Elmer *FT*i.r. 1720-X Spectrometer with the sample placed between polished sodium chloride windows.

FT-Raman analyses were made on a Perkin–Elmer *FT*-Raman 2000 Spectrometer with the sample held between glass windows.

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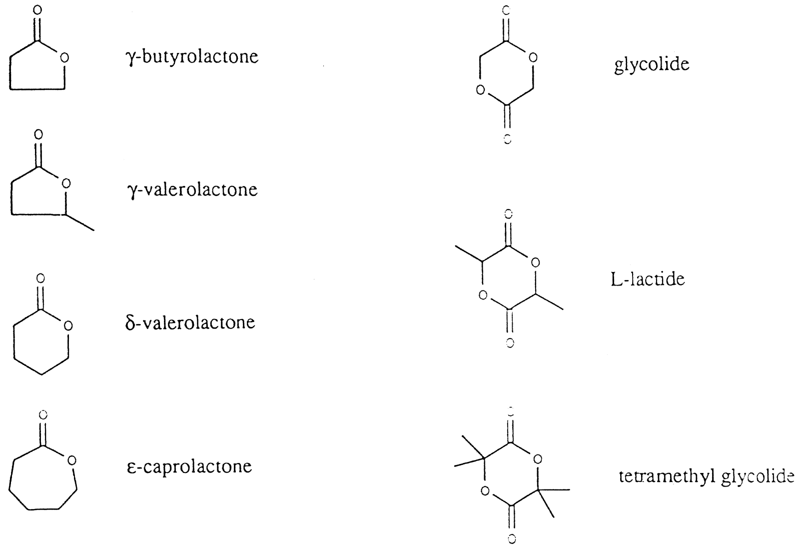


Figure 1 Chemical structures of the cyclic esters studied in this work

Molecular modelling

Molecular modelling was performed using the *Discover* software package[9] running on a SGI Indigo R4000 workstation, using the *Insight* interface to construct the models. The minimized energy of both the monomer (M) and the 4- and 5-mers of the polymer (P_4 and P_5) were obtained. The internal energy of a single polymer unit was estimated as the difference in energy between the 5- and 4-mers and so the change in internal energy upon polymerization (ΔH_p) could be calculated from:

$$\Delta H_p = (P_5 - P_4) - M$$

The normal modes of vibration, together with infrared frequencies, were calculated with *Discover*[9] using a method which involves the diagonalization of the second derivative of the energy function (the Hessian) at the calculated minimum energy conformation.

RESULTS AND DISCUSSION

Table 1 shows calculated bond lengths and bond angles for a series of cyclic esters studied. As the ring size increases from 5 to 7, the deviations from the forcefield equilibrium values (which would be close to those found in a non-cyclic molecule) increase. This correlates with the reported increases in strain energy[7] which are listed in *Table 2*.

Reported values of the change in free energy (ΔG_p) and entropy (ΔS_p) during the ring opening of cyclic esters[11] are included in *Table 2*. It can be seen that ΔS_p remains essentially constant over the series of lactones studied, which is as would be expected since the dominant factor in ΔS_p is the loss of translational entropy brought about by the large reduction in the number of molecules present, a factor which is relatively constant from system to system. Therefore, the variations in ΔH_p can be used to indicate the relative thermodynamic polymerizabilities in place of ΔG_p. Even though the thermodynamic parameters given in *Table 2* are not standard state values, their trends still allow for valid conclusions to be drawn since the various systems studied are closely comparable in physical terms.

Results from our molecular modelling calculations are compared with previous work[11] in *Figure 2* and the good agreement is evident for ring sizes in the range 5–7. It can be seen that, as the ring size increases from 5 to 7, the magnitude of ΔH_p changes significantly in a manner to be expected until it becomes essentially constant (values in the range − 35 to − 50 kJ/mol) for ring sizes of 8 to 16. From a thermodynamic standpoint, the larger cyclic monomers (more than eight units in the ring) can be more readily polymerized.

For the glycolide series, ΔH_p decreases with increasing substitution on the α-carbon atom. Interactions between substituents are generally more pronounced in linear than in cyclic molecules. Thus, substitution, mostly affecting the enthalpy of polymerization, usually decreases polymerizability. Substituents are kept well separated in cyclic monomers but once they are in the linear polymer chain, chain flexibility allows a greater probability of close proximity.

The frequencies of the O–C(=O), O–CH_2 and C=O stretching vibrations for the cyclic ester monomers obtained by the different methods employed are compared in *Table 3*. The frequencies show similar trends in all cases but slightly different values depending on the method. In the case of the spectroscopic results, these differences can be attributed to

Table 1 Comparison of the calculated bond angles and lengths of the cyclic esters studied

	Bond angle (deg.)			Bond length (Å)		
	C–O–(C=O)	O–(C=O)–C	C–C–C	O–C	O–(C=O)	C–C
γ-butyrolactone	109.0	110.3	102.1	1.44	1.38	1.53
γ-valerolactone	109.0	110.4	102.1	1.44	1.38	1.53
δ-valerolactone	121.0	114.9	113.9	1.46	1.40	1.55
ϵ-caprolactone	125.5	117.6	114.4	1.46	1.40	1.54
Forcefield equilibrium value	109.5	110.0	110.5	1.425	1.370	1.526

Table 2 Comparison of strain energies with calculated and reported heats of polymerization

	Strain energy (kJ mol^{-1})	ΔH_p (calc) (kJ mol^{-1})	ΔH_p (Ref. 11) (kJ mol^{-1})	ΔS_p (Ref. 11) (J mol^{-1} K^{-1})	ΔG_p (Ref. 11) (kJ mol^{-1})
γ-butyrolactone	32.2 (Ref. 7)	– 15.4	– 6.8	– 65	12.6
γ-valerolactone	30.5 (Ref. 7)	– 7.1			
δ-valerolactone	39.7 (Ref. 7)	– 26.8	– 27.4	– 65	– 8.0
ϵ-caprolactone		– 35.9	– 28.8	– 54	– 12.8
Glycolide	31.0 (Ref. 10)	– 23.0	– 34.0	– 0.3	– 32.1
Lactide		– 20.9			
Tetramethyl glycolide		– 13.5			

Table 3 Comparison of vibrational frequencies of the cyclic ester monomers from three different methods (all frequencies expressed as cm^{-1})

	γ-butyrolactone (ring size = 5)			δ-valerolactone (ring size = 6)			ϵ-caprolactone (ring size = 7)		
	*FT*i.r.	*FT*-Raman	Molecular modelling	*FT*i.r.	*FT*-Raman	Molecular modelling	*FT*i.r.	*FT*-Raman	Molecular modelling
C=O	1762	1764	1714	1734	1728	1716	1729	1728	1714
O–(C=O)	1241	1245	1231	1279	1280	1262	1292	1286	1276
O–CH$_2$	1038	1038	1038	1056	1055	1033	1089	1091	1065

instrumental limitations or calibration methods or to difficulties in accurately measuring the centre of the band. This error is estimated to be ± 2 cm^{-1}. Examples of the *FT*i.r. and *FT*-Raman spectra are shown in *Figure 3* for δ-valerolactone as evidence of spectral quality.

Molecular modelling calculations are very dependent on the accuracy of the forcefield used and in calculations of the type carried out here the functional form used produces a large difference in the absolute values of the calculated frequencies. However, trends within the molecular modelling data are more accurately calculated.

The absorption frequencies of the carbonyl (C=O) group in cyclic esters have been reported[12]. However, these reported values do not correlate well with ring strain because this bond is not part of the ring. On the other hand, the O–C(=O) and O–CH$_2$ vibrations are for groups within the ring and so may be expected to be more directly affected by the ring strain. As the ring size increases from 5 to 7, it becomes more strained, as discussed above. This leads to a more rigid structure and hence the vibrational frequencies increase.

The experimental results shown in *Table 3* show a reduction in the frequency of the carbonyl group as the ring size increases. This suggests that the group becomes held less rigidly as the ring size increases, which may be expected as the internal O–(C=O)–C angle is increasing. In the force field used in the molecular modelling results, this interaction is not included and so these data show no such effect.

CONCLUSIONS

As mentioned at the outset of this paper, a detailed understanding of the factors affecting the ring-opening polymerization of cyclic esters is essential for tailoring polymer properties to meet specific requirements in specialist applications. Central to this understanding is the study of ring strain and thermodynamic polymerizability of the cyclic monomer, properties which this work has shown are determinable through a combination of experimental (*FT*i.r./Raman spectroscopy) and simulation (molecular modelling) methods.

The foregoing results have demonstrated that, for the lactone series, as the ring size increases from 5 to 7 in the order:

$$\gamma\text{-butyrolactone} \rightarrow \delta\text{-valerolactone} \rightarrow \epsilon\text{-caprolactone}$$

the ring strain and the thermodynamic polymerizability also increase. The observed trends in bond angle (*Table 1*), strain energy and ΔH_p (*Table 2*) and C–O bond stretching frequencies (*Table 3*) all combine to support this view.

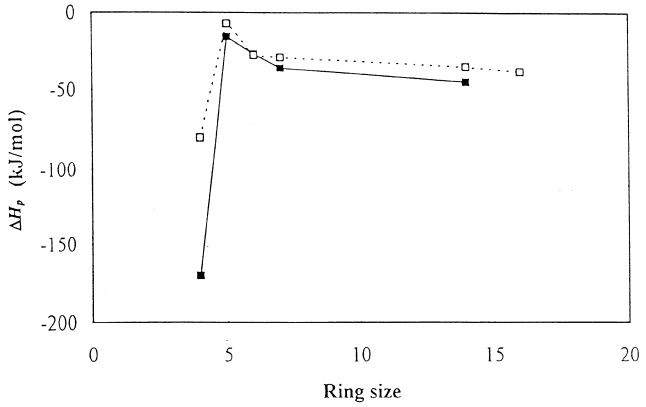
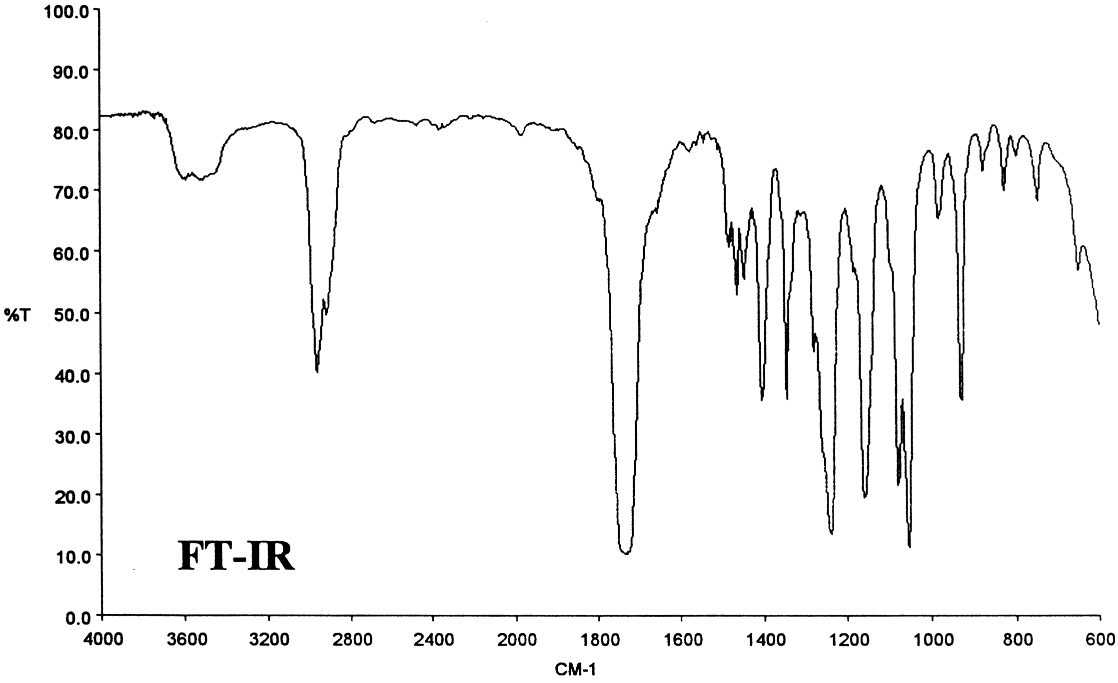


Figure 2 ΔH_p values calculated in this work (——) and from Ref. 11 (- - -) for a series of lactones of different ring sizes



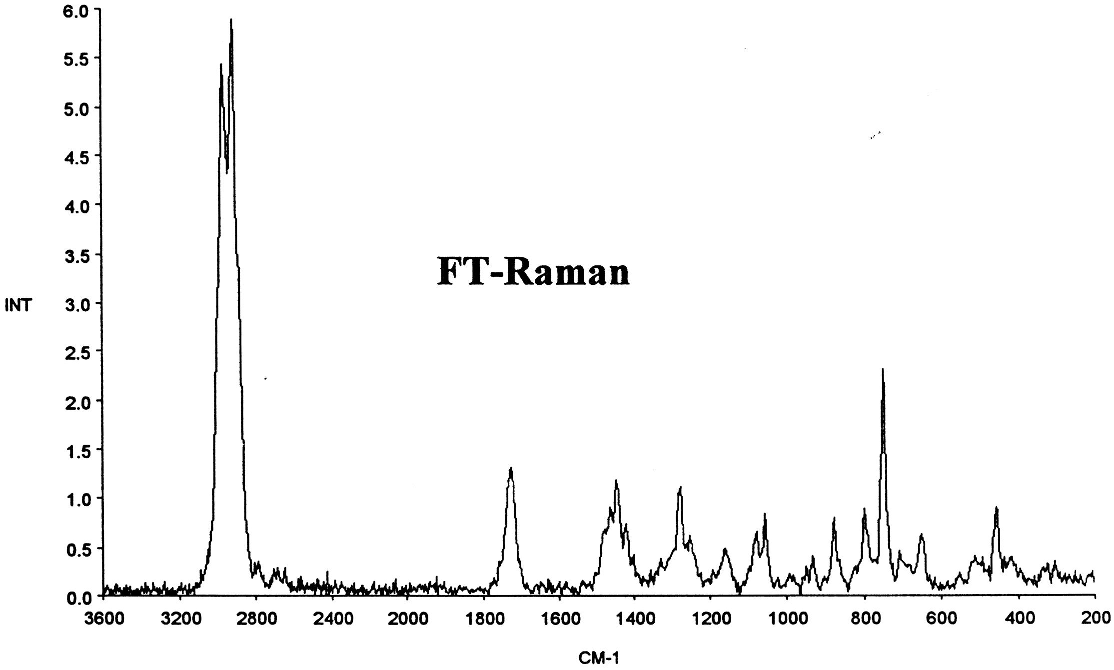


Figure 3 The *FT*i.r. (above) and *FT*-Raman (below) spectra of δ-valerolactone

When the ring size is kept constant, as in the glycolide series, increasing substitution on the α-carbon decreases polymerizability, mainly due to a decrease in ΔH_p. This serves to emphasize the fact that, while ring strain is obviously an important factor, ring substitution also exerts a powerful influence. Increasing either the number or size of the substituents decreases polymerizability as a result of increased intramolecular steric repulsions in the chain relative to the ring. Indeed, this steric effect is so influential that tetrasubstituted glycolides, such as tetramethyl glycolide, are found not to polymerize.

Despite the long history of previous work in the field of ring-opening polymerization, there are still certain aspects of ring-chain inter-conversion which remain unclear. For example, which molecular features in different systems might stabilize chains more than rings, or *vice versa*? What roles do the mechanisms of polymerization (and hence the choice of initiator or catalyst) and thermal depolymerization play? Answers to these and other questions that still remain may possibly be provided in the near future by a combination of methods such as those which have been employed in this study.

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