

Thermodynamic Control of the Polymerizability of Five-, Six-, and Seven-Membered Lactones

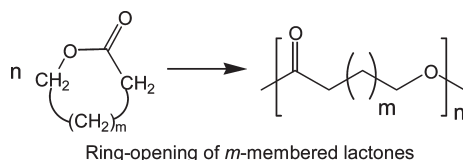
Carlos Alemán,^{*,†,‡} Oscar Betran,[§] Jordi Casanovas,^{||} K. N. Houk,^{*,⊥} and H. K. Hall Jr.^{*,#}

[†]Departament d'Enginyeria Química, ETS d'Enginyers Industrials de Barcelona, Universitat Politècnica de Catalunya, Diagonal 647, Barcelona E-08028, Spain, [‡]Center for Research in Nano-Engineering, Universitat Politècnica de Catalunya, Campus Sud, Edifici C', C/Pasqual i Vila s/n, Barcelona E-08028, Spain,

[§]Departament d'Enginyeria Química, EUETII, Universitat Politècnica de Catalunya, Pça Rei 15, Igualada 08700, Spain, ^{||}Departament de Química, Escola Politècnica Superior, Universitat de Lleida, c/Jaume II n° 69, Lleida E-25001, Spain, [⊥]Department of Chemistry and Biochemistry, University of California Los Angeles, California 90024-1569, and [#]Department of Chemistry, The University of Arizona, Tucson, Arizona 85721

carlos.aleman@upc.edu; houk@chem.ucla.edu; hkh@email.arizona.edu

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The thermodynamics of polymerization of ϵ -caprolactone and 1,4-dioxan-2-one has been investigated theoretically and compared with that recently reported for δ -valerolactone and γ -butyrolactone. Specifically, the ability of these monomers to polymerize has been related to the strain of the rings, the Gibbs free energy of simple models for ring-opening reactions of the cyclic lactones, and the conformational preferences of linear model compounds of the corresponding homopolyesters. The results are fully consistent with the lack of polymerizability of γ -butyrolactone, while the ring openings of ϵ -caprolactone and δ -valerolactone have been found to be exergonic processes. Polymerizability of 1,4-dioxan-2-one has been found to be favored, even though less than that of ϵ -caprolactone and δ -valerolactone. Two factors explain these features: (i) the strain of the ester group in the lactones increases with the exergonic character of the ring-opening process, and (ii) the stability of coiled conformations in model compounds follows this order: poly-4-hydroxybutyrate > poly(1,4-dioxan-2-one) > poly-6-hydroxycaproate \approx poly-5-hydroxyvalerate. Finally, the influence of the environment on the polymerizability of the three cyclic lactones is discussed in detail.

Introduction

Aliphatic polyesters, prepared by ring-opening polymerization of lactones, are an important class of versatile polymers with excellent properties¹ that make them useful for a wide range of applications. These extend from those based on large-scale production of simple commodity thermoplastics² to specialty biomedical and pharmaceutical applications, e.g., resorbable implant material and controlled drug delivery.³

For example, lactones are quite reactive and readily convert to their linear counterparts. Polymerization of unsubstituted monocyclic lactones depends mostly on the enthalpy of polymerization, which has been related to the release of the monomer ring strain.^{1b,1c} Thus, the four-membered cyclic ester polymerizes practically to completion. Similarly, the six membered cyclic ester (δ -valerolactone, hereafter denoted δ -VL) polymerizes merely on storage at room temperature, doubtless caused by adventitious initiation by hydroxylic impurities. Completely different behavior is shown by the five-membered cyclic ester (γ -butyrolactone, hereafter abbreviated γ -BL), which is just on the verge of polymerizability. Thus, under high pressure,⁴ γ -BL

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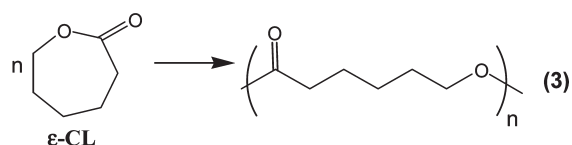
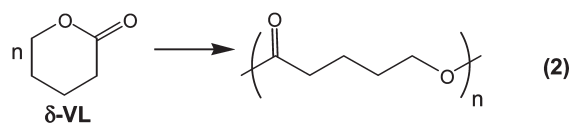
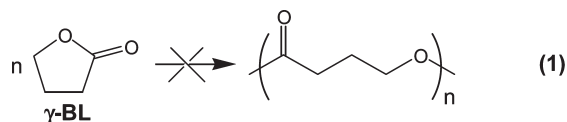
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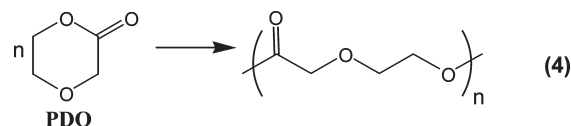
polymerizes in moderate yield. Duda and Penczek oligomerized γ -BL up to decamers and studied the thermodynamics of this reaction.⁵ Marchessault and co-workers were also able to obtain a mixture of oligomers using lipase catalyst.⁶ In recent studies, enzymatic catalysis was used to produce a high molecular weight homopolymer of γ -BL.⁷ On the other hand, the polymerization of macrolides, i.e., higher lactones, which present unfavorable enthalpies of polymerization, is due to the positive entropic contribution.⁸

In a very recent study, we modeled the thermodynamics of polymerization of γ -BL and δ -VL (eqs 1 and 2) using quantum mechanical calculations.⁹ The results indicated that the lack of polymerizability of γ -BL can be attributed to the low strain of the ring, which shows much less geometric distortion in the ester group than in δ -VL, and also to the notable stability of the coiled conformations found in model compounds of poly-4-hydroxybutyrate. However, no theoretical study about the thermodynamics of the ring opening of higher lactones, such as caprolactone (hereafter denoted ϵ -CL; eq 3), have been reported yet. It is worth noting that a detailed comparison of the polymerizabilities of γ -BL, δ -VL, and ϵ -CL should provide information about how the phenomena described above extends with the size of the cycle.



Poly(1,4-dioxan-2-one) is a kind of aliphatic polyester with outstanding flexibility, biodegradability, and biocompatibility due to the co-existence of ester and ether bonds in the repeat unit.¹⁰ This aliphatic polyester is prepared by the ring-opening polymerization of 1,4-dioxan-2-one (hereafter denoted PDO; eq 4) with the existence of certain initiators. Interestingly, conventional initiators (such as triethylaluminum, aluminum isopropoxide, zinc lactate, etc.) do not

provide satisfactory results, which was attributed to the stability of the six-membered ring.^{10b,11} Polymerization conditions were improved in a very recent work by using a single-component rare compound, lanthanum isopropoxide, as initiator.¹² All these features suggest that a theoretical comparison between the polymerizabilities of PDO and δ -VL is highly desirable.



In this work we extend our previous theoretical study on γ -BL and δ -VL to the polymerizability of ϵ -CL and PDO. For this purpose, the ring opening of ϵ -CL and PDO were studied using simple model reactions. Results have been compared with those derived for δ -VL and γ -BL, which have been recalculated using the same computational procedure. For completeness, the influence of both conformational and medium effects on the thermodynamics of such reactions has been examined in detail. The conformational preferences of linear model compounds of poly-6-hydroxycaproate and poly(1,4-dioxan-2-one), the homopolyesters produced by ring-opening polymerization of ϵ -CL and PDO, respectively, have been examined and compared with those of the corresponding homopolyesters derived from δ -VL and γ -BL.

Methods

All quantum mechanical calculations were performed with Gaussian 03,¹³ while force-field simulations were carried out with NAMD.¹⁴ All geometry optimizations were performed using the MP2¹⁵ method combined with the 6-31G(d)¹⁶ basis set. Frequency analyses were carried out to verify the nature of the minimum state of all of the stationary points obtained and to calculate the zero-point vibrational energies (ZPVE) and both thermal and entropic corrections at 298 K. In addition, the electronic energy of all minima was re-evaluated using single point calculations at the MP2/6-311G(d,p) level.¹⁷ Accordingly, the best estimate to the free energy in the gas phase (ΔG^{gp}) was obtained by adding the statistical corrections calculated at the MP2/6-31G(d) level to the latter electronic energies.

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To obtain an estimation of the environmental effects, single point calculations were conducted on the gas-phase optimized structures using a SCRFF model. Specifically, the polarizable continuum model (PCM) developed by Tomasi and co-workers¹⁸ was used to describe chloroform ($\epsilon = 4.9$) and acetonitrile ($\epsilon = 36.64$) as solvents. The PCM method represents the polarization of the liquid by a charge density appearing on the surface of the cavity created in the solvent. This cavity is built using a molecular shape algorithm. PCM calculations were performed in the framework of the HF/6-311G(d,p) level using the standard protocol. Within this context, it should be recalled that previous studies indicated that the free energy of solvation (ΔG_{sol}) obtained using solute geometry relaxations in solution and single point calculations on the optimized geometries in the gas phase are almost identical.¹⁹ The conformational free energies in solution (ΔG^{sol}) were estimated using the classical thermodynamics scheme, i.e., adding ΔG_{sol} to ΔG^{gp} .

The conformational preferences of $\text{CH}_3\text{OCO}(\text{CH}_2)_5\text{OCOCH}_3$ and $\text{CH}_3\text{OCO-CH}_2\text{-O}(\text{CH}_2)_2\text{-OCOCH}_3$, hereafter denoted **1** and **2**, respectively, were determined using a conformational search strategy that combines classical Molecular Dynamics (MD) simulations and geometry optimizations at the MP2/6-31G(d) level. Specifically, a preliminary exploration of their potential energy hypersurfaces was performed using a procedure based on consecutive series of heating–cooling MD cycles, following the principles of classic simulated annealing (SA) strategy.^{20,21} Thus, two initial conformations, i.e., those with all flexible dihedral angles arranged in *trans* and *gauche*⁺, were brought to 800 K and kept at that temperature for 20 ns, coordinates and velocities being stored every 200 ps. These $2 \times 100 = 200$ structures were cooled down to 298 K at a rate of 6 K per 25 ps, and subsequently, their conformational energies were minimized applying 3×10^3 steps of conjugated gradient. All classical calculations, i.e., MD simulations and energy minimizations, were performed using the NAMD program.²² Energies were calculated using the AMBER force-field,²³ the required parameters being taken from the AMBER libraries with the exception of the electrostatic ones. Atomic charges were explicitly developed for **1** and **2** using a procedure previously reported,²⁴ which is fully compatible with AMBER parameters: the quantum mechanical molecular electrostatic potential calculated at the HF/6-31G(d)²⁵ was fitted to the classical Coulombic expression.

To provide a list of unique minimum energy conformations for each compound, the structures minimized using the AMBER force-field were compared among them. The rotamers were classified as follows: *antiperiplanar* or *trans* (t, for $150^\circ \leq \chi_i < 210^\circ$), *anticlinal*[−] or *skew*[−] (s[−], for $210^\circ \leq \chi_i < 270^\circ$), *syn-clinical*[−] or *gauche*[−] (g[−], for $270^\circ \leq \chi_i < 330^\circ$), *syn-periplanar* or *cis* (c, for $330^\circ \leq \chi_i < 360^\circ$), *syn-clinical*⁺ or *gauche*⁺ (g⁺, for 30°

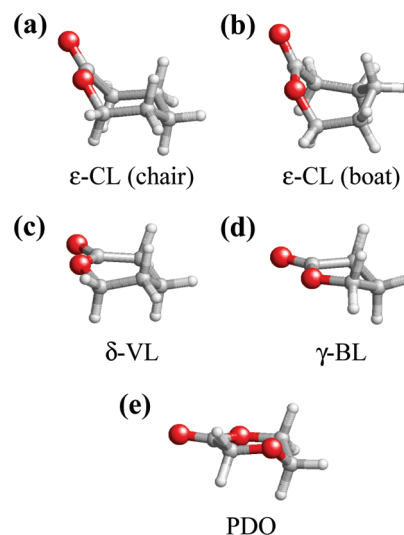


FIGURE 1. MP2/6-31G(d) optimized structures of ϵ -CL chair (a) and boat (b) conformations, δ -VL (c), and γ -BL (d).

$\leq \chi_i < 90^\circ$), and *anticlinal*⁺ or *skew*⁺ (s⁺, for $90^\circ \leq \chi_i < 150^\circ$). Two structures were considered different when they differ in at least one of their six flexible dihedral angles by more than 30° . After this, full geometry optimization of all unique minima within a threshold of 3.0 kcal/mol was carried out at the MP2/6-31G(d) level. Finally, for all minima obtained within an energy threshold of 5.0 kcal/mol we performed the following calculations: frequencies at the MP2/6-31G(d) level, electronic energy evaluation at the MP2/6-311G(d,p) level, and ΔG_{sol} using the PCM procedure in the framework of the HF/6-311G(d,p) level.

It is worth noting that recent studies²⁶ demonstrated that the combination of MD-SA with geometry optimizations allows generation of a representative set of minimum energy conformations, i.e., minima located at the more stable regions of the potential energy hypersurface. Furthermore, systematic conformational searches previously developed for $\text{CH}_3\text{OCO}(\text{CH}_2)_4\text{OCOCH}_3$ and $\text{CH}_3\text{OCO}(\text{CH}_2)_3\text{OCOCH}_3$ (denoted **3** and **4**, respectively), which were performed using the rigorous multidimensional conformational analysis, indicated that the contribution of many minima to the thermodynamics characteristics of these homologues of **1** was negligible.⁹ Considering that the application of rigorous multidimensional conformational analysis involves a huge amount of computational resources (for example, the number of minima that can be anticipated for **1**, assuming three minima for each of the six flexible dihedral angles, is $3^6 = 729$), the conformational search procedure used for **1** and **2** in this work has allowed accurate results using reasonable computational effort.

Results and Discussion

Molecular Geometry of Lactones. Figure 1a and b shows the chair and boat conformations of ϵ -CL derived from ab initio MP2/6-31G(d) calculations. The former conformation was energetically favored with respect to the latter by 2.6 and 2.2 kcal/mol at the MP2/6-31G(d) and MP2/6-311G(d,p) levels, respectively. The conformational free energy in the gas phase ($\Delta G_{\text{conf}}^{\text{gp}}$) of the boat conformation, which was estimated by adding the ZPE, thermal and entropic corrections obtained at the MP2/6-31G(d) level to the MP2/6-311G(d,p) electronic energy, was higher than that of the

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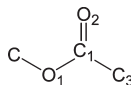
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TABLE 1. Selected Geometrical Parameters (deg) around the Ester Bond for the Minimum Energy Conformations Calculated for ϵ -CL, δ -VL, and γ -BL at the MP2/6-31G(d) Level; Parameters for *s-trans* and *s-cis* Conformers of MA Included for Comparison



	ϵ -CL (chair) ^a	ϵ -CL (boat) ^b	δ -VL ^c	γ -BL ^d	PDO ^e	MA (<i>s-trans</i>)	MA (<i>s-cis</i>)
O ₁ -C ₁ -C ₃	118.7	117.6	118.6	108.9	118.8	110.5	110.5
O ₁ -C ₁ =O ₂	122.9	118.6	118.7	122.4	120.1	123.4	118.5
O ₂ =C ₁ -C ₃	118.3	123.8	122.4	128.7	120.9	126.0	126.0
C-O ₁ -C ₁ -C ₃	-2.8	6.0	-20.7	2.4	-9.1	180.0	0.0
C-O ₁ -C ₁ =O ₂	179.2	-174.6	164.8	-177.3	175.1	0.0	180.0

^aChair conformation of ϵ -CL (Figure 1a). ^bBoat conformation of ϵ -CL (Figure 1b). ^cHalf-chair conformation of δ -VL (Figure 1c). ^dEnvelope conformation of γ -BL (Figure 1d). ^eHalf-chair conformation of PDO (Figure 1e).

chair one by 2.2 kcal/mol. Moreover, the $\Delta G_{\text{conf}}^{\text{sol}}$ of the boat form was 2.4 kcal/mol higher than that of the chair conformer in both chloroform and acetonitrile solutions. Other structures, e.g., half-chair and conformers with a *trans* lactone ring, were significantly higher in energy. Overall these results are in excellent agreement with those previously obtained using molecular mechanics calculations, which predicted the chair conformation as the most stable form of ϵ -CL, with the boat 2.7 kcal/mol higher in energy.²⁷ Moreover, microwave studies revealed that no significant amount of any conformer except the chair form is present in condensed media.²⁸ The most stable geometries found in our previous work for δ -VL and γ -BL were the half-chair (Figure 1c) and envelope (Figure 1d), respectively,⁹ which was in good agreement with both theoretical and experimental studies.^{26a,29,30} On the other hand, Figure 1e reports the only minimum energy conformation identified for PDO, which corresponds to a half-chair arrangement. As can be seen, this conformation resembles that found for δ -VL.

The more relevant geometrical parameters around the ester group obtained for the minimum energy conformations of ϵ -CL, δ -VL, γ -BL, and PDO are compared in Table 1. Furthermore, parameters for the optimized *s-cis* and *s-trans* forms of methyl acetate (MA) have also been included in Table 1. As was stated in our previous work,⁹ comparison with *s-trans* MA, which has been considered as the strain-free reference, indicates that δ -VL presents more strain deformation than γ -BL. The geometrical parameters of ϵ -CL (chair conformer) and PDO reveal important differences with respect to those of *s-trans* MA, especially for the bond angles $\angle\text{O}_1\text{-C}_1\text{-C}_3$ (8.2° and 8.8°, respectively) and $\angle\text{O}_2\text{=C}_1\text{-C}_3$ (7.7° and 5.1°, respectively). Interestingly, despite the deformation of the bond angles associated with the ester moiety being similar for ϵ -CL, PDO, and δ -VL, the distortion of dihedral angles defined by C-O₁-C₁=O₂ and C-O₁-C₁-C₃ varies in the following order: ϵ -CL < PDO < δ -VL. The significant difference between ϵ -CL and the other two lactones should be attributed to the conformational flexibility of the ring, which grows with the size, i.e., flexibility is significantly

TABLE 2. Thermochemistry^a of Reactions of Methyl Acetate with ϵ -CL (Reaction 5) and PDO (Reaction 6) in the Gas Phase,^b Chloroform Solution,^c and in an Environment with Variable Polarity^{d,e}

	reaction 5	reaction 6	reaction 7	reaction 8
$\Delta H_{\text{rxn}}^{\text{gp}}$	-15.4	-13.2	-16.2	-11.5
$\Delta G_{\text{rxn}}^{\text{gp}}$	-2.4	-0.5	-1.9	+1.2
$\Delta H_{\text{rxn}}^{\text{chl}}$	-9.6	-8.5	-12.6	-9.4
$\Delta G_{\text{rxn}}^{\text{chl}}$	-1.7	-0.8	-2.7	+2.8
$\Delta H_{\text{rxn}}^{\text{p/np}}$	-10.0	-8.2	-12.2	-9.1
$\Delta G_{\text{rxn}}^{\text{p/np}}$	-2.3	-1.0	-2.5	+2.9

^aIn kcal/mol. ^b $\Delta H_{\text{rxn}}^{\text{gp}}$ and $\Delta G_{\text{rxn}}^{\text{gp}}$ are the enthalpy and free energy in the gas phase, respectively. ^c $\Delta H_{\text{rxn}}^{\text{chl}}$ and $\Delta G_{\text{rxn}}^{\text{chl}}$ are the enthalpy and free energy in chloroform solution, respectively. ^d $\Delta H_{\text{rxn}}^{\text{p/np}}$ and $\Delta G_{\text{rxn}}^{\text{p/np}}$ are the enthalpy and free energy, respectively, calculated considering a polar environment ($\epsilon = 36.64$) for cyclic lactones and MA and a nonpolar environment ($\epsilon = 4.9$) for the linear compounds (see text). ^eEstimations were obtained considering two strategies: the corresponding linear compounds were described using (a) only the lowest energy minimum (LEM) or (b) a weighted distribution of all minima (WDM) provided by the conformational search. Thermochemical parameters for δ -VL (reaction 7) and γ -BL (reaction 8) have been recalculated and included in the table for comparison.

higher in ϵ -CL than in δ -VL and PDO. However, the geometrical differences between the PDO and δ -VL are intrinsic to their chemical constitution. Accordingly, the replacement of a methylene unit by the ether functionality suggests a reduction of the polymerizability.

Ring-Opening Reaction. Reactions 5 and 6 are simple models for the ring-opening reaction of ϵ -CL and PDO, respectively. The enthalpies and Gibbs free energies in the gas phase ($\Delta H_{\text{rxn}}^{\text{gp}}$ and $\Delta G_{\text{rxn}}^{\text{gp}}$, respectively) of the ring-opening reaction for these two cyclic compounds have been calculated using the whole set of minimum energy structures obtained after a conformational search for **1** and **2**.

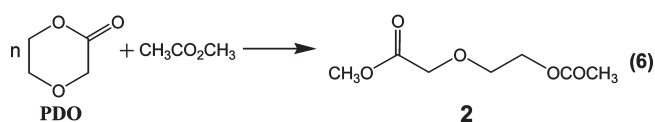
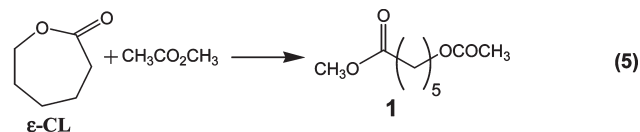


Table 2 lists the values of $\Delta H_{\text{rxn}}^{\text{gp}}$ and $\Delta G_{\text{rxn}}^{\text{gp}}$ values for reactions 5 and 6. The thermochemical parameters of the ring-opening reactions of δ -VL and γ -BL were calculated in our previous work at the CBS-QB3 level using the model

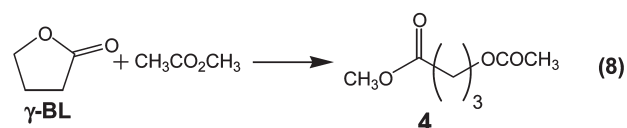
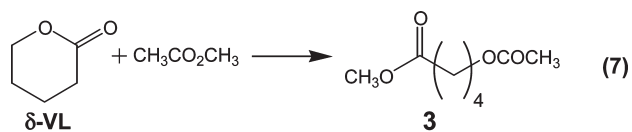
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reactions 7 and 8 and considering the lowest energy minimum of **3** and **4**.⁹ In this work we have re-evaluated these parameters at the MP2 level using the methodology described in the Methods section and using the whole set of minimum energy conformations identified for **3** and **4** through a weighted Boltzmann distribution. This represents a significant improvement with respect to our previous work, results being included in Table 2, for comparison. The conformational preferences of **1** and **2** have been explicitly developed in this work (see next sections for details), whereas those of **3** and **4** were reported in our previous study.⁹



The $\Delta G_{\text{rxn}}^{\text{gp}}$ values obtained for γ -BL, δ -VL, and ϵ -CL are +1.2, -1.9, and -2.4 kcal/mol, respectively. Thus, reactions 5 and 7 are predicted to be exergonic, whereas an endergonic behavior is found for reaction 8. Although environmental effects have not been considered yet, these results are in very good agreement with experimental determinations of enthalpies of polymerization, which range from -1.9 to -2.4 kcal/mol³¹ and from -2.6 to -3.8 kcal/mol^{31b,32–35} for δ -VL and ϵ -CL, respectively. Comparison of the results obtained for PDO and δ -VL reveals that the polymerizability of the former lactone is significantly lower than that of the latter one. Indeed, the $\Delta G_{\text{rxn}}^{\text{gp}}$ predicted for PDO, -0.5 kcal/mol, is more exergonic than the reported experimental determinations, which range from -0.1 to -0.2 kcal/mol.^{10b,11a,12} Moreover, the $\Delta G_{\text{rxn}}^{\text{gp}}$ values predicted at the MP2 level for the model ring-opening reactions 5–8 is consistent with the polymerizability order derived from the molecular geometries of the corresponding lactones (see Table 1).

To ascertain the influence of the medium in the thermochemistry of reactions 4–7, the free energies of solvation in chloroform solution of ϵ -CL, PDO, δ -VL, γ -BL, MA, and all minimum energy conformations characterized for the linear compounds **1**–**4** have been calculated. Results have been used to estimate the enthalpies and Gibbs free energies in chloroform solution ($\Delta H_{\text{rxn}}^{\text{chl}}$ and $\Delta G_{\text{rxn}}^{\text{chl}}$, respectively) of the ring-opening reaction for the three lactones, which are listed in Table 2.

The $\Delta G_{\text{rxn}}^{\text{chl}}$ calculated for reactions 5–8 using a Boltzmann distribution of the minimum energy conformation found for

the linear compounds are -1.7, -0.8, -2.7, and +2.8 kcal/mol, respectively. These values indicate that the role of the medium in the ring-opening reaction of lactones is very significant. Thus, the ring opening of δ -VL in chloroform solution is favored over γ -BL by 5.5 kcal/mol, while in the gas phase it was stabilized by only 3.1 kcal/mol. This increase, which is produced by the higher endergonic character of reaction 8 in chloroform solution, is fully consistent with the experimental observations discussed in the Introduction section and in our previous work.⁹ Reaction 5 is less exergonic in solution than reaction 7 by 1.0 kcal/mol. This should be attributed to the strength of the interaction between the linear compound involved in such reaction and the solvent, which is more repulsive for **1** than for **3**. Thus, the ΔG_{sol} values of ϵ -CL and δ -VL are relatively similar (-5.2 and -4.9 kcal/mol, respectively), while the ΔG_{sol} for the different conformers of **1** and **3** range from -0.1 to 4.2 kcal/mol and from -2.3 to +1.3 kcal/mol, respectively. Comparison between reactions 5 and 6 indicates that the latter is less exergonic than the former by 0.9 kcal/mol, even though the ring opening of PDO is more favored in solution than in the gas phase by 0.3 kcal/mol. The latter is because the interaction with the solvent is more favorable for PDO ($\Delta G_{\text{sol}} = -6.4$ kcal/mol) than for **2** (ΔG_{sol} ranging from -4.9 to +0.1 kcal/mol). It is worth noting that for reaction 7 the change from gas phase to chloroform solution produced a very similar stabilizing effect, i.e., 0.8 kcal/mol. This feature suggests that the low polymerizability of PDO with respect to δ -VL is due to the differences in the conformational preferences of the linear compounds **2** and **3**, which will be discussed below.

Influence of the Polarity of the Environment in the Ring-Opening Reaction. To mimic the experimental conditions used by Duda et al.^{32,33} and Zhu et al.¹² to determine the free energy of polymerization of ϵ -CL ($\Delta G_{\text{p}} = -2.6$ and -3.1 kcal/mol when the monomer–polymer states are liquid–liquid and liquid–condensed, respectively) and PDO ($\Delta G_{\text{p}} \approx -0.1$ kcal/mol when the monomer–polymer states are liquid–liquid), respectively, a new solvation strategy was used to describe the environmental effects in reactions 4–7. In this strategy the dielectric constants of the acetonitrile ($\epsilon = 36.64$) and chloroform ($\epsilon = 4.9$) solvents were used to determine the electrostatic component of ΔG_{sol} for reactants (polar lactones and MA) and products (nonpolar linear segments), respectively. This electrostatic contribution was calculated using the PCM method,¹⁸ the standard protocols for the above-mentioned solvents being used. Thus, the cavitation and van der Waals contributions produced by these solvents to ΔG_{sol} , which are typically evaluated by the standard PCM method, were not considered in this strategy. In other words, the variation in the polarity of the medium occurring during the polar monomer (in polar environment) \rightarrow nonpolar polymer (in nonpolar environment) polymerization process was the only factor included in the evaluation of the enthalpies and Gibbs free energies ($\Delta H_{\text{rxn}}^{\text{p/np}}$ and $\Delta G_{\text{rxn}}^{\text{p/np}}$, respectively) of reactions 5–8. Results obtained using Boltzmann distributions of minima for **1**–**4** are included in Table 2.

As can be seen, from a qualitative point of view, results were similar to those obtained in chloroform solution. Thus, the values of $\Delta H_{\text{rxn}}^{\text{p/np}}$ and $\Delta G_{\text{rxn}}^{\text{p/np}}$ followed the same relative order in all cases, which suggests that the ring opening of

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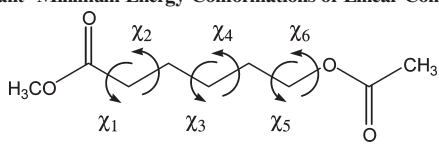
δ -VL and γ -BL is the most and the least favored process, respectively. A detailed inspection to the values listed in Table 2 reveals that the free energy difference between reactions (5) and (7) decreases from 1.0 to 0.2 kcal/mol when the description of the environment varies from chloroform solution to the model with different dielectrics for reactants and products. Thus, the ring opening of ε -CL and δ -VL become similarly favored exergonic processes if the variation in the environmental polarity produced by the polymerization process is taken into account. On the other hand, the free energy determined for reaction 6 decreases 0.2 kcal/mol when chloroform is replaced by environments with different polarities. Accordingly, it can be stated that although it is a favored process, the ring opening of PDO is less favored than that of ε -CL and δ -VL, which is consistent with the thermodynamics parameters determined experimentally.

Conformational Preferences of the Model Compounds of Homopolyesters. Linear compounds **1**, **2**, **3** and **4** should be considered as model systems of poly-6-hydroxycaproate, poly(1,4-dioxan-2-one), poly-5-hydroxyvalerate and poly-4-hydroxybutyrate, respectively, i.e. homopolyesters derived from ε -CL, PDO, δ -VL and γ -BL, respectively. In this section we examine the conformational preferences of **1** and **2**, and compare these results with those reported in our previous study⁸ of **3** and **4**.

The conformational preferences of **1** and **2** were determined using the strategy reported in the Methods section. MD simulations and subsequent energy minimizations using a classical potential based on the AMBER force-field led to 188 and 89 minima, respectively, 52 and 46 of them being within a relative energy threshold of 3.0 kcal/mol. All of these structures were reoptimized at the MP2/6-31G(d) level, which produced 47 and 44 different minimum energy conformations for **1** and **2**, respectively. Frequencies obtained at the MP2/6-31G(d) level combined with electronic energies determined by single point calculations at the MP2/6-311G(d,p) level, which were calculated for the 38 and 44 structures within a relative energy threshold of 5.0 kcal/mol, were used to estimate the $\Delta G_{\text{conf}}^{\text{gp}}$ values.

Tables 3 and 4 list the dihedral angles of the 12 and 17 significant minima (those with $\Delta G_{\text{conf}}^{\text{gp}} \leq 1.5$ kcal/mol) found for **1** and **2**, respectively, the population expected for the remaining conformations being negligible. As can be seen, for **1** the global minimum ($g^+g^+tg^+g^+$) in the gas phase corresponds to a coiled conformation (Figure 2a) with five of the six flexible dihedral angles arranged in *gauche*⁺. The Boltzmann distribution used to describe the conformational preferences of **1** in the gas phase shows that the population of the global minimum is 28%. However, the most remarkable result is that the fully extended conformation (ttttt) is destabilized with respect to the global minimum by only 0.6 kcal/mol (population: 11%). Interestingly, the relative $\Delta G_{\text{conf}}^{\text{gp}}$ estimated for the extended conformation of **3** and **4** was 1.0 and 1.2 kcal/mol, respectively.⁹ The stability of the extended conformation increases with the size of the central aliphatic segment. Regarding **2**, the conformation with the lowest free energy in the gas phase corresponds to the tg^+tg^-t (Figure 2b). The population of this semiextended structure, which shows three dihedral angles arranged in *trans*, is 18%. The fully extended conformation is 1.1 kcal/mol unfavored with respect to the global minimum. However, the population of the latter conformation, if a Boltzmann distribution is

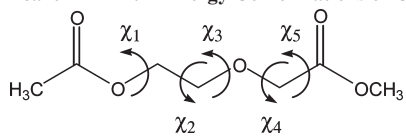
TABLE 3. Dihedral Angles (deg) and Conformational Free Energy in the Gas Phase ($\Delta G_{\text{conf}}^{\text{gp}}$, kcal/mol) and Chloroform Solution ($\Delta G_{\text{conf}}^{\text{chl}}$, kcal/mol) for Significant^a Minimum Energy Conformations of Linear Compound **1**



	χ_1	χ_2	χ_3	χ_4	χ_5	χ_6	$\Delta G_{\text{conf}}^{\text{gp}}$	$\Delta G_{\text{conf}}^{\text{chl}}$
$g^+g^+tg^+g^+$	65.6	60.0	175.7	58.9	49.5	80.8	0.0	0.0
$g^+g^+tg^-g^-s^+$	63.3	55.6	173.5	-68.2	-63.9	102.8	0.6	2.3
ttttt	179.9	180.0	180.0	180.0	180.0	180.0	0.6	0.3
$s^-g^+g^+g^+g^+g^+$	-117.7	57.0	56.2	55.1	50.4	81.4	0.7	1.9
$g^+tttg^+g^+$	68.3	178.3	179.6	179.9	57.8	82.6	0.8	1.5
$s^+g^+tg^+g^-s^-$	98.3	73.9	-169.5	68.6	58.5	-108.1	0.9	5.0
$s^+g^-ttg^-s^+$	104.6	-51.9	-173.3	-168.5	-58.2	100.9	1.0	2.4
$g^+g^+g^+g^+g^+g^+$	67.5	51.9	55.5	54.9	50.0	81.5	1.0	2.3
$tg^-tg^+g^-g^-$	164.4	-68.7	174.4	68.4	-67.6	-81.5	1.1	2.0
$g^-tg^+tg^+g^+$	67.7	173.7	64.0	176.2	58.0	81.8	1.2	2.0
$g^+g^+ts^+g^-s^+$	70.9	59.8	-177.7	90.2	-61.1	107.7	1.3	1.4
$g^+tg^-tg^+g^+$	67.7	173.7	64.0	176.2	58.0	81.8	1.4	1.9

^aMinimum energy conformations with $\Delta G_{\text{conf}}^{\text{gp}} \leq 1.5$ kcal/mol.

TABLE 4. Dihedral Angles (deg) and Conformational Free Energy in the Gas Phase ($\Delta G_{\text{conf}}^{\text{gp}}$, kcal/mol) and Chloroform Solution ($\Delta G_{\text{conf}}^{\text{chl}}$, kcal/mol) for Significant^a Minimum Energy Conformations of Compound **2**



#	χ_1	χ_2	χ_3	χ_4	χ_5	$\Delta G_{\text{conf}}^{\text{gp}}$	$\Delta G_{\text{conf}}^{\text{chl}}$
tg^+tg^-t	-179.1	67.9	-175.0	-73.6	-177.7	0.0	0.7
$g^+g^+tg^-t$	80.3	62.4	-175.8	-74.4	-178.3	0.2	1.3
$g^-g^+tg^+t$	76.4	62.8	-157.5	75.4	179.4	0.2	2.0
$tg^+g^-g^+c$	-164.8	76.5	-70.8	89.3	16.6	0.4	1.1
$tg^+g^-g^+t$	-173.6	76.0	-67.2	91.1	-173.2	0.6	0.0
$tg^+s^-g^-t$	-179.1	69.3	-97.1	-75.3	-172.6	0.7	1.6
tg^+tg^-c	-178.8	68.0	-175.4	-73.1	-14.7	0.8	1.6
$s^+g^-tg^+t$	106.5	-65.9	169.6	73.3	176.4	0.8	1.4
$g^+g^-g^-g^-t$	94.7	-57.2	-79.4	-74.7	-174.1	1.0	2.5
$g^+g^-g^+g^+c$	80.4	70.1	-78.1	87.1	24.8	1.1	2.2
ttttt	180.0	180.0	179.9	180.0	179.9	1.1	1.4
$g^+g^+tg^-c$	80.5	62.9	-176.2	-73.8	-13.7	1.2	2.1
$g^-g^+tg^+c$	72.2	53.5	-166.2	70.7	12.1	1.2	1.3
$g^+g^+g^+g^+t$	80.4	71.7	-70.2	89.4	-164.0	1.2	2.2
$g^+g^+g^-g^-t$	81.4	73.8	-66.1	-61.1	165.1	1.4	1.8
$tg^+s^-g^-c$	-178.9	69.0	-97.6	-77.7	0.5	1.4	2.1
$s^+g^-tg^-t$	97.5	-71.0	160.5	-78.4	177.0	1.5	2.4

^aMinimum energy conformations with $\Delta G_{\text{conf}}^{\text{gp}} \leq 1.5$ kcal/mol.

assumed, is 3% only since there is a number coiled conformations with lower energy.

The conformational free energy in chloroform solution ($\Delta G_{\text{conf}}^{\text{chl}}$) for all minima of **1** and **2** was estimated by adding the ΔG_{sol} , which was calculated using the PCM method, to the $\Delta G_{\text{conf}}^{\text{gp}}$. For **1** only three of the structures listed in Table 3 can be considered as significant conformations in solution, the $\Delta G_{\text{conf}}^{\text{chl}}$ for the remaining 26 minima being larger than 1.5 kcal/mol. The global minimum is the same in chloroform solution as that in the gas phase, even although in general the solvent tends to destabilize the minima with coiled conformations (Table 3). However, the most

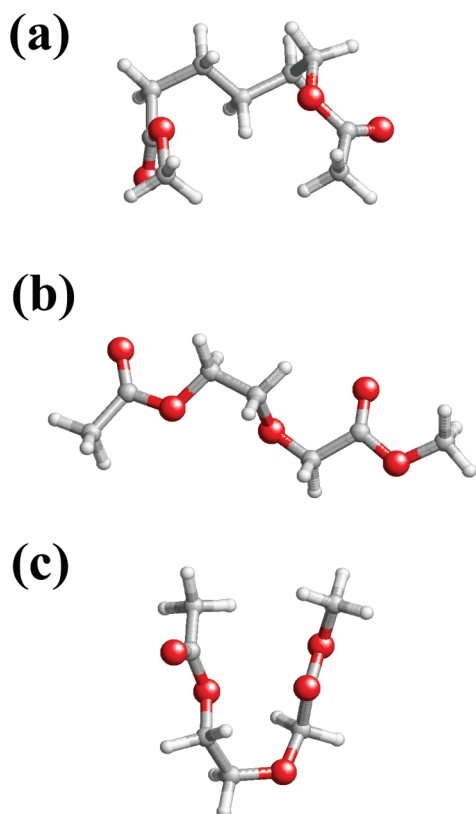


FIGURE 2. Lowest energy minimum of **1** in both the gas phase and chloroform solution (a), **2** in the gas phase (b), and **2** in chloroform solution (c).

remarkable feature is that the stability of the fully extended conformation increases in chloroform solution. Thus, the population estimated in solution for the global minimum and the fully extended conformation is 50% and 28%, respectively. For **2** the most favored conformation in chloroform solution is the $tg^+g^-g^+t$ (Figure 2c). The population predicted for this coiled conformation in solution is 44%. The $\Delta G_{\text{conf}}^{\text{gp}}$ of the semiextended tg^+tg^-t conformation, which was the preferred in the gas phase, increases to 0.7 kcal/mol. However, the most striking feature is that the all-trans conformation is disfavored in chloroform solution by 1.2 kcal/mol, its population being 6% only.

The overall results showed in Tables 3 and 4 indicate that the conformational tendencies of **1** are similar to those found for **3** but clearly different from those of **2** and **4**. In our previous study we concluded that the stability of the extended conformation was significantly higher, especially in solution, for **3** than for **4**.⁹ Moreover, our conformational studies on many other organic molecules containing small aliphatic segments flanked by oxygen-containing functional groups, e.g., ω -hydroxyacids [$\text{HO}-(\text{CH}_2)_n-\text{COOH}$],³⁶ ω -methoxy methyl esters [$\text{CH}_3\text{O}-(\text{CH}_2)_n-\text{COOCH}_3$],³⁷

diamides [$\text{CH}_3\text{NHCO}-(\text{CH}_2)_n-\text{CONHCH}_3$],³⁸ and diketones [$\text{CH}_3\text{CO}-(\text{CH}_2)_n-\text{COCH}_3$],³⁹ systematically showed that compounds with $n \leq 3$ clearly prefer folded coiled conformations while the stability of extended and semiextended arrangements is enhanced when $n \geq 4$. Furthermore, this effect was found to be more pronounced when the oxygen-containing functional groups involved C=O rather than the ether functionality.^{36–39} This feature is consistent with the conformational differences found between **2** and **3**, even although these compounds are probably affected by other electronic effects, e.g., the *gauche* effect. The overall of these features are in excellent agreement with results obtained in the previous sections, which showed both the ability of ϵ -CL and δ -VL to polymerize, the stability of the γ -BL monomer and the intermediate situation of PDO.

Conclusions

The polymerizability of ϵ -CL and PDO has been investigated and compared with that of δ -VL and γ -BL. For this purpose, quantum mechanical calculations at the MP2 level have been performed on these cyclic lactones as well as in the simple model compounds of the corresponding homopolyesters. Results indicate that the thermodynamic polymerizabilities of ϵ -CL and δ -VL are very similar. Thus, the free energies of the ring-opening reactions calculated for these lactones are -2.3 and -2.5 kcal/mol, respectively, when the variation of the polarity of the environment is considered. In contrast, ring-opening polymerization of γ -BL is endergonic by $+2.9$ kcal/mol, while the behavior predicted for PDO is halfway with a free energy of -1.0 kcal/mol. Overall these results are fully consistent with the free energies of polymerization reported in the literature, even though they spread out over a relatively wide interval of values as a result of the experimental conditions, i.e., from -1.0 to -3.8 kcal/mol for ϵ -CL,^{31b,32–35} from -1.9 to -2.4 kcal/mol for δ -VL,³¹ and from -0.1 to -0.2 kcal/mol for PDO.^{10b,11a,12}

Analyses of both the ring strain of cyclic esters and the conformational preferences of linear model compounds for the corresponding homopolyesters explain the results. Comparison of the cyclic lactones with the *s-trans* MA, the strain-free reference, reveals significant distortions in the molecular geometry of ester groups of ϵ -CL, PDO and δ -VL. In contrast, the geometry of the ester group is very similar for *s-trans* MA and γ -BL, and the latter is not strained. The model compound for poly-4-hydroxybutyrate shows a remarkable tendency to adopt coiled conformations, whereas the extended conformation is significantly more stable in the model compounds of poly-6-hydroxycaproate and poly-5-hydroxyvalerate. The model compound for poly(1,4-dioxan-2-one) also prefers a coiled conformation but with less intensity than that of poly-4-hydroxybutyrate. These results are consistent with the free energies calculated for the ring-opening reaction of ϵ -CL, PDO, δ -VL, and γ -BL.

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Supporting Information Available: Coordinates and energy of the minimum energy conformations characterized for ϵ -CL, PDO, **1** and **2**. This material is available free of charge via the Internet at <http://pubs.acs.org>.