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ARTICLE *in* THE JOURNAL OF ORGANIC CHEMISTRY · MAY 2008

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Why δ-Valerolactone Polymerizes and γ-Butyrolactone Does Not

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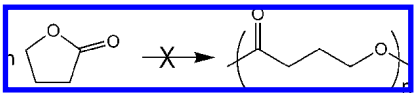
Received November 29, 2007



γ-Butyrolactone, unlike δ-valerolactone, does not polymerize despite a strain energy of ~8 kcal mol^{-1} which could be relieved by opening the s-cis lactone ester bond to an s-trans ester bond in the polymer. To explain this anomaly, we have applied quantum mechanical methods to study the thermochemistry involved in the ring-opening reactions of γ-butyrolactone and δ-valerolactone, the conformational preferences of model molecules that mimic their corresponding homopolyesters, and the variation of enthalpy associated to the polymerizability of such two cyclic lactones. The overall results indicate that the lack of polymerizability of γ-butyrolactone should be attributed to the low strain of the ring, which shows much less geometric distortion in the ester group than δ-valerolactone, and the notable stability of the coiled conformations found in model compounds of poly-4-hydroxybutyrate.

Introduction

Aliphatic polyesters, prepared by ring-opening polymerization of lactones, are versatile polymers with good mechanical properties, hydrolyzability, and biocompatibility.[1] These attributes make them leading candidates in biomedical and pharmaceutical industries as a resorbable implant material and a vehicle for controlled drug delivery.[2]

Lactones are quite reactive and readily convert to their linear counterparts. A few lactones polymerize spontaneously on standing or heating, while most do so in the presence of catalysts or initiators. Carboxylates, alkoxides, and oxides of titanium, tin, and aluminum are effective initiators for the controlled synthesis of polyesters using ring-opening polymerization of lactones.

Early studies of unsubstituted monocyclic lactones with different ring sizes showed that they all polymerized except γ-butyrolactone (**1**),[1,2] which is just on the verge of polymerizability. Thus, δ-valerolactone (**2**) transforms into linear polyester merely on storage at room temperature, doubtless caused by adventitious initiation by hydroxylic impurities. In contrast, under high pressure, **1** polymerizes in moderate yield and also copolymerizes under these conditions.[3] It can be copolymerized at normal pressure with ϵ-caprolactone and other monomers.[4] Duda and Penczek oligomerized γ-butyrolactone up to decamers and studied the thermodynamics of this reaction.[4a] Marchessault and co-workers were also able to obtain

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10.1021/jo702567v CCC: $40.75
Published on Web 03/07/2008

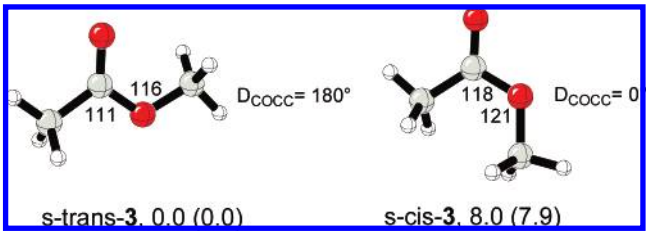
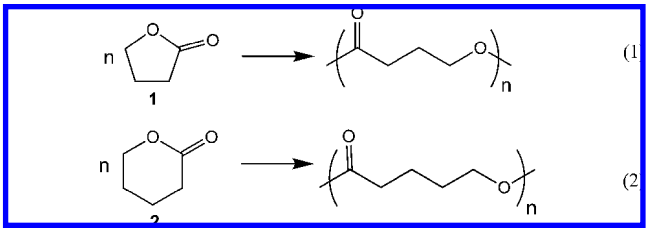


FIGURE 1. Geometries and relative Gibbs free energies (CBS-QB3) of s-cis and s-trans methyl acetate **3**. The values in parentheses are DFT results. Bond angles and dihedral angles are in degrees.

a mixture of oligomers using lipase catalyst.[5] A high molecular weight homopolymer of γ-butyrolactone, namely poly-4-hydroxybutyrate, has been synthesized by enzymatic catalysis.[6]



The strain energies of the 5- and 6-membered lactones have been shown by both direct calorimetric heats of combustion and from their enthalpies of hydrolysis and reduction to be approximately 8 kcal/mol for the neat lactone.[7] Although this might be thought to be more than enough to cause γ-butyrolactone to polymerize, **1** does not polymerize.

Esters such as methyl acetate (**3**) exist as two conformers, the planar s-trans and s-cis forms (Figure 1). B3LYP and CBS-QB3 predict that s-trans is more stable by about 8.0 kcal/mol in the gas phase, which is in good agreement with experimental results.[8] The difference has been attributed to the difference in lone pair−lone pair repulsions.[9] This value is strongly dependent on solvent, decreasing to as little as 1.6 kcal/ mol in polar solvents.[10] Huisgen and Ott pointed out that this factor make lactones more reactive than ordinary esters.[11]

In this work, we report quantum chemical calculations that model the thermodynamics of the polymerization of γ-butyrolactone **1** and δ-valerolactone **2**. More specifically, in a first stage we studied the ring-opening reactions of lactones **1** and **2** using simple model reactions. After this, the conformational preferences of simple model molecules of homopolyesters derived from lactones **1** and **2** have been determined using a systematic conformational search procedure.

Methods

All calculations were performed with the Gaussian 03 suite of programs.[12] Geometry optimizations and frequency calculations to study the ring-opening reactions of lactones **1** and **2** were performed using the B3LYP[13] density functional method in conjunction with the 6-31G(d) basis set.[14] Additional calculations for thermodynamic discussion were performed with the CBS-QB3 method[15] developed by Petersson using the geometries optimized at the B3LYP/6-31G-(d) level.

The conformational preferences of linear model molecules were examined thorough the multidimensional conformational analysis (MDCA) strategy: all of the minima that can be anticipated considering that each flexible dihedral angle is expected to have three minima (3^k, where k is the number of flexible dihedral angles), were constructed and subsequently optimized. Geometry optimizations and frequency calculations of linear compounds were performed using the MP2/6-31G(d) method.[16] Additionally, electronic energies of the resulting minima were re-evaluated using single-point calculations at the MP2/6-311G(d,p) level.[17] Thus, our best estimate to the free energy ($\Delta G^{\ddagger}$) was obtained by combining the electronic energies computed at the MP2/6-311G(d,p) level with the thermodynamic corrections derived from MP2/6-31G(d) calculations.

To obtain an estimation of the solvation effects on linear compounds, single-point calculations were also conducted on the MP2/6-31G(d) energy minima using a self-consistent reaction-field (SCRF) model. SCRF methods treat the solute at the quantum mechanical level, while the solvent is represented as a dielectric continuum. Specifically, we chose the polarizable continuum model (PCM) developed by Tomasi and co-workers to describe the bulk solvent.[18] The PCM represents the polarization of the liquid by a charge density appearing on the surface of the cavity created in the solvent, i.e., the solute/solvent interface. This cavity is built using a molecular shape algorithm. PCM calculations were performed in the framework of the ab initio HF/6-311G(d,p) level using the standard protocol and considering the dielectric constant of chloroform ($\epsilon = 4$). The conformational free energies in chloroform solution were computed using the classical thermodynamical scheme: the free energies of solvation provided by the PCM model were added to the values of $\Delta G^{\ddagger}$ calculated in the gas phase.

Results and Discussion

Ring-Opening Reactions. The ring-opening reactions of lactones **1** and **2** by methanol are simplified models for ring opening polymerizations (reactions 3 and 4, respectively, in Figure 2). The Gibbs free energies (gas phase, 25 °C, 1 atm) of ring opening of lactone **1** are endergonic by 0.3 kcal/mol. In contrast, the reaction of lactone **2** with methanol is exergonic by −2.4 kcal/mol. Both B3LYP/6-31G(d) and CBS-QB3 calculations predict a more favorable energy of ring-opening

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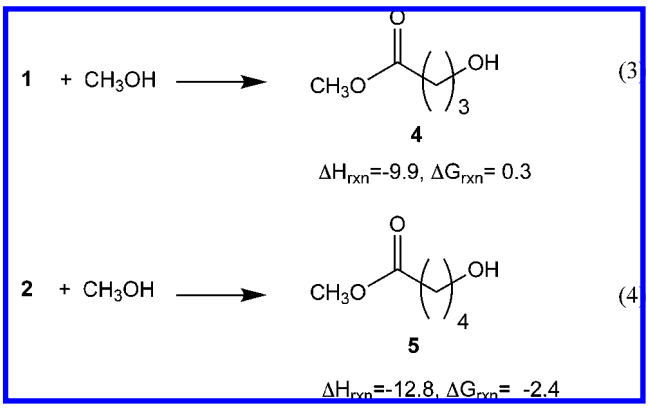

FIGURE 2. Thermochemistry of reaction of methanol with lactones **1** and **2**.

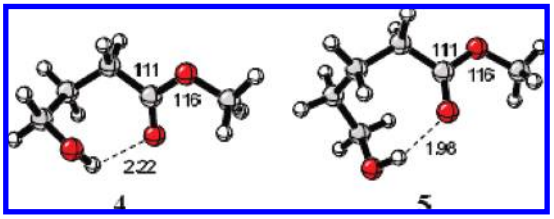

FIGURE 3. Most stable isomers of **4** and **5** calculated at the B3LYP/6-31G(d) level. Bond lengths are in angstroms. Bond angles are in degrees.

of **2**. Experimental determinations of the enthalpies of polymerization of δ-valerolactone range from −2.4 (ref 29) to −2.0 kcal/mol (ref 30), in good agreement with the calculated value. Correcting to a standard state of **1** mol/L and 298 K,[19] the Gibbs free energies for reactions 3 and 4 are 2.2 and −1.3 kcal/mol, respectively.

Wiberg and Wong[10a] derived strain energies from the enthalpies of hydrolysis and reduction of monocyclic lactones and indicated that valerolactone has higher strain than γ-butyrolactone by about 2.4 kcal/mol. The most stable conformers of **4** and **5** are shown in Figure 3. Both compounds possess internal hydrogen bonds, and both have a trans configuration around the ester group.

The reactions of lactones **1** and **2** with methyl acetate (reactions 5 and 6, respectively, in Figure 4) were also studied to eliminate the effect of hydrogen bonds in the ring-opening polymerizations of **1** and **2**. The Gibbs free energies for reactions 5 and 6 in the gas phase are 1.0 and −1.3 kcal/mol, respectively, which also indicates that the ring opening of valerolactone **2** is favored over butyrolactone **1** by 2.3 kcal/mol. These results show that the internal hydrogen bonds in products of reactions 3 and 4 do not have significant effect on the thermochemistry of the reaction.

The most stable isomers of **6** and **7** are used in this comparison. A more detailed discussion of the numerous available conformers and their relative stabilities is reported below. The great strain release in valerolactone is what ultimately causes the ring opening polymerization to be exergonic, whereas the more stable γ-butyrolactone polymerization is endergonic. What is its origin?

The optimized structures of lactones **1** and **2** and their corresponding structural parameters are depicted in Figure 5.

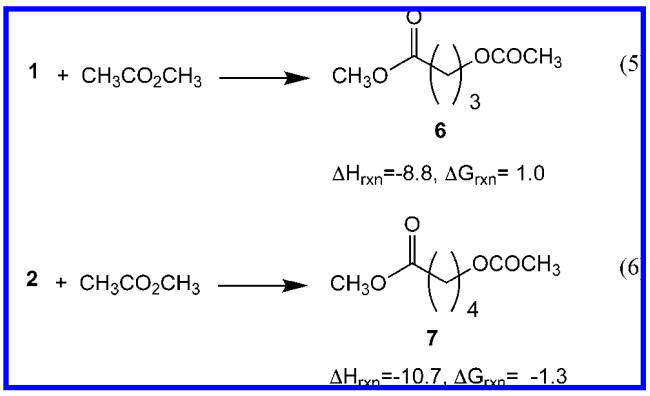

FIGURE 4. Thermochemistry of reactions of methyl acetate with lactones **1** and **2**.

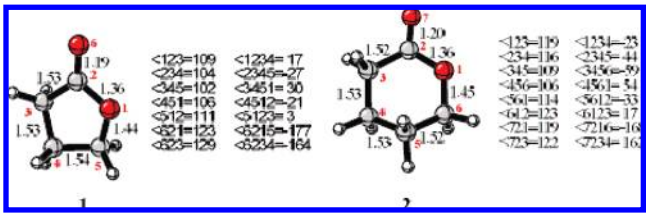

FIGURE 5. Optimized structures of lactones **1** and **2**.

As can be seen, there are no significant differences between the bond lengths in **1** and **2**. However, the bond angles around the breaking bond (CO−O) ∠123 and ∠512 in lactone **1** are 109° and 111°, respectively, in contrast to the corresponding bond angles ∠123 and ∠612 in lactone **2** of 119° and 123°, respectively. The bond angles of lactone **1** are closer to corresponding bond angles (111° and 116°) in *s-trans*-**3**, the strain-free reference, indicating less strain than in valerolactone, **2**. Also, valerolactone **2** has a distorted dihedral angle (compare ∠5123 = 3° in **1** and ∠6123 = 17° in **2**). Further calculations on *s-cis*-**3** indicated that increasing the COCC dihedral angle from 0° to 3° degrees (similar to **1**) does not have any effect on the stability of the ester, but by increasing this dihedral angle to 17° (similar to lactone **2**) the energy increases by 0.6 kcal/mol.

In summary, the calculations reported in this section describe one major factor responsible for unusual reactivity of ring opening polymerization of valerolactone over butyrolactone. The main reason for this behavior is related to larger distortion of bond and dihedral angles around the ester moiety in valerolactone in contrast to butyrolactone. The second factor will now be described.

Conformational Preferences of Linear Model Compounds. In recent studies, the conformational preferences of ω-hydroxy acids **8** and **9** and ω-methoxy methyl esters **10** and **11** were investigated.[20] In spite of their simplicity, these molecules may be considered as model systems of poly-4-hydroxybutyrate (**8** and **10**) and poly-5-hydroxyvalerate (**9** and **11**), i.e., homopolyesters derived from lactones **1** and **2**. Results derived from an exhaustive conformational search thorough a MDCA indicated that **8** and **10** prefer coiled conformations in both the gas-phase and chloroform solution, even although the relative stability between the extended and semiextended conformations is

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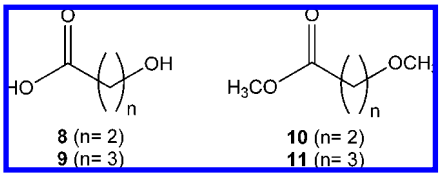
TABLE 1. Dihedral Angles[a] (deg) and Relative Free Energies[b] (kcal/mol) of the Global Minimum Characterized for Compounds 6−11

compd	no.	χ_1	χ_2	χ_3	χ_4	$\Delta G^{\ddagger}$ [c]
6	tg^+g^+t	−167.7	67.4	60.3	−179.4	−1.2
8[d]	$g^+g^+g^-t$	50.9	47.9	−77.8	166.3	−1.9
10[e]	tg^+g^+t	−178.2	59.1	69.1	−170.4	−1.6

compd	no.	χ_1	χ_2	χ_3	χ_4	χ_5	$\Delta G^{\ddagger}$ [c]
7	$tg^+g^+g^+s^-$	179.7	55.2	52.3	56.5	−127.5	−1.0
9[d]	$g^-g^+g^+g^-t$	−79.1	60.0	64.8	−84.2	171.5	−1.8
11[e]	$tg^+g^+g^+s^-$	−179.9	53.1	51.8	57.3	−131.9	−1.0

[a] From MP2/6-31G(d) geometry optimizations. The dihedral angles are defined using the atomic sequences defined in ref 20a,b. [b] Estimated by adding the electronic energies calculated at the MP2/6-311G(d,p)//MP2/6-31G(d) level to the MP2/6-31G(d)//MP2/6-31G(d) thermodynamical corrections. [c] Relative to the fully extended (all the dihedral angles in trans) minimum energy conformation. [d] From ref 20a. [e] From ref 20b.

slightly higher in **10** than in **8**. This is because in the latter compound the formation of intramolecular hydrogen bonds provides extra stability to the coiled conformations. Analysis of the conformational preferences of **9** and **11** indicated the stability of the coiled conformations decreases significantly when the aliphatic segment grows one methylene unit. Thus, according to a Boltzmann distribution of minima the population predicted in chloroform solution for the extended and semiextended conformations of **9** and **11** is 16% and 58%, respectively, these values being twice as high as those calculated for **8** and **10** (7% and 27%, respectively).[20]



In this work, we have examined the conformational preferences of methyl 4-acetoxybutyrate **6** and methyl 5-acetoxyvalerate **7**, which should be considered better model compounds of homopolyesters than those studied previously. Furthermore, these compounds were used to evaluate the thermodynamics of ring reactions of lactones **1** and **2** (reactions 5 and 6). Calculations were performed using the MP2 method combined with the 6-31G(d) and 6-311G(d,p) basis sets for consistency with our previous studies on ω-hydroxy acids and ω-methoxy methyl esters.[20] However, this theoretical method and those used to study the ring-opening reactions 1−4 are expected to be fully consistent from a qualitative point of view.

Results obtained for **6** and **7** were very similar to those found for **10** and **11**, respectively. This is evidenced in Table 1, which compares the lowest energy conformation of **6** and **7** with those of the model compounds previously studied.[20] Estimated values of $\Delta G^{\ddagger}$ indicated that the fully extended conformation of **6** and **7** is destabilized with respect to the global minimum by 1.2 and 1.0 kcal/mol, respectively.

On the other hand, Table 2 compares the fractional population calculated for the coiled conformations of **6** and **7** with those of **8**−**11** in both the gas phase and chloroform solution. As can be seen, the population predicted for the conformations with two or more dihedral angles in *gauche*$^{\pm}$ is lower for compounds containing four methylenic units in aliphatic segment than for those that only involve three methylene units. Furthermore, the stability of the coiled conformations is significantly influenced by the environment, the difference in the population calculated for **6** and **7** in chloroform solution being considerably higher than those obtained in the gas phase.

TABLE 2. Populations Calculated for the Coiled[a] Conformations of Compounds 6−11 in Both Gas-Phase and Chloroform Solution

	6	**8**	**10**	**7**	**9**	**11**
gas phase	0.82	0.96	0.85	0.76	0.91	0.82
chloroform solution	0.65	0.93	0.73	0.43	0.84	0.66

[a] For **6**, **8**, and **10**, coiled conformations refer to structures with less than three dihedral angles in the trans position. For **7**, **9**, and **11**, coiled conformations refer to structures with less than four dihedral angles in the trans position.

The overall results obtained for **6**−**11** indicate that the stability of the extended and semiextended conformations increases, especially in solution, with the size of the aliphatic segment. This effect is particularly evident for **6** and **7**. Thus, in chloroform solution the population of coiled conformations predicted for **6** is 65%, while it is only 43% for **7**. Although the tendency of small aliphatic segments to adopt coiled conformations was also detected in other organic molecules as diamides,[21] diesters[22] and diketones,[23] in the case of model compounds of poly-4-hydroxybutyrate and poly-5-hydroxyvalerate is particularly relevant due to their chemical implications. The difference in the conformational preferences of $-(CH_2)_3-$ and $-(CH_2)_4-$ containing model compounds provides another view to explain the difference in polymerizability of γ-butyrolactone and δ-valerolactone. The MDCA using ab initio calculations show that compounds with the smallest aliphatic segment favors coiled conformations, while for model compounds of poly-5-hydroxyvalerate the population of extended and semiextended conformations are becomes closer or even higher than that of the coiled conformations. The relative populations of coiled conformations of homopolyesters model compounds are in full agreement with the ability of their corresponding cyclic monomers to polymerize.

It is gratifying to note that this explanation is similar to the explanation accepted for the general lack of polymerizability shown by substituted cyclic monomers such as alkylcaprolactones. This is essentially the "*gem*-dimethyl" effect of organic chemistry applied to polymer chemistry. Brown and van Gulick[24] first showed that conformational effects accounted for the remarkable acceleration caused by alkyl and aryl groups in the cyclizations of 4-bromobutylamines: "The substituents profoundly affected the distribution of rotational conformations ... favoring coiled conformations over the energetically preferred extended conformation of the unsubstituted molecule. The decrease in entropy for the coiled molecule upon going into the transition state would be less than that for the parent molecule, thus increasing the cyclization probability." Bruice and Pandit[25] took the same point of view to interpret the cyclization rate enhancement caused by substitution in succinic

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TABLE 3. Comparison of Calculated and Experimental Heats of Polymerization (in kcal/mol)

	ΔH_p (calcd, $n = 3$)[a]	ΔH_p (calcd, $n = 4$)[a]	ΔH_p (calcd)[b]	ΔH_p (exptl)[c]
γ-butyrolactone	−9.6	−8.4	−3.7	
δ-valerolactone	−11.3	−10.9	−6.4	−2.4[d] −2.0[d]

[a] This work. [b] Reference 7b. [c] Reference 29. [d] Reference 30.

and glutaric acids. Allinger and Zalkow[26] placed the thermodynamics of ring closure for hydrocarbons on a quantitative basis using this approach.

Polymerizability of Cyclic Esters. The polymerizability of cyclic lactones (reactions 1 and 2) can be expressed by the extent to which the free energy of the polymerizing system changes as it converts into polymer.[27,28] Unfortunately, a complete sampling of the configurational space of the polymer is required to evaluate the free energy of polymerization (ΔG_p), which is very difficult, or even impossible, by the computational techniques available at present time. In this section, we used MP2/6-31G(d) calculations to obtain the internal energy difference between the homopolyesters (poly-4- hydroxybutyrate and poly-5-hydroxyvalerate) and the corresponding monomers (**1** and **2**, respectively), which provided an estimation of the enthalpy of polymerization (ΔH_p). However, it should be noted that the entropy of polymerization (ΔS_p) of cyclic lactones was almost independent of the ring size since it mainly controlled by the loss of translational entropy brought about by the large reduction in the number of molecules present,[27] this factor being very similar from system to system. Accordingly, ΔH_p are expected to provide a correct description of the relative thermodynamic polymerizabilities.

The values of ΔH_p were estimated using an approach previously proposed to evaluate the intrinsic conformational preferences of polypeptides.[28] Specifically, the variation in internal energy upon polymerization is calculated as

$$\Delta H_p = \mathrm{EI}_{\mathrm{CRU}} - E_M = (E_n - E_{n-1}) - E_M \qquad (9)$$

where $\mathrm{EI}_{\mathrm{CRU}}$ is the chemical repeating unit (CRU) energy increment that results when a single chemical repeating unit fragment is inserted in the polymer chain and E_M is the electronic energy of the cyclic monomer, i.e., **1** and **2**. $\mathrm{EI}_{\mathrm{CRU}}$ is calculated as difference between the electronic energies of model compounds containing $n + 1$ and n (with $n \geq 3$) CRUs (see reactions 1 and 2). The values of ΔH_p calculated using $n = 3$ and 4 are compared in Table 3 with other theoretical and experimental estimations.

As can be seen, there is a general qualitative agreement, ΔH_p, being in all cases smaller for δ-valerolactone than for γ-butyrolactone. However, there is a quantitative discrepancy between our estimations and the other theoretical and experimental values displayed in Table 3. Such discrepancy is due to two limitations: the low value of n considered in our calculations and the omission of conformational variability. As was mentioned above, we are using quantum chemical calculations at the MP2/6-31G(d) level to estimate the values of ΔH_p. This level of theory, which requires a huge amount of computer resources, restricts the size of the investigated systems to model compounds with 4 or less CRUs. However, the variation of ΔH_p predicted when n increases from 3 to 4 is fully consistent with experimental data, i.e., ΔH_p decreases 1.2 and 0.4 kcal/mol for **1** and **2**, respectively, which increases the gap between the two compounds. On the other hand, the fully extended was the only conformation considered for all the model compounds, a rigorous and systematic MDCA being not possible for compounds with more than one CRU. It should be noted that the theoretical estimations of Ward and co-workers,[7b] which are closer to experimental values than our predictions, were obtained using classical force-field simulations and considering a set of conformations for model compounds with 4 and 5 CRUs.

The overall of the results reported in Table 3 consistently indicates that the thermodynamic polymerizability increases with the size of the cyclic lactone, δ-valerolactone being more easily polymerized than γ-butyrolactone. The calculations consistently show a difference of ca. 2 kcal mol^{-1} between γ-butyrolactons and δ-valerolactone, and this is enough to explain their contrasting polymerization behavior. According to the results displayed in previous sections, the lower ΔH_p value of δ-valerolactone is due to a combination of two different factors: both the ring strain and the stability of the fully extended conformation are higher for δ-valerolactone than for γ-butyrolactone.

Acknowledgment. We are grateful to the National Science Foundation and to the Ministerio de Educación y Ciencia (Grant No. MAT2006-04029) for financial support of this research.

Supporting Information Available: Atomic coordinates of reported structures. This material is available free of charge via the Internet at http://pubs.acs.org.

JO702567V

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