Lactone Ring-opening Equilibria in Methanol by ^{1}H NMR Analysis: An Assessment of the Ring-opening Polymerizability of Lactone Monomers

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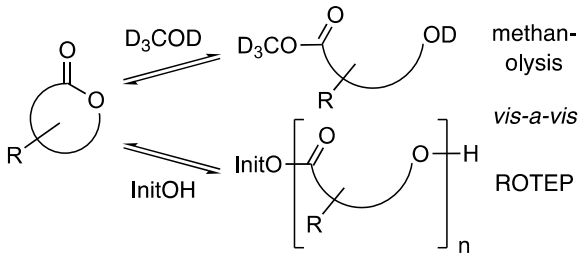

ABSTRACT: The purpose of this study was to learn if a convenient ^{1}H NMR method could be developed to serve as a tool for estimating the propensity of a given lactone to participate in ring-opening transesterification polymerization (ROTEP). The methanolysis of each of 18 lactones was initially examined in CD_3OD solution in the presence of sulfuric acid as a Brønsted catalyst at ambient temperature. Once equilibrium was established, the ratio of remaining lactone to the ring-opened methyl ester/alcohol could be readily measured by NMR spectroscopy. The observed thermodynamic driving force observed for the methanol ring-openings are roughly in line with the extent of ROTEP for the various classes of lactones. This is the case even though the reaction conditions for these methanolyses vs. ROTEP reactions are substantially different. Qualitative evaluations of the rates of the ring-opening methanolyses were also made, and several non-obvious relative reactivities were observed. Finally, employing this simple NMR methanolysis using low concentrations of methanol in $CDCl_3$ is recommended as the preferred protocol for initial evaluation of the polymerizability of any new lactone monomer that researchers may prepare in the future.

INTRODUCTION

Ring-opening trans-esterification polymerization (ROTEP) of lactones to produce polyesters (**I** to **II**, Fig. 1a) is one of the most widely used means of preparing this valuable class of polymeric materials. Under conveniently achieved reaction conditions, living polymerization can be established, leading to well-controlled reaction rates and well-defined materials. ROTEP polymers can be made with low dispersity, and various polymer architectures (block, star, brush, etc.) can be accessed. Myriad studies in and reviews of[1,2,3,4] this extensive field have appeared over the last half-dozen or so decades.

The thermodynamic parameters for polymerization of ring-opening of a given lactone directly impact the equilibrium monomer concentration ($[M]_{eq}$) that is unique to each monomer/polymer pair.[5] Several compilations of the free energies for lactone ROTEPs have appeared.[6] The temperature, the physical state of both the lactone and the corresponding polyester polymer (liquid, glass, amorphous solid, (semi)crystalline solid), and the nature of the solvent, if any, also impact the equilibrium ratio.[7] This complexity introduces experimental challenges that complicate the interpretation of the free energy, enthalpy, and entropy of polymerization (($\Delta G°_p$, $\Delta H°_p$, and $\Delta S°_p$) reported from different studies of, nominally, the same reaction. Nonetheless, the fundamental change in ring strain and overall entropy change for the polymerization of any given monomer are important contributors.[5]

EPERIMENTAL SECTION

All experimental details can be found in the Supporting Information (SI) PDF (see SI statement at end of the manuscript for a description of what is included).

RESULTS AND DISCUSSION

A convenient method for estimating the degree of polymerization for a lactone would be of benefit to researchers, especially in instances where new lactones are being created as potential ROTEP monomers. We wondered whether the thermodynamics of a simple lactone ring-opening experiment might provide a reliable means of judging the ability to achieve high monomer conversion for any given known (or, especially, yet unknown)

lactone; that is, would the free energy differences of unimolecular ring-openings among a series of lactones correlate, at least roughly, with the extent of monomer conversion in the homopolymerization reaction of that same lactone? Of course, all lactones would be expected to open essentially completely to their hydroxy carboxylates in aqueous hydroxide solutions, but the thermodynamics of the acid-base reaction between RCO2H and HO– would then obscure the underlying free energy changes of the ring-opening itself.

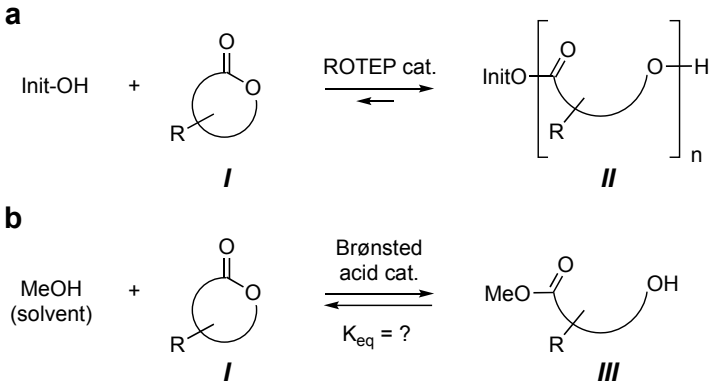

Figure 1. (a) Ring-opening transesterification polymerization (ROTEP) of a generic lactone (**I**) to its polyester **II**. (b) Simple ring-opening methanolysis of the lactone **I** to the methyl ester of its hydroxyacid (**III**).

We instead elected to use the ring-opening transesterification of lactones in methanol, catalyzed by a Brønsted acid (HA), to produce the methyl ester of the hydroxyacid[8] (**I** to **III**, Fig. 1b) to establish the equilibrium mixtures. We judged that this methanolysis reaction would offer several advantages. The reaction mixtures should be homogenous throughout, a wider array of more hydrophobic lactones (cf. **1**-**18**, Fig. 3) could be studied relative to those amenable to analysis in aqueous solution, the amount and nature of HA could be easily controlled, and, importantly, the ratio of lactone to hydroxyester products could be assessed directly (in situ) by ^{1}H NMR spectroscopy in CD_3OD. Our studies began with experiments performed in 100% methanol solution. They evolved to the use of low concentrations of methanol (in CDCl3). Readers interested primarily in learning the best method for how to evaluate a lactone's propensity to serve as a ROTEP monomer are directed to the section near the end of the Discussion and Results having the header "Recommended protocol for preliminary evaluation of a new lactone to undergo ROTEP."

In several initial experiments using methanolic HCl, we observed (GC-MS and ^{1}H NMR) slow, competing formation of small amounts of several additional compounds. One that was positively identified arose by net conversion of the alcohol functionality in **III** to the corresponding chloride. This complicated, at least somewhat,

the interpretation of the NMR spectral data from which we were seeking to deduce the equilibrium ratio for the primary ring-opening event. This complication was avoided when we instead turned to using sulfuric acid as the Brønsted acid catalyst.

Shown in Fig. 2 is an example demonstrating the experimental protocol. In this particular case, α-methyl-γ-butyrolactone (**17**) was dissolved in CD_3OD (ca. 0.07 M) containing 10 mM conc. H_2SO_4. The progress of the ring-opening to the methyl ester **17'** was then monitored over time by ^1H NMR spectroscopy. Spectra were collected at intervals until two successive measurements, taken at a large time interval, showed essentially no difference in the integrated intensity of resonances for the starting lactone (blue) vs. the opened methyl ester (red). In this example the final equilibrium ratio was 71:29 (**17**:**17'**). While this extent of ring-opening might appear surprising at first, given the sometimes-held sense that butyrolactones are non-polymerizable,[9,10] it should be recognized that the large excess of methanol present in this methanolysis experiment will drive the equilibration reaction to a much further degree than in ROTEP using only a small amount of initiator. Finally, notice that this experiment also gives some ancillary information about the rate of the ring-opening, from which we could qualitatively deduce the approximate half-life for the reaction to have reached the equilibrium-dictated ratio (see later discussion).

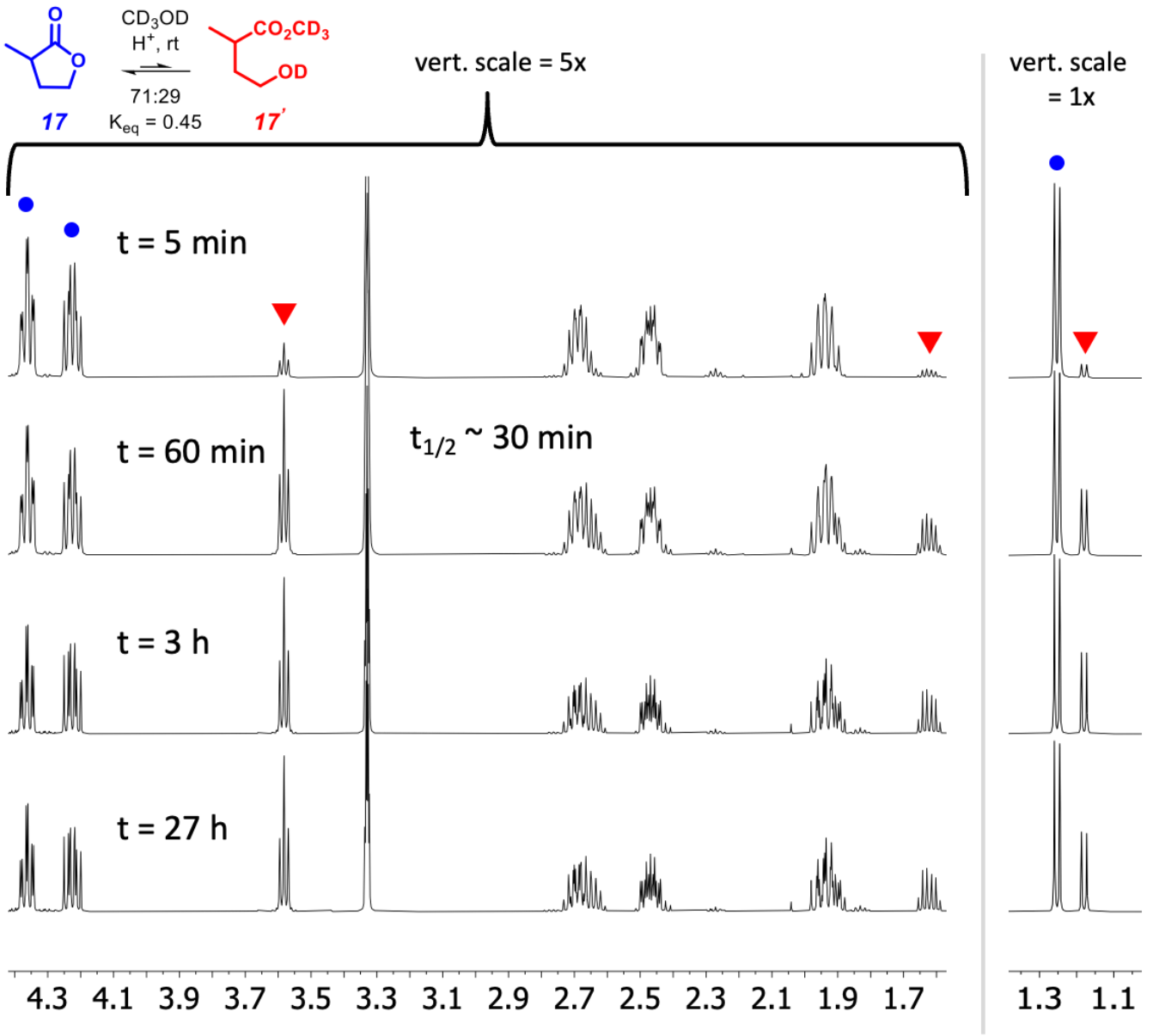

Figure 2. An example of an acid-catalyzed lactone ring-opening [for α-methyl-γ-butyrolactone (**17**)] in CD_3OD (here containing 10 mM H_2SO_4). In the data for the longest pair of time points, no appreciable change in the equilibrium ratio was detected, leading to the measured K_{eq} value of 71:29. Earlier time points (not shown) allowed for an estimation of the time required to achieve 50% conversion to the equilibrium ratio (ca. 30 min for this example).

The array of (18) lactones that we examined is shown in Fig. 3. These are presented sequentially according to the largest to smallest percent of ring-opened product present in the equilibrated methanol solution. The lactones encompass examples with ring-sizes ranging from 4- to 7-members and include most of the commonly used lactone ROTEP monomers. Not surprisingly, the five-membered lactones **14** and **16–18** showed a lower thermodynamic preference to ring-open (78% of the hydroxy methyl ester **14'** down to 26% of **18'**). The isochromanone **15**, which has the same number of rotatable bonds (rotational degrees of freedom) upon ring-

opening as the γ-lactones (i.e., five), showed a similar value (49% of its hydroxy methyl ester **15'**). The 4- and 7-membered β- and ε-lactones **1** and **2**, respectively, as well as α-methyl-δ-valerolactone (**3**), lactide (**4**), and glycolide (**5**) all ring-opened to such a large extent that the remaining lactone was not detectable. δ-Valerolactone itself (**6**) as well as the other substituted, six-membered δ-valerolactones **7**-**13** opened to extents ranging from 91% to 99.2%.

Because of the aforementioned vagaries in measuring the free energy, enthalpy, and entropy of polymerization ($\Delta G°_p$, $\Delta H°_p$, and $\Delta S°_p$) of ROTEP reactions, quantitative correlation of these thermodynamic parameters for polymerizations vs. the methanolysis data recorded here is not fruitful. In other words, although all of the results for the methanolyses measured in this study are internally self-consistent, all having been measured as homogenous solutions in the same solvent at nearly the same temperature and starting concentration of lactone, this is not the case for the free energies of polymerization of this same array of lactones. The difference in solvation energies afforded by the polar protic MeOH medium vs. a ROTEP solution (or bulk) reaction medium is an additional significant factor that makes it unreasonable to expect quantitative correlations between the methanolysis vs. ROTEP thermodynamics.

The most surprising behavior among these (six-membered) δ-lactones was that of **3**, α-methyl-δ-valerolactone. It showed a significantly enhanced preference for the ring-opened product compared to the other three mono-methylated δ-valerolactones **8**, **9**, and **11**; those showed experimental $\Delta G°$s for opening within 0.5 kcal mol^{-1} of one another. The α-isomer **3**, however, clearly possesses an additional free energy change driving its ring-opening. This thermodynamic feature is consistent with the reported more favorable $\Delta G°$ for bulk polymerization of the monomer **3** when compared to that for **8**, **9**, or **11**, all measured under the same conditions and at temperatures resulting in amorphous material.[7]

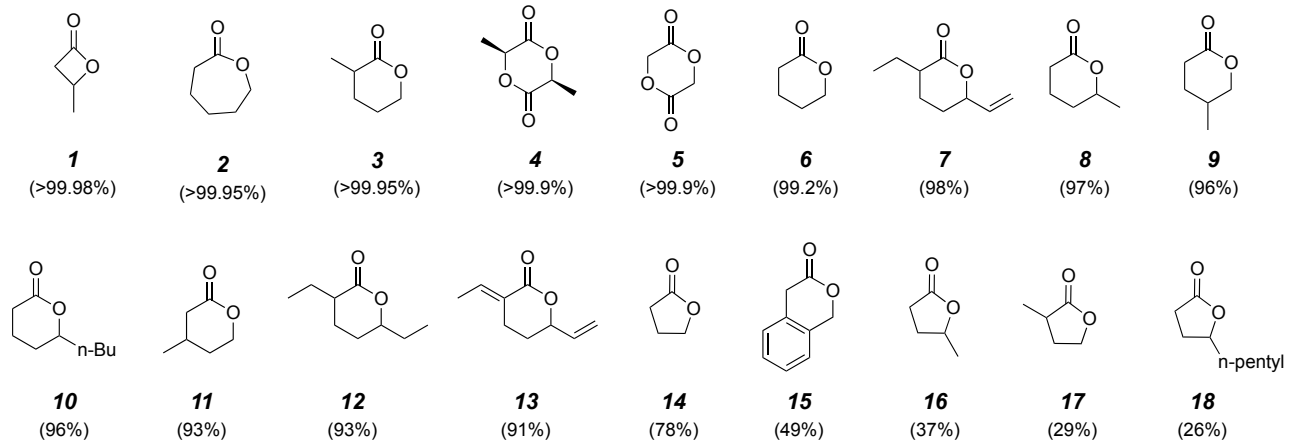

Figure 3. The array of lactones analyzed, listed according to their extents of ring-opening at equilibrium in acidic methanol (% Me ester @ equilibrium in Table 1; to the nearest whole percent for any values <99%).

Table 1. Equilibrium and Approximate Half-life ($t_{1/2}$) Values for the Ring-opening of Lactones 1-18 in 100% CD_3OD, Catalyzed by H_2SO_4

lactone #	%lactone @ equilibrium	%Me ester @ equilibrium[a]	ΔG°[b] (kcal/mol)	[H_2SO_4] (mM)	ca. $t_{1/2}$ (to equilibrium) (h)	lactone #
1	<0.02[c]	>99.98[c]	<-3.14	if 0.50[d]	600	**1**
2	<0.05[c]	>99.95[c]	<-2.60	0.50	1.5	**2**
3	<0.05[c]	>99.95[c]	<-2.60	0.50	0.25	**3**
4	<0.1[c]	>99.9[c]	<-2.60	if 0.50[d]	30	**4**
5	<0.02[c]	>99.98[c]	<-2.60	if 0.50[d]	6.7	**5**
6	0.8	99.2	-0.96	0.50	0.17	**6**
7	2	98	-0.41	0.50	16	**7**
8	3	97	-0.16	0.50	0.25	**8**
9	4	96	+0.01	0.50	0.25	**9**
10	4	96	+0.01	0.50	0.75	**10**
11	7	93	+0.36	0.50	0.33	**11**
12	7	93	+0.36	0.50	4.0	**12**
13	9	91	+0.53	if 0.50[d]	60	**13**
14	22	78	+1.15	if 0.50[d]	6.7	**14**
15	51	49	+1.91	0.50	3.0	**15**
16	63	37	+2.21	if 0.50[d]	5.0	**16**
17	71	29	+2.43	if 0.50[d]	10.0	**17**
18	74	26	+2.52	If 0.50[d]	6.7	**18**

[a] Values are given to the nearest whole percent of ring-opened ester for those showing equilibrium ratios of <99:1. [b] $\Delta G° = -RT\ln\{[\#']/([\#]\bullet 24.6)\}$ for the equilibrium mixture in 100% methanol at ca. 25 °C. [c] No residual lactone detected within the limits of the S/N level of the spectrum. [d] The $t_{1/2}$ value for this relatively slow-reacting lactone has been extrapolated, assuming a first order dependence on the [cat.], from the experimental measurement using a sample containing 10 rather than 0.5 mM H_2SO_4.

We used DFT computations to provide insight to the greater thermodynamic propensity for **3** to undergo this simple ring-opening with methanol. Hall, Houk, and coworkers used a similar DFT approach to explore the origin of differences in the thermodynamic preference for δ-valerolactone (**6**) vs. γ-butyrolactone (**14**) to undergo ROTEP conversion to their respective polyesters.[10,11,12] This led them to provide an alternative explanation to the earlier held notion that the greater number of rotatable bonds (by one) in the six-membered lactone was primarily responsible for this thermodynamic difference. Specifically, they suggested i) that the δ-valerolactone showed a higher inherent degree of ring strain compared to the γ-butyrolactone homolog (associated with the geometric differences between the distortion of the s-cis ester moiety in each of these lactones)[13,14] and ii) that there was a greater population of lower energy, extended conformations accessible within the product polyvalerolactone (from **6**) compared to that in polybutyrolactone (from **14**).

In our studies we computed the reaction energies for the overall isodesmic reaction[11b] shown in Fig. 4, comprised of the parallel hypothetical equilibrations between the α- and β-methyl-δ-valerolactones **3** and **11** (eq a) and their respective hydroxy esters **3'** and **11'** (eq b). A full conformation search with molecular mechanics (OPLS) and subsequent DFT optimization of each of the resulting conformers for each of these four species was performed. Methanol solvation (SMD) was used. The energies of all conformers of the **3**/**11** and **3'**/**11'** pairs were then Boltzmann averaged to provide a computed free energy difference for each of the hypothetical isomerizations a) and b). Perhaps unsurprisingly, there is very little difference in the computed stabilities of **3'** and **11'**. The extra thermodynamic push for the overall process to favor the right-hand pair of structures in Fig. 4 ($\Delta\Delta G^\circ$ = -0.718 kcal mol^{-1}) seemingly originates in the destabilization of the α-methyl-δ-valerolactone **3** relative to the β-methyl-δ-valerolactone isomer **11**. Although we looked for differences in geometric features of the computed conformers of **3** vs. **11** (four for each), no obvious structural element stands out as a potential explanation for this difference in their relative stability. We reperformed the calculation in the gas phase (i.e., no SMD), and the equilibrium then slightly favored the left hand pair ($\Delta\Delta G^\circ$ = +0.181 kcal mol^{-1}), which suggests that the difference in the free energy of ring-openings of **3** vs. **11** resides in differential solvation parameters of the lactone vs. hydroxy methyl ester.

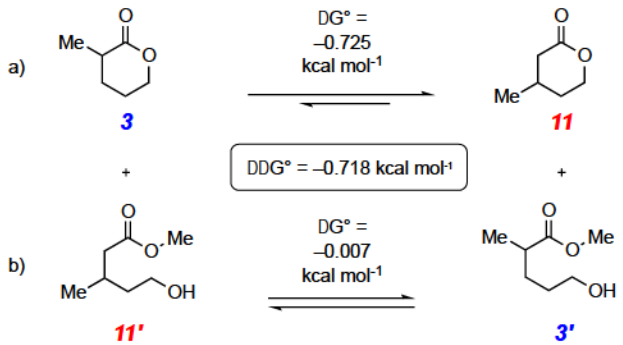

Figure 4. The computed (DFT) energy difference for the isodesmic reaction of **3** + **11'** to give **11** + **3'**. [SMD(methanol)/UMN15/6-31+G(d)].

To assess whether the properties of the bulk solvent had a significant effect on relative extents of ring-opening, we also examined the analogous reactions of a subset of the less hydrophobic lactones in acidic D_2O instead of CD_3OD (Fig. 5 and Table 2). The equilibrium amounts of ring-opened products, now hydroxyacids, were measured in analogous fashion to those in the methanolysis reactions. As with the methanolyses, there was no detectable lactone remaining for β-methyl-β-propiolactone (**1**). With caprolactone (**2**), we could now detect that a small amount of **2** remained. Thus, the hydration reaction was not favoring the ring-opened hydroxyacid to as large of an extent as seen for the methyl ester formation. This was also the case for all of the remaining lactones that we measured in even more clearcut fashion (Table 2); i.e., the extent of ring-opened vs. ring-closed species were reliably quantifiable for both the hydrolysis and the methanolysis reactions. This is consistent with the facts that a) the bond dissociation energy of the O–H bond in water (DH° = 119 kcal mol^{-1}) is substantially larger than that of the weaker O–H in methanol (DH° = 105 kcal mol^{-1}) and b) the bond dissociation energy of the new O–H in the

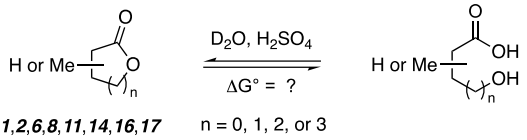

Figure 5. The less hydrophobic set of lactones subjected to ring-opening in water to measure the equilibrium amounts of the corresponding hydroxyacids (data in Table 2).

Table 2. Equilibrium Values for the Ring-opening of Selected Lactones in D_2O and the Differences in Free Energies (ΔΔG°) for the Extent of Ring-opening between the Hydration and the Methanolysis Equilibria

lactone #	%lactone @ equilibrium	%hydroxyacid @ equilibrium[a]	ΔG° (H_2O) (kcal/mol)	ΔG° (MeOH) (kcal/mol) (from Table 1)	$\|\Delta\Delta G°\|^b$ (MeOH – H_2O) (kcal/mol)
1	<0.02[c]	>99.98[c]	<-2.72	<-3.14	–
2	0.05	99.95	-2.17	<-2.60	–
6	8	92	+0.88	-0.96	1.84
8	19	81	+1.47	-0.16	1.63
11	44	56	+2.18	+0.36	1.82
14	70	30	+2.83	+1.15	1.68
16	93	7	+3.86	+2.21	1.65
17	95	5	+4.07	+2.43	1.64

[a] Values are given to the nearest whole percent of ring-opened hydroxy acid for those showing equilibrium ratios of <99:1. [b] $\Delta G° = -RT\ln\{[\#']/([\#]\bullet 50.8)\}$ for the equilibrium mixture in 100% D_2O at ca. 25 °C. [c] No residual lactone detected within the limits of the S/N level of the spectrum.

carboxylic acid is ca. 12 kcal mol^{-1} more stable than that of the O–CH_3 bond in the methyl ester.[15] For those final six examples in Table 2, it is interesting that the difference in free energy change (i.e., $\Delta\Delta G°$, final column) between the water vs. methanol experiments are all very similar. Moreover they are well aligned with the ca. 2 kcal mol^{-1} $\Delta\Delta G°$ one estimates from the pairs of bond dissociation energies just mentioned. Of course, differences in solvation energies will also contribute to the overall free energy changes, but the similarity of all of the $\Delta\Delta G°$ values suggest that these differences are more or less constant from one lactone to the next and their contributions to the free energies tend to cancel.

Qualitative relative rates of ring-opening. We also measured the approximate time required to achieve 50% of the ring-opening necessary to arrive at the final equilibrated product mixture (i.e., the half-life, $t_{1/2}$). These are listed in the right-most column of data in Table 1. A number of aspects are worth mentioning, including some that may seem non-intuitive. As a class, the six-membered δ-valerolactones are the fastest to ring-open, and the presence of a single substituent on one of the carbons does not appreciably impact the rate (all within a factor of ca. 3). The rate of caprolactone (**2**) methanolysis is similar. As a class, the γ-butyrolactones **14** and **16**–**18** all ring-open at rates within a factor of ca. 2 of one another, but they react considerably slower than the δ-valerolactones. Somewhat surprisingly, L-lactide (**4**) and glycolide (**5**) both open rather slowly, the rate of the former being further retarded relative to the latter by the methyl substituents. The presence of the alkene in the conjugate enoate **13** slows its ring-opening considerably because the resonance energy renders the carbonyl carbon less electrophilic and the process requires loss of resonance stabilization upon formation of the tetrahedral intermediate (TI). Finally and most counterintuitive of all, the strained, four-membered β-methyl-β-propiolactone (**1**) is, by far, the least reactive of all the lactones studied. This likely is a reflection of the reduced basicity of the lactone carbonyl in the β-lactone[16] and the accordingly lower concentration of the protonated lactone, the obligate intermediate preceding TI formation by addition of methanol. The reactivity for the ring-opening of **1** is consistent with the report of its quite slow ROTEP reaction under Brønsted acid catalysis.[17] All of the trends seen here are well aligned with previous kinetic studies of acid-catalyzed lactone hydrolyses, both by computation[18] and experiment.[19]

Lactide (**4**) is the most widely used, bio-sourced ROTEP monomer and, as such, its methanolysis behavior warrants a bit more discussion.[20] Its resulting polyester, PLA, is, of course, the showcase example of a bio-derived polymer and has valuable post-use degradation properties (e.g., industrial composting) as well. Progress of the ring-opening of **4** in methanol over time is shown in Fig. 6. Initial formation of the diester **4'** was observed, although, as mentioned, that reaction was noticeably slower ($t_{1/2}$ ca. 90 min in 10 mM H_2SO_4) than the rates of opening of nearly all other six-membered, δ-valerolactones. This rate difference could reflect a lower

concentration of the inductively destabilized protonated lactone carbonyl oxygen (if formation of the TI is rate limiting) or of the cyclic ether-like oxygen in that TI (if breakdown of the tetrahedral intermediate is rate limiting). Onset of a second, slower event ($t_{1/2}$ ca. 2 days) was also observed – namely, the transesterification of the internal ester in **4'** by additional methanol,[21] a process that simultaneously produces two molecules of methyl lactate (**4''**). This became the overall thermodynamic sink for the system given the fact that methanol was the bulk solvent. Nonetheless, at intermediate time points (e.g., 24 h) the lactide (**4**) is no longer observable, allowing us to conclude that >99.9% of **4** was in the ring-opened form **4'** within the lactone/methyl ester equilibrium.

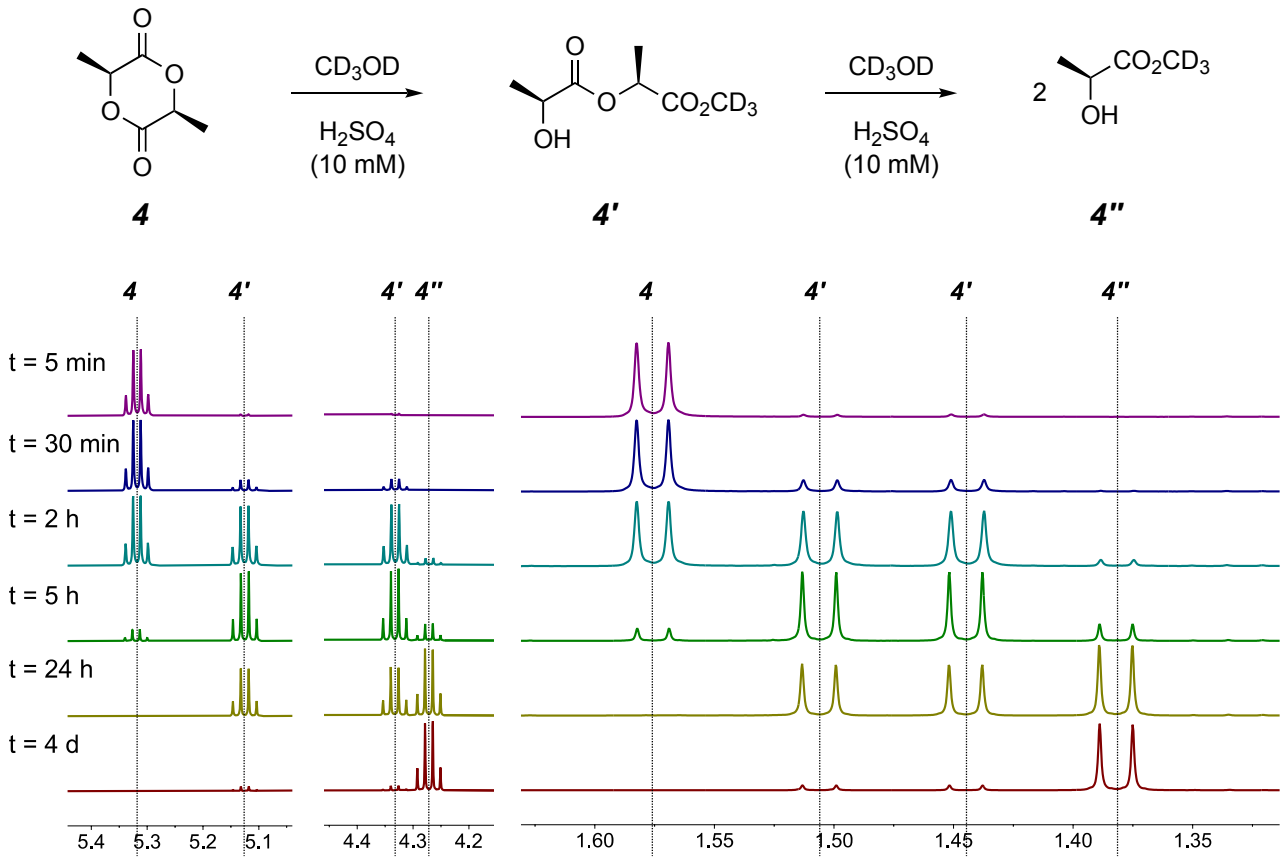

Figure 6. The acid catalyzed lactone ring-opening of L-lactide (**4**) in CD_3OD containing 10 mM H_2SO_4 at ambient temperature. At ≥24 h no detectable amount of **4** remained. Given the estimated limits of detection, K_{eq} was >1000:1. The $t_{1/2}$ for the ring-opening was ca. 90 min. The onset of secondary conversion of the metastable diester **4'** to methyl lactate **4''** was observable at the 2 h timepoint but had not yet achieved 50% conversion at 24 h. The vertical scale of the downfield panels of quartets have been increased for easier viewing of the changes.

Recommended protocol for preliminary evaluation of a new lactone to undergo ROTEP. At the point of the study as described above, peer review of an early version of the manuscript garnered valuable comments. We were asked if there was a more discriminating criterion based on this method that could be developed to more

reliably assess the likelihood of a lactone's ability to undergo a thermodynamically favorable ROTEP. In particular, the reviewers felt that the fact that lactones **13**–**18** all showed reasonably high levels of ring-opening (cf. Fig. 3 and Table 1) in 100% methanol, yet are poor monomers for ROTEPs under the most commonly used reaction conditions (cf. ref. 10 for the notable exception of the Chen group's polymerization of **14** with highly active catalysts that function at very low temperature), represented a limitation to the protocol being presented in this study as a tool for estimating the likelihood for ROTEP of new lactones. It (only) then occurred to us that examining the extent of ring-opening in the presence of lower concentrations of methanol could lead to a more discriminating metric. That prompted us to carry out the experiments that are now summarized in Table 3 and Figure 7.

We examined the extent of ring-opening of a small subset of the lactones in $CDCl_3$ containing 5 or 2 vol% CH_3OH (i.e., [methanol] = 1.23 or 0.49 M, respectively). We chose valerolactone (**6**) as a representative of lactones that readily engage in ROTEP and butyrolactone (**14**) and isochromanone (**15**) as two that are reluctant to homopolymerize. As seen in the data in Table 3, now in the presence of increasingly limited amounts of methanol, the extent of ring-opening of **14** and **15** is more accentuated compared to the results in 100% methanol. As with the earlier pure methanol experiments, to ensure that equilibrium had been reached, two successive NMR measurements, appropriately spaced in time and having essentially the same ratio of lactone:methyl ester alcohol, were performed. For the slower reacting lactones **14** and **15** (cf. Table 1) in 2 vol% MeOH/$CDCl_3$, a final interval of several days was used.

Table 3. Percent of Ring-opened Products from Lactones 6, 14, and 15 $CDCl_3$ containing 5 vol% and 2 vol% CH_3OH/10 mM H_2SO_4

lactone #	100 vol% methanol (from Table 1)	5 vol% $CH_3OH/CDCl_3$ [MeOH] = 1.2 M	2 vol% $CH_3OH/CDCl_3$ [MeOH] = 0.49 M
δ-valerolactone (6)	99.2	93.3	86.8
γ-butyrolactone (14)	78	28.7	18.7
3-isochromanone (15)	49	11.5	6.5

To show this graphically, we created the series of curves presented in Figure 7 of the theoretical extent of ring-opening vs. [methanol] for the three lactones. The curves in Figure 7a were constructed using the K_{eq} value measured in 100% CD_3OD (= 24.6 M) for each lactone and then calculating the theoretical equilibrium ratio at varying lower concentrations of methanol using equations 1 and 2 [shown, for example, for valerolactone (**6**) and its ring-opened methyl ester **6'**]. The initial concentration of lactone (i.e., $[\mathbf{6}]_0$) was 0.07 M.

$$K_{eq} = \frac{[\mathbf{6'}]}{\{[\mathbf{6}]_0 - [\mathbf{6'}]\} \bullet \{[CD_3OD]_0 - [\mathbf{6'}]\}} \qquad \text{eq (1)}$$

$$\%\ \text{ring-opening} = [\mathbf{6'}]/[\mathbf{6}]_0 \qquad \text{eq (2)}$$

In Figure 7b we have shown an expansion of the low methanol concentration regime for the graph in Figure 7a. The experimental data points for the values in Table 3 for each of lactones **6**, **14**, and **15** at 5 vol% and 2 vol% methanol are shown as black triangles. The theoretical points (circles) in Figure 7b have been empirically adjusted by iteratively changing the K_{eq} value in eq (1) for each lactone to fit the experimental equilibrium data. We used this scaling operation as a means to account for the differential solvation energies of the lactones vs. their ring-opened methyl ester alcohols in methanol vs. in chloroform containing only small amounts of methanol. The solvation enthalpy, otherwise quite challenging to assess, impacts the overall free energy of the systems.

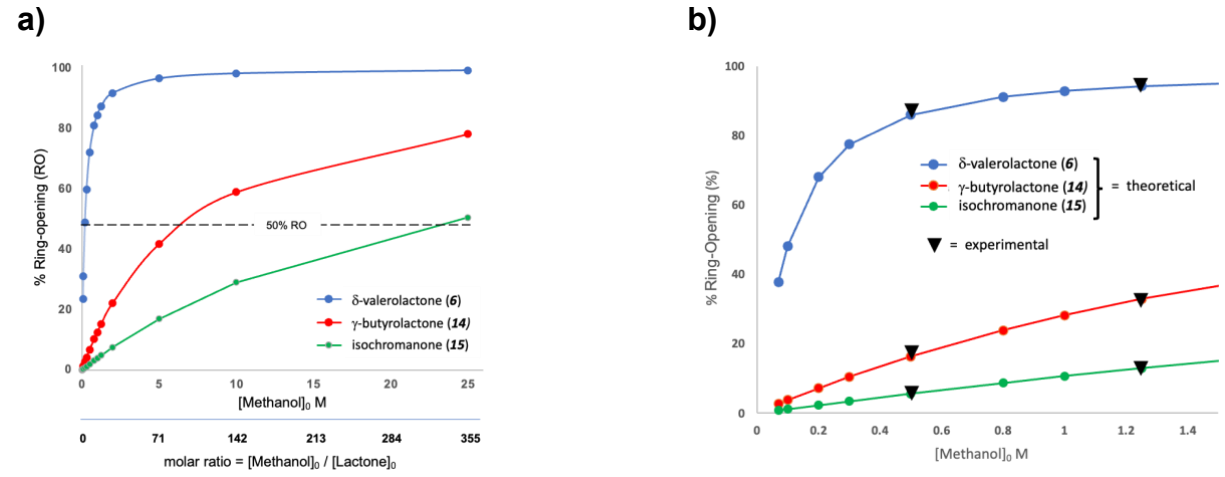

Figure 7. Curves showing the theoretical (dots) extent of lactone ring-opening vs. initial methanol concentration for a well-behaved ROTEP monomer (δ-valerolactone, blue) vs. marginally or poorly polymerizable lactones (γ-butyrolactone, red; and 3-isochromanone, green). **a)** Graph over the full range (0–25 M) of methanol concentration. **b)** Graph of the lowest range (0–1.5 M) of methanol concentration; the theoretical values have been adjusted as described in the text.

Finally, we can offer the following guidance for someone wanting to preliminarily test the propensity of any new lactone (even if it is initially available in only a small quantity and/or at a marginal level of purity) to undergo a thermodynamically favorable ROTEP. Performing an equilibrium measurement using, e.g., 2% CD_3OD in $CDCl_3$ (see the SI for a detailed description of the protocol) and comparing the resulting extent of ring-opened methyl ester with the extents indicated by the curves in Figure 7b (i.e., those for the well-behaved **6** down to the progressively poorly performing ROTEP monomers **14** and **15**) will provide a good indication of whether further pursuit of ROTEP studies of that potential monomer is warranted.

CONCLUSIONS

In summary, we have described here a convenient NMR method for estimating the polymerizability of various lactones, reflected by the thermodynamics of their methanolyses. The trends in the percentages of ring-opened methyl ester alcohol correlate at least approximately with the effectiveness of ROTEP for the same lactones. It is unreasonable to expect a matching of the *absolute* values of the free energy changes for the methanolysis reactions described here vis-a-vis the analogous ROTEP ΔG_p°s because the enthalpic solvation of the reactant lactones and products [**#** vs. **#'** for the methanolyses here and **#** vs. **poly(#)** for the ROTEP reactions] are quite different in methanol vs. the polymerization medium (e.g., solvents such as dichloromethane or bulk conditions); the entropic contributors are also dissimilar for the two. Nonetheless, the *relative* energies for the methanolyses roughly reflect those for the ROTEPs. We also examined the hydrolytic ring-opening of a subset of the lactones in D_2O. The extent of ring-opening was found to be less than that for the corresponding methanolyses and, interestingly, by nearly the same difference in free energy change (i.e., $\Delta\Delta G°$) for each of lactones. Performing similar methanolysis experiments in the presence of much smaller amounts of methanol provides a more discriminating metric for judging the likelihood of a given lactone for participating in ROTEP. We can recommend that researchers wanting to evaluate preliminarily any new lactone should perform the simple methanolysis described here. A practical advantage of doing so is that it would not be necessary to prepare a significant quantity of a pristinely pure lactone in order to initially judge its polymerizability.

ASSOCIATED CONTENT

Supporting Information.

The Supporting Information is available free of charge on the ACS Publications website.

Experimental details for collection of equilibrium and kinetic data; characterization data for previously unknown hydroxy esters; copies of their ^{1}H and ^{13}C NMR spectra; copies of ^{1}H NMR spectra of the final equilibrated samples in methanol, water, and 5 or 2% methanol in $CDCl_3$; and methods and results of the DFT computations; all in a single PDF.

A .zip file ("FID for Publication") of the raw .fid NMR files for the previously unknown methyl esters as well as for the spectra of the final equilibrated mixtures for the methanolyses of **1**–**18** in 100% CD_3OD; for the hydrolyses of **1**, **2**, **6**, **8**, **11**, **14**, **16**, and **17** in D_2O; and for the methanolyses of **6**, **14**, and **15** in 2% and 5% CH_3OH in $CDCl_3$.

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Notes

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