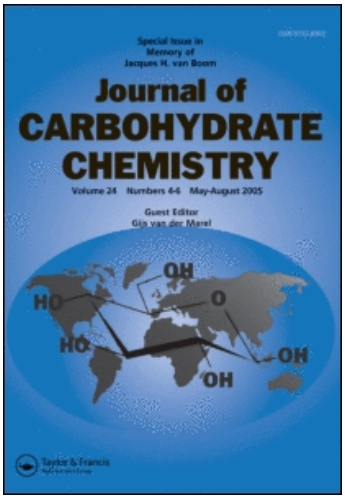

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Mechanisms for the Formation of Diamides and Polyamides by Aminolysis of d-Glucaric Acid Esters

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Mechanisms for the Formation of Diamides and Polyamides by Aminolysis of D-Glucaric Acid Esters

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ABSTRACT

^{1}H and ^{13}C NMR were employed to chart the conversion of the five-membered lactone esters methyl D-glucarate 1,4-lactone (**1**) and ethyl D-glucarate 6,3-lactone (**5**) to *N,N′*-dipropyl-D-glucaramide with *n*-propylamine in DMSO-d_6. These experiments were carried out to model the amide forming steps in polycondensation reactions between esterified D-glucaric acid and diamines to give poly(D-glucaramides). It was clear from the resulting NMR spectra that the lactones **1** and **5** were each converted in three consecutive steps to the product diamides; aminolysis of the lactone ester to the corresponding acyclic *N*-propyl-D-glucaramide monoester, followed by lactonization to a five-membered lactone amide, and concluding with aminolyis of the lactone amide to *N,N′*-dipropyl-D-glucaramide (**4**). Comparison of the reaction pathways from **1** and **5** by ^{1}H NMR analysis suggests that ring opening of the 1,4-lactone ester (**1**) and 1,4-lactone amide (**7**) is faster than ring opening of the corresponding 6,3-lactone ester (**5**) and 6,3-lactone amide (**3**). Aminolysis of dimethyl L-tartrate, which cannot form a five-membered lactone, with *n*-propylamine in DMSO-d_6 was much slower than

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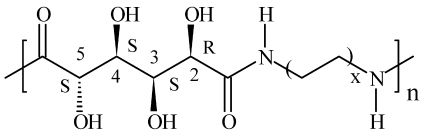
aminolysis of esterified glucaric acid, indicating that the lactone forming/lactone aminolysis steps are the dominant aminolysis rate enhancing steps from glucarate.

Key Words: Polyhydroxypolyamides; Aminolysis; Mechanism; Five-membered lactones; NMR, D-glucaric acid esters.

INTRODUCTION

Polyhydroxypolyamides (PHPAs) are synthetic polyamides prepared by polycondensation of esterified aldaric acids with 1° diamines in polar solvents. The first reported examples of such polyamides were from the lab of Ogata and coworkers in Japan based upon aminolysis of dimethyl L-tartrate and diethyl mucate (*meso*-galactarate).[1–4] Other PHPAs derived from D-glucaric acid and D-mannaric acid were reported by Hashimoto and coworkers,[5,6] while Kiely and coworkers have prepared a variety of PHPAs from the above hexaric acids plus *meso*-xylaric acid.[7–12] The polyamides derived from D-glucaric acid, as illustrated by a poly(alkylene D-glucaramide) in Figure 1, are of the greatest interest because of the availability and low cost of D-glucose as the direct precursor of D-glucaric acid, a method of preparation that does not require hydroxyl protection- deprotection steps, plus the opportunity to prepare a wide structural variety of polyamides[1–12] that may offer good biodegradability properties.[13] Using ^{13}C NMR techniques, Hoagland studied the reaction pathway for the conversion of both *meso*-galactaric[14] and *meso*-xylaric[15] acid diesters to diamides with a 1° alkylamine, and determined that these esterified aldaric acids are initially lactonized under base catalysis to a five-membered mono-lactone ester which rapidly undergoes aminolysis to an acylic amido-ester. The latter molecule in the basic medium is converted to a five-membered amido lactone which then is ring opened to the final diamide.

In this study we set out to monitor the course of aminolysis of methyl D-glucarate 1,4-lactone (**1**, Figure 2) and ethyl D-glucarate 6,3-lactone (**5**, Figure 3) to *N,N′*-dipropyl-D-glucaramide (**4**) with *n*-propylamine in DMSO-d_6 as models for aminolysis of esterified D-glucaric acid with a primary diamine in methanol, a typical procedure for preparing the poly(D-glucaramides).[11] *n*-Propylamine was our amine of choice because the product diamide was soluble in DMSO. Aminolysis of esterified aldaric acids in DMSO-d_6 avoids transesterification of esterified D-glucaric acid that occurs in methanol,[16] and as shown by Hoagland,[14,15] and is slow enough to allow monitoring of the reaction using NMR techniques. Our first goal was to determine if the amide



Poly(alkylene D-glucaramides)

Figure 1. General structure of a poly(alkylene D-glucaramide).

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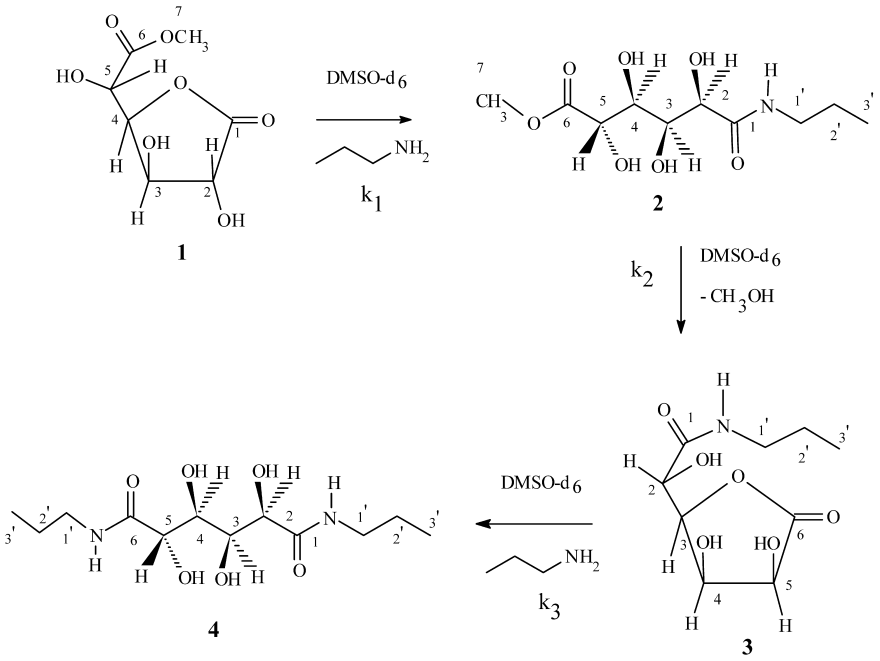

Figure 2. Proposed and elucidated stepwise reaction pathway for the conversion of methyl D-glucarate 1,4-lactone (**1**) with *n*-propylamine to *N,N′*-dipropyl-D-glucaramide (**4**) in DMSO-d_6.

forming mechanism as described by Hoagland for esterified *meso*-galactaric and *meso*-xylaric acids carried over to esterified D-glucaric acid. However, we were to find that using ^{1}H NMR, over ^{13}C NMR, as our primary analytical tool would give more detailed structural information. Since D-glucaric acid is not symmetrical, the ester γ-lactones (1,4 and 6,3) are diastereoisomeric, unlike those of *meso*-galactaric and xylaric acids which are enantiomeric, and would be expected to react at different rates. Consequently, we were also very interested in seeing if we could qualitatively detect rate differences in any of the proposed steps starting from the two different starting ester lactones. A final goal was to determine how much of a role direct aminolysis of the diester played in amide formation as compared to aminolysis of a five-membered lactone.

RESULTS AND DISCUSSION

The ^{1}H and ^{13}C NMR spectra of the starting methyl D-glucarate 1,4-lactone (**1**) and ethyl D-glucarate 6,3-lactone (**5**), and the product *N,N′*-dipropyl-D-glucaramide (**4**) were first recorded in DMSO-d_6. The starting lactone esters **1** and **5** in DMSO-d_6 were then separately reacted with two molar equivalents of *n*-propylamine, typical reaction mixtures being 0.44 M in glucaric ester-lactones **1** and/or **5** and 0.88 M in *n*-propylamine. Reaction progress was then directly monitored by ^{1}H or ^{13}C NMR.

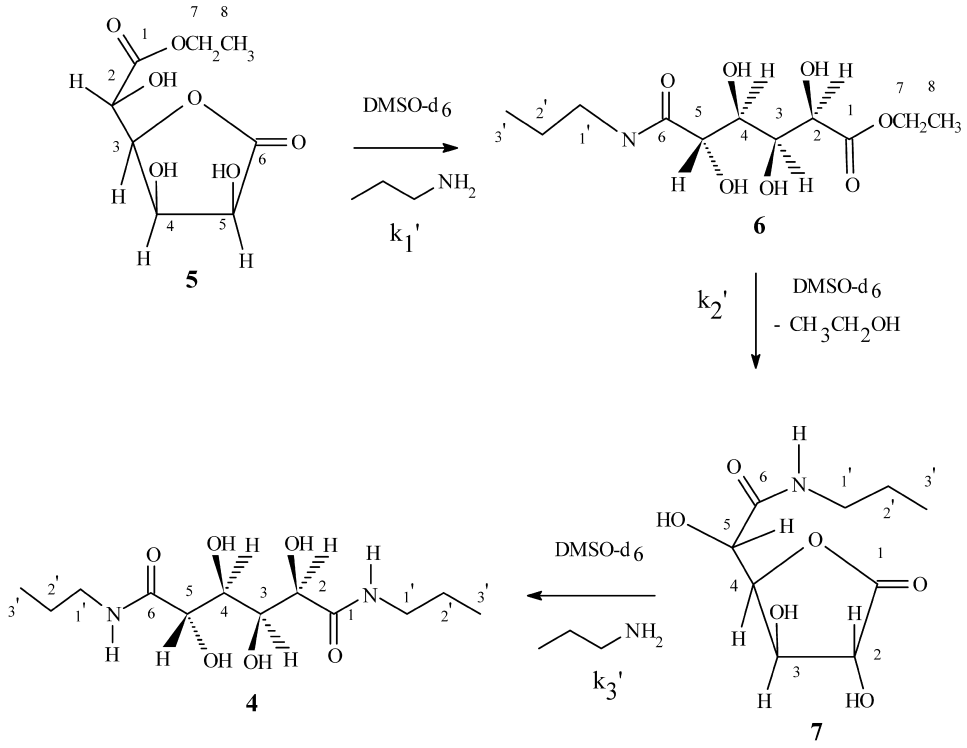

Figure 3. Proposed and elucidated stepwise reaction pathway for the conversion of ethyl D-glucarate 6,3-lactone (**5**) with *n*-propylamine to *N,N′*-dipropyl-D-glucaramide (**4**) in DMSO-d_6.

^{1}H NMR Monitoring of the Aminolysis of 1 and 5 with *n*-Propylamine

Employing ^{1}H NMR monitoring, ring opening of the five-membered lactone ring of **1** and **5** was found to be quite rapid. Figures 4 and 5 show the spectral changes that occur over a 30 minute time period for the above reaction of **1** and **5**, respectively. Initially, the hydroxyl protons (not displayed) are seen as separate signals in the 5.4–6.2 ppm region of the spectra, but over the course of five minutes they undergo rapid proton exchange with the amine and eventually move downfield to *ca*. 5.3 ppm as a broad signal beyond the carbon bonded hydrogens of interest. Hence, some of the downfield peaks in the spectrum taken before five minutes of reaction were masked by a broad hydroxyl hump (*ca*. 4.42 –4.60 ppm). In the early stages of the reactions the downfield (4.2–4.8 ppm range) five-membered ring lactone proton signals diminish rapidly, while some new upfield region signals (3.6–4.2 ppm) began to emerge. These upfield signals are consistent with the formation of the final acyclic diamide (**4**) and acyclic ester amide intermediates (**2** and **6**), Figures 4 and 5.

Peak positions and proton assignments for **1**–**7**, which were facilitated using ^{1}H–^{1}H COSY experiments, are given in Table 1. It is noted that the proton on the carbon adjacent to the ester carbonyl is downfield by about 0.2 ppm to the one adjacent

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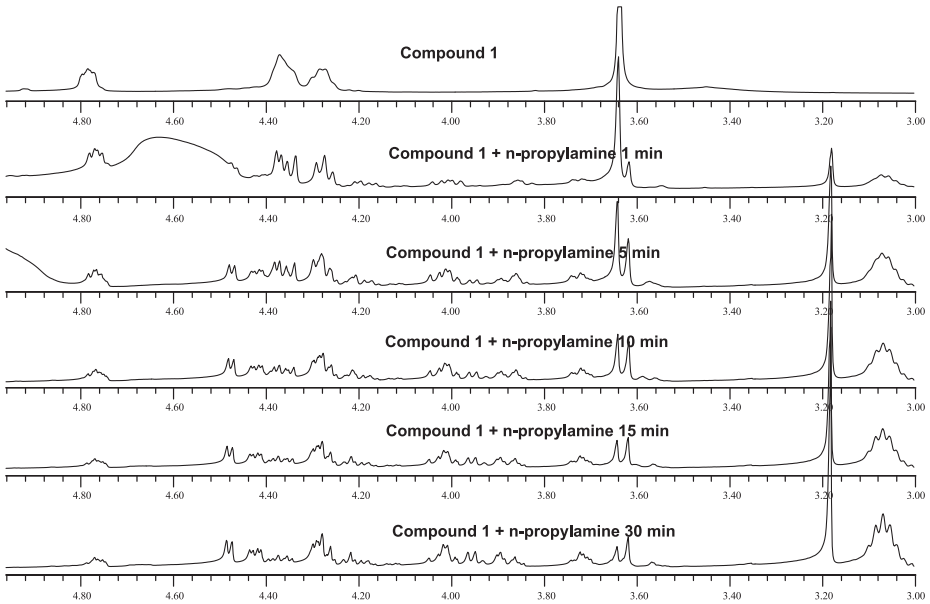

Figure 4. ^{1}H NMR spectra (400 MHz) from the reaction of methyl D-glucarate 1,4-lactone (**1**) with *n*-propylamine (2:1 molar ratio) in DMSO-d_6 over 30 minutes.

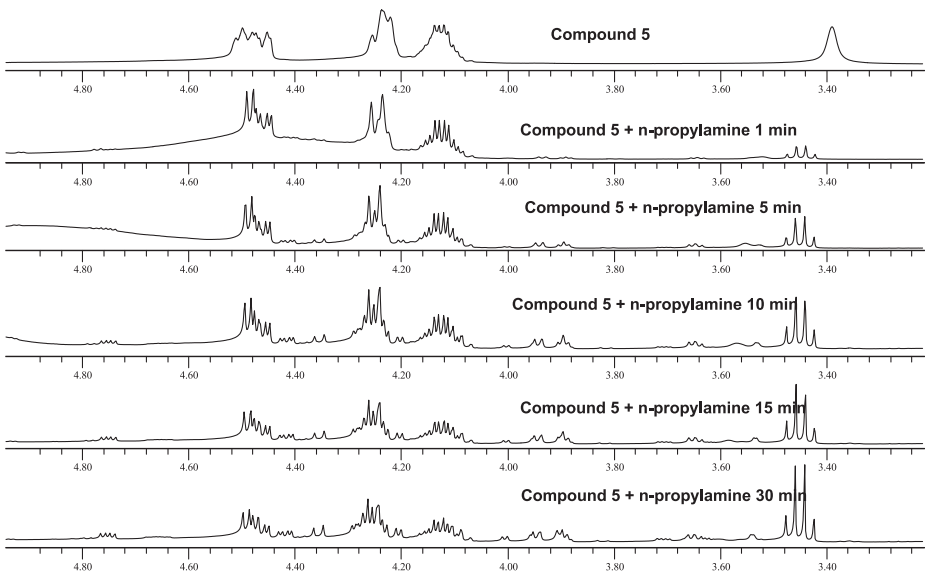

Figure 5. ^{1}H NMR spectra (400 MHz) from the reaction of ethyl D-glucarate 6,3-lactone (**5**) with *n*-propylamine (2:1 molar ratio) in DMSO-d_6 over 30 minutes.

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Table 1. ^{1}H NMR peak positions of the starting material, intermediate species and the final product during the reaction of **1** and **5** *n*-propylamine in DMSO-d_6.

Peak position in ppm downfield from TMS (multiplicity of peaks)				
	1	**2**	**3**	**4**
H-2	4.36(d)	3.94(d)	4.25(b)	3.99(d)
H-3	4.27(dd)	3.86(t)	4.48(d)	3.88(t)
H-4	4.78(dd)	3.68(dd)	4.42(dd)	3.66(t)
H-5	4.34(d)	4.18(d)	4.2(b)	3.92(d)
OCH_3	3.7(s)	3.61(s)		
	5	**6**	**7**	**4**
H-2	4.24(t)	4.2(d)	4.33(b)	3.99(d)
H-3	4.5(d)	3.9(b)	4.42(dd)	3.88(t)
H-4	4.24(t)	3.64(dd)	4.74(dd)	3.66(t)
H-5	4.47(dd)	3.94(b)	4.35(b)	3.92(d)
OCH_2	4.13(q)			
CH_2CH_3	1.22(t)			

to the amide carbonyl. The ester lactone ring proton signals were found to be almost coincidental or slightly downfield by about 0.05 ppm with respect to the corresponding signals from the amide lactone proton signals, but were well enough resolved to allow identification.

The relative intensities, and thus the relative mole fractions, of the individual species were obtained from the integration values from the ^{1}H NMR spectra at different time points. These mole fractions were plotted against reaction time as shown in Figures 6 and 7. In order to ensure that the listed chemical shift values (Table 1) and mole fractions indicated were as accurate as possible, equimolar amounts of starting **1** and **5** were reacted with *n*-propylamine in the same NMR tube with DMSO-d_6 as

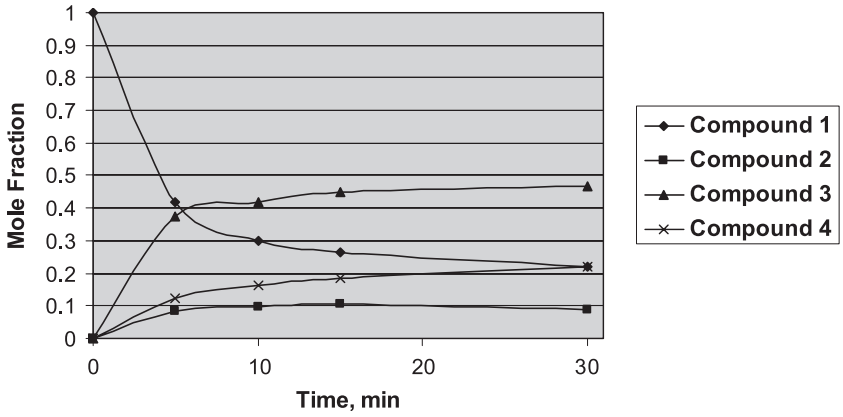

Figure 6. Mole fractions of the individual species during the reaction of **1** with *n*-propylamine.

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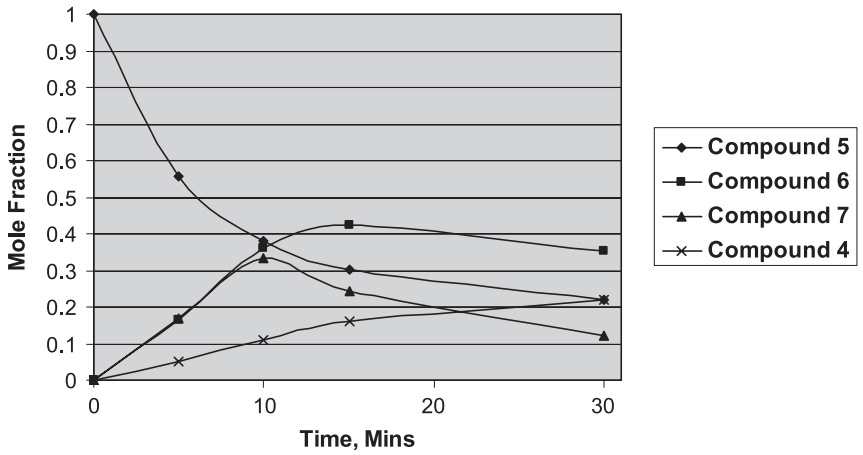

Figure 7. Mole fractions of individual species in the reaction of **5** with *n*-propylamine.

solvent. Although integration of some downfield signals within the first minute of reaction was not possible due to the overlap of the broad hydroxyl hump with those signals, the spectra from the subsequent time points were better resolved and thus could be used for comparing relative molar amounts of reaction mixture components.

Evaluation of the mol fraction vs reaction time plots in Figures 6 and 7 provides some insight into the relative reaction rates and stabilities of the starting ester lactones and proposed intermediates shown in Figures 2 and 3. The first proposed step is ring opening aminolysis of the ester lactones **1** and **5**. A look at the initial slopes for the aminolysis of **1** and **5** to the resultant acyclic ester amides **2** and **6** suggests that D-*gluco* ring lactone ester **1** undergoes ring opening somewhat faster than the L-*gulo* ring lactone ester **5**. It is also clear from a comparison of the relative molar amounts of the acyclic ester amides **2** and **6** that the mole fraction of **2** remains low (*ca*. 0.1) throughout the reaction, compared to that of **6**, which rises to *ca*. 0.4 over fifteen minutes before beginning to drop slightly. These results suggest that ester amide **2** is converted to lactone amide **3** considerably faster than ester amide **6** is converted to lactone amide **7**. The observed faster overall conversion of **1** to **3** compared to that of **5** to **7** should also be reflected in a faster rate of methanol over ethanol production from the lactonization of the precursor ester amides **2** and **6**. In fact, methanol was produced faster than ethanol during the first five minutes with the molar ratio being on average about 1.0:0.85. As the reaction continued, this ratio gradually approached 1.0:1.0.

Given the above results, and noting that the overall rate of formation of the final diamide **4** (Figures 6 and 7) is essentially the same from both pathways, it is concluded that the third step, aminolysis of a lactone amide, is faster for **7** to **4** than for **3** to **4**.

Our primary interests in these two reaction pathways have been to identify the intermediates formed during the conversions, and to determine if there is any observable qualitative difference in the rate of formation and subsequent ring opening of the D-*gluco* (**1** and **7**) versus the L-*gulo* (**5** and **3**) five-membered lactone rings involved in overall conversion to product diamides. Although no attempt has been made to determine actual rate constants for the individual reactions, based on the mole fraction

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versus reaction time data obtained, we have classified the individual reactions as being either ''fast'' or ''slow'' in order to roughly compare the individual steps within a single reaction pathway. From the data in the plots shown in Figures 6 and 7, for conversion of **1** to **4**, the relative rates of steps 1–3 are fast, fast and slow, respectively; for the conversion of **5** to **4** (Figure 3), the relative rates of steps 1–3 are slow, slow and fast, respectively. Since **4** is formed at comparable rates from **1** and **5**, a determination of the actual individual rate constants would be in order to appreciate the kinetics of each step, but that is beyond the scope of this report.

We have also compared the relative rates of the corresponding steps in the two pathways and have included identifying rate constants in Figures 2 and 3; k_1 and k_1', k_2 and k_2', k_3 and k_3' corresponding to the three steps for the separate pathways. Thus in step 1, the D-*gluco* configured five-membered ring undergoes aminolysis faster than does the L-*gulo* five-membered lactone ring ($k_1 > k_1'$), and similarly in step 3 ($k_3' > k_3$). In parallel with these results is the observation that $k_2 > k_2'$, signifying that formation of the more stable (less reactive) L-*gulo* five membered lactone amide **3** is faster than that of the less stable (more reactive) D-*gluco* five membered lactone amide (**7**). Thus, the differences in reaction rates we observe in each of the three steps for these conversions is governed by D-*gluco* five membered ring lactones being more reactive (less stable) and less easy to form than the less reactive (more stable) L-*gulo* five-membered lactone ring.

To see what comparisons had been previously noted concerning relative reactivities (stabilities) and ease of formation of D-*gluco* versus L-*gulo* five-membered lactone rings, we looked to previously reported NMR studies on the equilibrium composition of D-gluconic and D-gulonic acids and their lactones in D_2O.[17] The D-gulonic acid composition is dominated by the five-membered 1,4-lactone ring structure (87%), with the remaining (13%) as the acyclic acid. In contrast, the D-gluconic acid composition contained minor amounts of the five and six-membered ring lactones, 17% and 18%, respectively, with the acyclic acid being most abundant (66%). The significantly greater percentage of five-membered *gulo* lactone over the *gluco* lactone is a measure of the higher stability of the *gulo* lactone structure. These earlier findings are in keeping with our observations that the L-*gulo* lactone ester (**5**) and amide (**3**) are more stable than the D-*gluco* ester (**1**) and amide (**7**).

^{13}C NMR Monitoring of the Aminolysis of 1 and 5 with *n*-Propylamine

We initially charted the aminolysis course of ester lactones **1** and **5** with *n*-propylamine in DMSO-d_6 using ^{13}C NMR in the manner that Hoagland described for the aminolysis studies of diethyl galactarate[14] and diethyl xylarate[15] with ethanolamine. However, the shortcoming of ^{13}C NMR for this kind of study is that the accumulation of free-induction-decays for ^{13}C NMR is relatively long and consequently this technique does not provide as much information in the early stages of the reaction as do ^{1}H NMR methods. Nonetheless, we carried out aminolysis/ ^{13}C NMR studies with both **1** and **5** to determine if their mode of aminolysis was consistent with Hoagland's reports.[14,15] Whereas both of these starting diesters are *meso* compounds, the intermediate ester lactones, ester amides, and lactone amides are racemic mixtures, and generate less complex NMR spectra than the corresponding diastereoisomeric mixtures

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Table 2. Relative ^{13}C NMR intensities from reaction species during reaction of *n*-propylamine with methyl D-glucarate 1,4-lactone (**1**) in DMSO-d_6 at 31°C.

Cpd			0 min	10 min	30 min	1 h	2 h	4 h	6 h	10 h	12 h	24 h	48 h
1	C-6	175.38	6.02	2.48									
	C-1	171.19	11.89	2.52									
	C-4	78.68	16.80	4.61	1.41								
	C-2	73.13	13.92	6.75	0.96								
	C-3	71.91	20.37	5.96	1.65								
	C-5	68.51	23.09	6.89	1.99								
	C-7	51.46	7.91	4.07	1.64								
2	C-6	175.50				0.90	1.04	0.87	0.81	0.68	0.74		
	C-1	173.92					0.79						
	C-5	73.51		2.22	1.08	1.10	1.19	0.77	1.06				
	C-2	72.76		2.11	1.99	1.31	0.93						
	C-4	71.49		2.36	2.02	1.39	1.03	0.78	0.82				
	C-3	70.79		1.69		1.04	1.29						
	C-7	51.10			1.68	1.33	0.79						
3	C-6	170.64			0.92	1.33	1.09	0.67					
	C-3	79.95		1.65	1.62		1.20						
	C-5	71.18			0.82	1.29	1.80	0.96					
	C-4	70.18		6.30				5.70					
	C-2	69.91		2.91	2.44	1.45	1.00	0.66	0.75				
4	C-6	173.22		1.16	2.35	3.24	3.24	2.61	2.16	1.34	1.12	1.20	1.50
	C-1	172.22			1.48	1.86	2.79	3.23	4.06	4.14	4.06	4.25	3.35
	C-5	73.36		1.29	2.69	3.27	3.89	3.98	4.24	4.56	4.54	4.86	3.90
	C-2	73.06		2.20	2.93	3.61	3.94	3.82	4.52	4.79	4.93	5.02	3.94
	C-4	71.6		1.08		2.69	3.50	3.78	4.75	5.35	5.39	5.75	4.59
	C-3	70.42			9.18	8.81	7.31	5.34	5.83	5.70	5.40	5.40	7.30
	C-1′	40.04		8.42	10.73	11.03	10.66	9.88	10.35	10.57	10.29	10.51	5.24
	C-2′	22.3		3.31	4.39	4.19	4.13	4.36	5.12	5.79	5.81	6.14	5.50
	C-3′	11.25		6.76	6.01	6.70	7.18	8.23	10.24	11.42	11.77	12.34	9.96

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Table 3. Relative ^{13}C NMR intensities from reaction species during reaction of *n*-propylamine with ethyl D-glucarate 6,3-lactone (**5**) in DMSO-d_6 at 31°C.

Cpd			0 min	1 min	5 min	15 min	30 min	1 h	2 h	4 h	6 h	8 h	10 h
5	C-1	175.8	4.16	3.44	0.99			0.43					
	C-6	170.04	3.31	2.51									
	C-3	80.1	9.84	5.4	2.11	1.03	0.9	0.67					
	C-5	70.15	15.85	9.02	5.87								
	C-2	69.6	15.5	6.19	1.69								
	C-4	69.24	13.34	4.47	1.84								
	C-7	60.32	8.66	5.98	1.52								
	C-8	13.87	8.41	5.43	1.63								
6	C-1	175.55			1.01	1.38	1.69	0.95	0.84				
	C-6	172.5			1.29		0.59						
	C-5	72.9		3.15	0.98								
	C-2	72.36		2	2.05	1.29	0.72						
	C-4	71.12			1.06	1.41	0.88						
	C-3	71.84		2.03	1.04	3.67							
	C-7	59.98			2.54	1.56	0.61						
	C-8	14.03			1.85	1.85	0.86						

7	C-6	172.7			1.9		0.59					
	C-1	170.7			1.74	1.85	1.53	1.36	1	0.64	0.7	0.61
	C-4	79.95			2.55	2.7	2.85	1.99	1.37	0.98	0.93	0.86
	C-2	73.54			2.71	2.89	2.53	1.8	1.53	1.27	0.85	0.78
	C-5	72.18		1.74	1.88	2.81	2.77	2.12	1.67	1.02	0.89	0.73
	C-3	71.27		2.09	2.49			0.44	0.61		0.63	0.61
	C-1′	41.95		5.15	3.05	2.35	2.47					
	C-2′	23.3		2.93	1.65	1.15	1.57	0.75				
	C-3′	11.03			0.75		0.51	4.43				
4	C-6	173.22			1.96	2.99	3.99	3.39	4.45	4.8	5.3	5.29	5.74
	C-1	172.22			1.21	2.96	3.29	3.73	5.02	5.33	4.95	4.67	5.21
	C-5	73.36			2.9	4.34	6.25	6.68	7.56	7.86	7.64	7.66	8.25
	C-2	73.06			4.34	5.45	5.3	5.1	5.65	6.32	6.05	6.06	6.59
	C-4	71.6			3.22	4.86	5.36	5.58	5.88	6.08	6.01	6.01	6.47
	C-3	70.42			4.76	6.78	7.11	6.99	6.69	6.57	6.33	6.3	6.65
	C-1′	40.04		5.37	6.2	7.47	7.59	8.89	9.4	9.7	9.58	9.61	10.25
	C-2′	22.3		3.74	4.27	6.58	9.08	9.97	11.83	11.35	11.29	11.41	12.06
	C-3′	11.25		7.19	10.73	15.31	16.5	16.71	16.95	17.42	17.24	17.27	18.17

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Table 4. Relative ^{13}C NMR intensities from reaction species during reaction of *n*-propylamine with **8** in DMSO-d_6 at 31°C.

Cpd			30 min	2 h	4 h	6 h	8 h	10 h	12 h	16 h	44 h
4	171.68	7.27	4.57	7.13	7.86	6.17	4.91	3.07	3.02	3.63	
	72.40	42.77	26.58	23.39	26.70	30.30	28.36	28.47	26.39	14.55	
	51.73	49.96	11.16	6.11	6.24	4.86	4.93	4.06	3.33	2.66	
	174.76			0.69	1.17	1.41	1.87	2.30	2.06	1.02	
	74.33			1.49	2.22	2.22	2.91	3.15	3.64	2.14	
5	22.33				1.11						
	20.42			2.64	4.02	4.11	4.60	4.45	4.03	2.31	
	171.74					0.99	1.36	1.93	1.88	8.70	6.38
	72.40										21.40
6	39.99		2.23	3.57	5.26	5.06	5.27	6.95	8.97	11.75	9.82
	22.33			0.90	1.12	3.86	7.83	12.05	14.82	14.96	14.81
	11.20			1.03	1.21	1.47	1.49			11.29	20.58

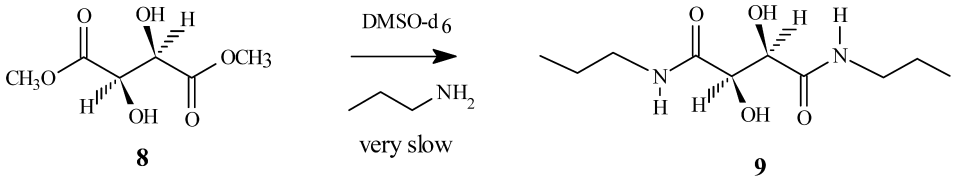

Figure 8. Direct, very slow aminolysis of dimethyl L-tartrate (**8**) with *n*-propylamine to *N,N′*-dipropyl-L-tartramide (**9**) in DMSO-d_6.

formed from D-glucarate. Hoagland observed the racemic intermediate ester amide formed from diethyl xylarate[15] but not from diethyl galactarate.[14] In our ^{13}C NMR studies, we observed signals for all the structures shown in Figures 2 and 3, consistent with the results we obtained from the ^{1}H NMR studies, including production of substantial amounts of the corresponding alcohol within the first 30 minutes. The ^{13}C NMR data are found in Tables 2–4.

Aminolysis of Dimethyl L-Tartrate Compared to 1 and 5

A final issue to be addressed for the aminolysis mechanism of esterified D-glucaric acid was the contribution that direct aminolysis of the ester carbonyl makes in this reaction. To that end we used dimethyl L-tartrate as a model of an α,α′-dihydroxy esterified aldaric acid that cannot form a five-membered lactone ring and experience aminolysis rate enhancement by such a mechanism. Ogata and coworkers showed many years ago that dimethyl L-tartrate (**8**)[1] and diethyl galactarate[2] undergo aminolysis at enhanced rates compared to aliphatic esters lacking an alpha hydroxyl group. It should also be noted that this reaction proceeds much faster in polar protic solvents such as methanol than in polar aprotic solvents such as DMSO or DMF. These workers postulated that this rate enhancement originated from the presence of electron withdrawing groups (e.g., SCN, CN, or OH) on the α,α′-carbons of the diester which further polarized the ester carbonyl group making it more susceptible to nucleophilic attack by an amine function.[18] However, they did not invoke the five membered lactone ring intermediate that Hoagland identified.[14,15] We carried out a simple experiment wherein dimethyl L-tartrate (**8**) was treated with two molar equivalents of *n*-propylamine in DMSO-d_6 and monitored the progress of the aminolysis by ^{1}H NMR. Over 30 minutes there was essentially no conversion to *N,N′*-dipropyl L-tartramide (**9**, Figure 8) as compared to *ca*. 50% conversion of **1** or **5** to *N,N′*-dipropyl D-glucaramide (**4**) during the same time period. Consequently, it appears very likely that direct aminolysis of esterified D-glucaric acid plays a very minor role in conversion to diamides or the polyamides of interest (Figure 1).

EXPERIMENTAL

General methods. Dimethyl L-tartrate and *n*-propylamine were obtained from Aldrich and were used without further purification. DMSO-d_6 was from Cambridge Isotope Laboratories and contained 1% v/v TMS. NMR spectra were recorded using a

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400 Varian Unity Plus spectrometer. ^{13}C NMR spectra were recorded with proton decoupling, a 52.8° pulse width, 2 s repetition rate and accumulation of at least 500 transients. The fids obtained were processed using the Mestre-C program Version 2.3a.[19] Data was collected and analyzed using an Excel spreadsheet program. The spectra of the reactants were obtained prior to addition of the amine. The spectra of products were recorded independently. Peak positions reported are relative to the solvent signal. Solvent evaporations were carried out at reduced pressure.

General procedure for NMR monitoring aminolysis of 1 and / or 5. The aminolysis of **1** or **5** was typically carried out and monitored in a ^{1}H or ^{13}C NMR tube. Typically, a spectrum of the starting ester lactone (0.44 M) in 1 mL of DMSO-d_6 was obtained at 31°C. The sample tube was then removed from the instrument and the appropriate 2 molar amount of *n*-propylamine was pipetted into the tube which was then vigorously shaken by hand. The NMR tube was then inserted into the instrument and spectra acquired at specific time intervals. The scan rate for both ^{1}H or ^{13}C NMR spectra was 16 scans/min, with ca. 1 min processing at designated time points. Aminolysis of a solution of **1** and **5** was carried out as above, but with each at a concentration of 0.22 M.

***N,N′*-Dipropyl-D-glucaramide (4).**[20] To D-glucaro-1,4:6,3-dilactone[5] (0.175 g, 1 mmol) dissolved in methanol (1 mL) was added *n*-propylamine (0.17 mL, 2 mmol). Although a solid white product began to precipitate almost immediately, the reaction mixed was stirred at room temperature for an additional 3 h. More precipitation was seen to occur. The precipitate was isolated by filtration, washed methanol (5 mL), and then dried under vacuum at room temperature for 24 h; yield. 0.281g, 96% yield, mp 162°C, lit.[20] mp 172°C.

***N,N′*-Dipropyl-L-tartramide (4).**[21] To a stirred solution of dimethyl L-tartrate (0.206 g, 1.15 mmol) in methanol (5 mL) was added *n*-propylamine (0.2 mL, 2.4 mmol) and the reaction allowed to proceed overnight. Solvent evaporation yielded the product as a white solid, which was washed with ethyl acetate, and then dried under vacuum at room temperature for 24 h: yield 0.212 g, 90.7%; mp 201°C.

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