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THE FORMATION OF INTERMEDIATE LACTONES DURING AMINOLYSIS OF DIETHYL GALACTARATE

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ABSTRACT

The aminolysis of diethyl galactarate has been found to proceed through intermediate γ-lactones. In dimethyl sulfoxide at 31°, the 1,6-diester is quickly converted into the 6-ester 1,4-lactone through base catalysis, and this lactone reacts with a primary amine to yield a 6-ethyl galactaric 1-amide that rapidly affords the 6,3-lactone, which reacts with the amine to give the galactaric diamide. The reaction sequence was established by ^{13}C-n.m.r. spectroscopy, which suggested competitive, consecutive, second-order kinetics in which $k_1 = k_2$ can be applied.

INTRODUCTION

Galactaric acid is readily obtained by the oxidation of lactose[1], a sugar available in large quantities from the huge volume of whey generated in the production of cheese. This laboratory is committed to finding new outlets for the lactose that is currently being discarded by cheese manufacturers.

Diethyl galactarate[2] has great reactivity towards amines, and has been polymerized with diamines under mild conditions[3,4]. Attempts in this laboratory to esterify lactobionic acid revealed how readily lactones can be formed[5]. As aminolysis of diethyl galactarate[3] occurs as readily as aminolysis of sugar lactones, the formation of intermediate lactones was suspected in the latter reaction. ^{13}C-N.m.r. spectroscopy was profitably employed to identify individual carbon atoms in the complex reaction.

RESULTS AND DISCUSSION

^{13}C-N.m.r. spectra were recorded for diethyl galactarate (**1**) and for 6-ethyl galactarate-1,4-lactone (**2**). Assignments for carbon atoms 2, 3, and 5 (see Table I) were made with the aid of substitutent δ-effects subsequently found for various monolactone-monoamide intermediates. The ease of lactonization of diethyl galactarate in dimethyl sulfoxide-d_6 in the presence of either H_2SO_4 or triethylamine was apparent from the ^{13}C-n.m.r. spectra, which showed that, after 24 h at 31°, ~50%

TABLE I

RELATIVE INTENSITIES OF CARBON-13 RESONANCES OF REACTION SPECIES DURING THE 2-AMINOETHANOLYSIS OF DIETHYL GALACTARATE IN Me_2SO-d_6 AT 31°

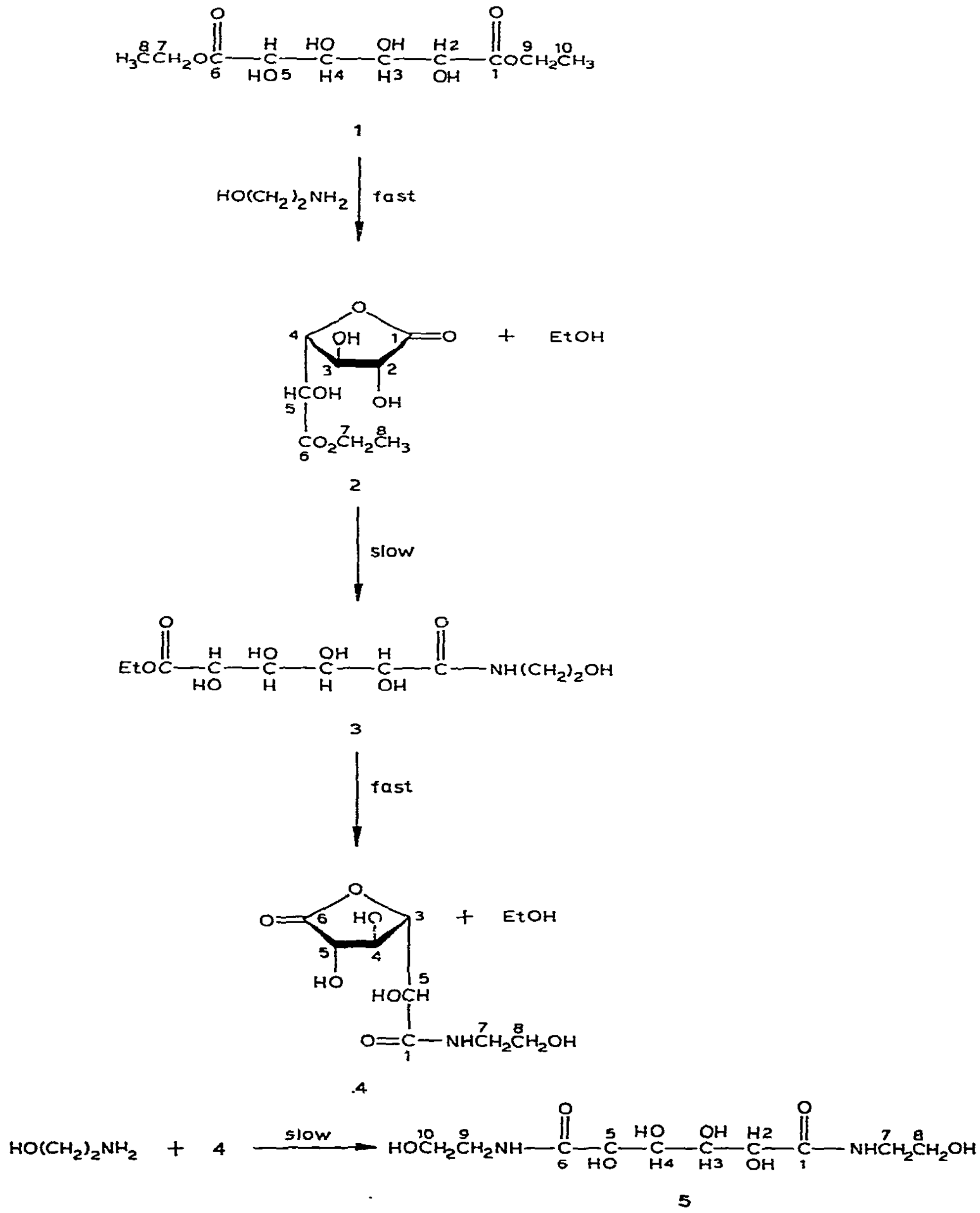
Compound	*Species*	δ *(p.p.m.)*	*Time (min)* 1	10	22	52	112	174	267	360	540	780	1080	1500
1	C-1 (6)	173.67	35	0										
	C-2 (5)	71.25	50	13	0									
	C-3 (4)	70.15	56	18	0									
	C-7 (9)	60.15	60	20	0									
2	C-6	174.13	0	14	11	11	0							
	C-1	171.46	0	16	16	12	0							
	C-4	80.48	0	30	30	23	13	12	0					
	C-2	73.59	0	32	34	24	17	0						
	C-3	72.29	0	32	29	23	14	9	0					
	C-5	67.36	0	29	31	20	13	11	0					
	C-7	60.86	0	36	34	22	15	10	0					
4	C-1	174.32			0	9	14	13	13	9	0			
	C-6	171.14			0	9	12	11	11	8	0			
	C-3	80.22			0	14	17	17	15	12	13	9	0	
	C-5	73.72			0	17	18	21	15	14	12	10	0	
	C-4	72.49			0	12	16	16	14	13	13	10	0	
	C-2	68.07			0	13	14	18	15	10	12	8	0	
	C-8	59.69		0	9	16	18	20	18	17	17	14	0	
5	C-1 (6)	173.54				0	16	26	31	41	49	53	49	46
	C-2 (3) (4) (5)	70.73			0	12	26	41	51	59	73	80	80	86
	C-7 (9)	41.18			0	20	27	33	38	50	58	53	52	60
	C-8 (10)	59.95				0	19	27	27	43	55	55	59	56
[a]	C-1	63.33	62	48	53	40	34	30	25	25	21	16	15	10
	C-2	44.17	54	52	56	46	35	35	31	24	20	19	15	0

[a] 2-Aminoethanol, $HO\underset{1}{CH_2}\underset{2}{CH_2}NH_2$.

of the ester had lactonized. Base catalysis of lactonization is not so well known as acid catalysis[1].

When diethyl galactarate reacted with octylamine in the molar ratio of 1:2 in Me_2SO-d_6 for 24 h at 31°, the diamide crystallized. The spectra recorded during the course of the reaction initially showed the starting materials, then the appearance of the ester-lactone (**2**), and then the octylamide-lactone; at no point did an ester-amide appear. The spectrum of the diamide was obtained by heating the crystalline mass to 90° in the sample tube, to effect dissolution.

To monitor the aminolysis of diethyl galactarate more completely, 2-aminoethanol was selected, in order to afford a soluble reaction-product. The spectrum of an authentic specimen of galactaric bis(2-hydroxyethylamide) (**5**) was recorded, and assignments were facilitated by the symmetry of the molecule and by the coincidence of the shifts for carbon atoms 2, 3, 4, and 5 (see Table I). The relative intensities of the carbon resonances in the ^{13}C-n.m.r. spectra acquired during 15 h are shown in Table I. Diethyl galactarate (**1**) disappears within ~20 min. Its 6-ester monolactone (**2**) appears after 1 min, and is then consumed by reaction with 2-aminoethanol within 300 min, to give compound **4**, which can be assigned the structure of the 1-amide-6,3-lactone. Because lactonization of the ester is so much faster than amino-



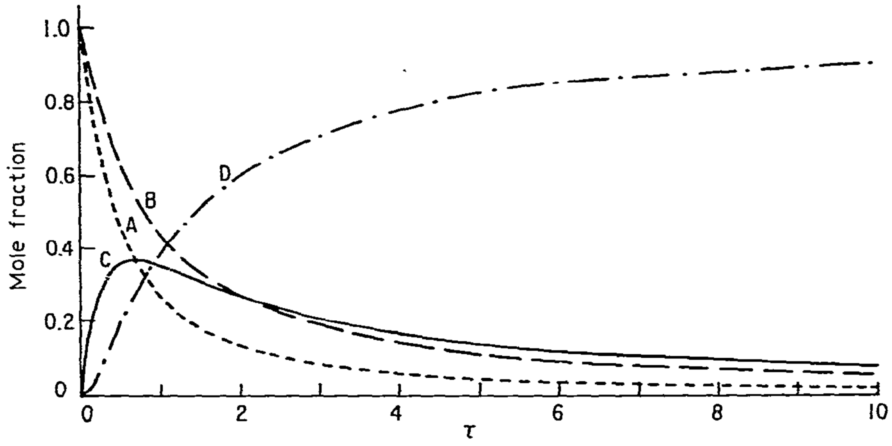


Fig. 1. Theoretical plots for reactants in a competitive, consecutive, second-order reaction in which $k_1 = k_2$, based on the treatment by Frost and Schwemer[6]. [A = 2-aminoethanol (A/Ao); B = 6-ethyl galactarate-(1,4-lactone) (2) (B/Bo); C = galactaric 1-amide-6,3-lactone (4) (C/Bo); and D = galactaric 1,6-diamide (5) (D/Bo), where Ao = initial concentration of 2-aminoethanol = 2 Bo, and Bo = initial concentration of 6-ethyl galactarate-1,4-lactone = 0.13M. $\tau = k$ Bot and $k = k_1 = k_2$, the rate constants for aminolysis of lactones **2** and **4**.

$$-k\mathrm{Bodt} = -e^2 \int_{\mu-2}^{\mu} \frac{e^{\mu} d\mu}{\mu}, \text{ where } \mu = 2 - \ln (\mathrm{B/Bo}).]$$

lysis of the lactone, the ester-amide (3) does not appear in the spectra. Indeed, formation of the amide-lactone (4) from the ester-lactone (2) may possibly be a concerted reaction. The amide-lactone has all been used up after 1000 min, leaving the sole spectrum of the diamide (5), which starts to appear after 20 min.

The appearance of ethanol during the reaction can now be understood as reflecting lactonization. Ogata *et al.*[3] used the production of ethanol to measure the reaction rates for the aminolysis of diethyl galactarate. These rates are appropriate for lactonization, especially if the simplifying assumption is made that the ester-amide 3 lactonizes at a rate similar to that for the diester **1**. The overall scheme for aminolysis is shown in the reaction diagram. Because the times for accumulation of free-induction decays (f.i.d.s) were very long, accurate kinetic information cannot be obtained from the spectra. However, the appearance of the product can be approximately fitted to a second-order equation in which the rates for aminolysis of **2** and **4** are similar. Idealized progress curves are presented in Fig. 1. They result from the equations developed by Frost and Schwemer[6] for competitive, consecutive, second-order reactions. The intermediate amide-lactone (C, in Fig. 1) reaches a theoretical, maximal concentration at $\tau = 0.6739$ at mole fraction Bo/e. The data in Table I suggest that this maximum occurs at ~150 min, a time that provides an estimate of the rate constant of ~0.4 $\mathrm{mol^{-1}.min^{-1}}$. The diester **1** is rapidly converted into the ester-lactone **2**, which decays within 5 h (see curve B in Fig. 1). The amide-lactone **4** peaks near 150 min (see Table I), with a theoretical, maximum mole fraction of

Bo/e (see curve C, Fig. 1). After 5 h, formation of the diamide follows second-order kinetics.

The data indicate that aminolysis of diethyl galactarate proceeds through intermediate lactones; this explains the observation of Ogata *et al.*[3] that this diester exhibits greater reactivity towards amines than either diethyl tartrate or diethyl adipate. Lactones of sugar acids are well known to react readily with amines[7,8].

The polymerization of diethyl galactarate with ethylenediamine was also observed to proceed through intermediate lactones. The carbon resonances of both the ester-lactone **2** and the amide-lactone appeared in, and then disappeared from, ^{13}C-n.m.r. spectra obtained over similar periods of time. The polymer precipitated from solution.

When the hydroxyl groups of diethyl galactarate are protected with isopropylidene groups, the rate of aminolysis of the ester is greatly lessened, and the ester requires several days at 60° to form a polymer with a diamine; this was to be expected, as lactonization is prevented when appropriate hydroxyl groups are made unavailable through isopropylidenation.

EXPERIMENTAL

Materials and methods. — Diethyl galactarate, 6-ethyl galactarate-1,4-lactone, and diethyl 2,3:4,5-di-*O*-isopropylidenegalactarate were prepared by known methods[1]. Aminolysis of diethyl galactarate[2] was performed in refluxing methanol according to Ogata *et al.*[3].

Spectra were recorded by using a 15.04-MHz field (JEOL FX60 Q*) with proton-noise decoupling, a 57° pulse-width, a 2-s pulse repetition-rate, and accumulation of 500 transients. The solutions in Me$_2$SO-d_6 were 0.13M in diethyl galactarate, and 0.26M in monoamine or 0.13M in diamine, and were maintained at 31°. Data points (8k) were used to collect f.i.d.s, and an analysis program normalized the stacked f.i.d.s. The spectrum of diethyl galactarate was recorded prior to addition of an amine. The spectra of products were obtained for independent preparations thereof. Carbon-13 shift assignments are given in Table I.

Galactaric bis(octylamide). — A mixture of diethyl galactarate[2] (2.66 g, 10 mmol), octylamine (1.29 g, 20 mmol; Eastman*), and absolute methanol (25 mL) was boiled under reflux, with stirring, for 16 h. The white material that separated on cooling was collected, washed with ether and petroleum ether, and dried in a stream of N$_2$; yield 2.55 g (84%); ν_{max} 1615 (Amide I) and 1540 cm^{-1} (Amide II).

Anal. Calc. for C$_{22}$H$_{44}$N$_2$O$_6$: C, 61.07; H, 10.26; N, 6.48. Found: C, 60.99; H, 10.26; N, 6.30.

Galactaric bis[(2-hydroxyethyl)amide]. — A solution of diethyl galactarate[2] (2.66 g, 10 mmol) and 2-aminoethanol (1.22 g, 20 mmol; Aldrich) in dimethyl

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*Reference to a brand or firm name does not constitute endorsement by the U.S. Department of Agriculture over others of a similar nature not mentioned.

sulfoxide (50 mL; Aldrich) was kept for 24 h at room temperature, and poured into acetone (200 mL); the precipitate was collected, washed with ether and petroleum ether, and dried in a stream of N_2; yield 2.48 g (84%); ν_{max} 1625 (Amide I) and 1545 cm^{-1} (Amide II).

Anal. Calc. for $C_{10}H_{20}N_2O_8$: C, 40.52; H, 6.81; N, 9.46. Found: C, 40.25; H, 6.29; N, 9.31.

Poly(galactaric 1,6-ethylene-1,6-diamide). — A mixture of diethyl galactarate[2] (13.3 g, 50 mmol), ethylenediamine (3.0 g, 50 mmol; Eastman, redistilled), and absolute methanol (100 mL) was boiled, and stirred, under reflux for 16 h, and then cooled. The white precipitate was collected, washed with ether and petroleum ether, and dried in a stream of N_2; yield 10.6 g (91%); ν_{max} 1640 (Amide I) and 1540 cm^{-1} (Amide II).

Anal. Calc. for $(C_8H_{14}N_2O_6)_n$: C, 41.03; H, 5.98; N, 11.97. Found: C, 40.74; H, 6.65; N, 11.20.

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