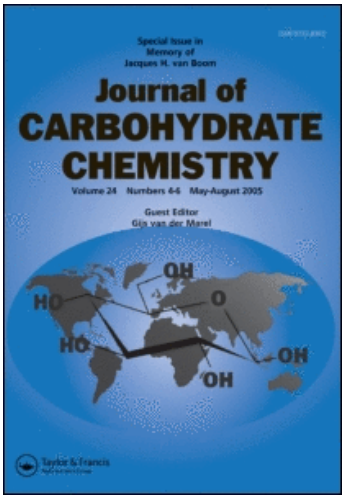

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An NMR Study of the Equilibration of d-Glucaric Acid with Lactone Forms in Aqueous Acid Solutions

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An NMR Study of the Equilibration of D-Glucaric Acid with Lactone Forms in Aqueous Acid Solutions

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The aqueous solution equilibration of D-glucaric acid with its lactone forms was studied by NMR with and without acid catalysis. The kinetics of the approach to equilibrium were simulated, and approximate equilibrium and rate constants were obtained.

Keywords D-Glucaric acid, Lactones, Equilibration, NMR, Kinetic modeling

INTRODUCTION

D-Glucaric acid is the chiral aldaric acid produced by direct oxidation of D-glucose,[1,2] and is of renewed interest as a potentially large-scale chemical building block for synthetic polymers and other potential products.[3]

Esterified D-glucaric acid serves as a convenient co-monomer with a variety of diamines to make polyhydroxypolyamides (PHPAs) of varying structures, molecular weights, and properties.[4–6]

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Under the basic conditions of a typical polymerization in alcohol solution, [7] esterified D-glucaric acid is composed of an equilibrium mixture of alkyl D-glucarate 1,4- and 6,3-lactones, and dialkyl D-glucarate,[8] and possibly a very small amount of D-glucaro-1,4:6,3-dilactone. The results presented here are concerned with the equilibrium behavior of D-glucaric acid in aqueous acid solution.

D-Glucaric acid in aqueous solution exists as an equilibrium mixture of the acyclic compound (**1**); two monolactones, D-glucaro-1,4-lactone (**2**) and D-glucaro-6,3-lactone (**3**); and the dilactone D-glucaro-1,4:6,3-dilactone (**4**) (Fig. 1).[9–11]

A study by paper chromatography demonstrated that elevated temperatures favored the formation of **4** and that acid resin catalyzed equilibration.[10] It was shown that the amount of **3** present at equilibrium was slightly greater than the amount of **2** and it was concluded that reciprocal equilibration of the monolactones **2** and **3** occurred via the acyclic species, **1**, rather than via the dilactone, **4**, which was not detectable except at elevated temperatures. A study of conformations of the lactones noted that **1** lactonized first to yield **3** and that **2** formed more slowly than **3** under neutral conditions.[11]

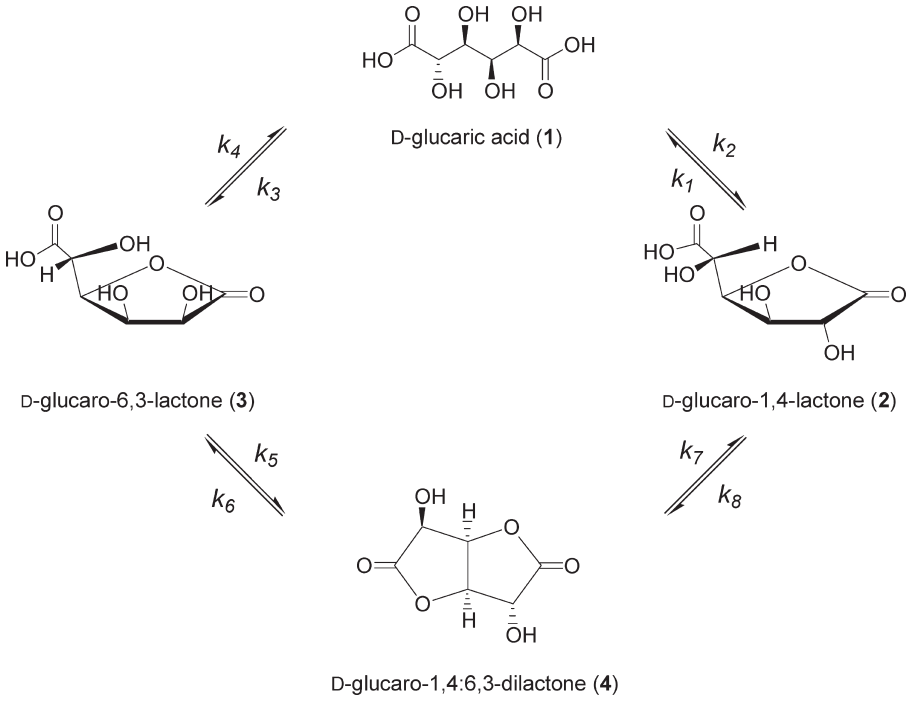

Figure 1: Equilibration of D-glucaric acid and D-glucarolactones.

We now report a study by NMR of the equilibration of acyclic D-glucaric acid with its lactones in aqueous solution with and without acid catalysis, and modeling of the kinetics of the process.

RESULTS AND DISCUSSION

The assignments of the NMR spectra in D_2O of **1**–**4** are given in Table 1; these differ slightly from reported values.[11] The spectrum of the equilibrated mixture contains signals from all four species and, because this results in signal overlap, where possible, single signals were selected for integration as representative of each species; 4.00 ppm (H-4, **1**), 5.15 ppm (H-4, **2**), and 5.49 ppm (H-4, **4**) were separated to baseline to permit accurate integration. In the case of **3**, there was no signal that was sufficiently well resolved because all signals fall within a region of the spectrum that contains three signals from **2** and one signal from **4**. An additional problem noted was that, in spectra where less than one molar equivalent of DCl was added, the HOD peak also occurred in this region. It was therefore only possible to measure **3** when one or more molar equivalents of DCl were present. The measurement was achieved by integration of the entire region and subtraction of the theoretical value of the integrals of the overlapping signals (Fig. 2).

All experiments were carried out in D_2O using **2** and **4** as starting materials. The equilibration was investigated in the presence of 0, 0.25, 0.5, 0.75, 1.0, and 1.5 molar equivalents of strong acid (DCl). This corresponded to 0, 0.1, 0.21, 0.325, 0.43, or 0.65 M DCl with **2**, which was itself at 0.43 M, and 0.12, 0.24, 0.36, 0.48, or 0.72 M DCl with **4**, which was itself at 0.48 M. Under neutral conditions, **2** showed a gradual decline to about 80% of its original value over 20,000 sec (Fig. 3a), after which it

Table 1: NMR assignments of **1**–**4**.

	Compound							
	1		**2**		**3**		**4**	
	Chemical shift (ppm)[a]							
Carbon No.	**C**	**H**	**C**	**H**	**C**	**H**	**C**	**H**
1	176.1	—	177.5	—	173.9	—	175.8	—
2	71.9	4.50	72.3	4.77	69.3	4.69	71.2	4.59
3	71.8	4.17	73.8	4.63	71.0	4.74	80.4	5.18
4	73.4	4.00	80.2	5.15	70.7	4.71	79.2	5.39
5	71.7	4.39	69.4	4.67	81.0	4.76	68.9	4.96
6	175.8	—	174.5	—	178.2	—	175.8	—

[a]Assignment in D_2O referenced to external tetramethylsilane.

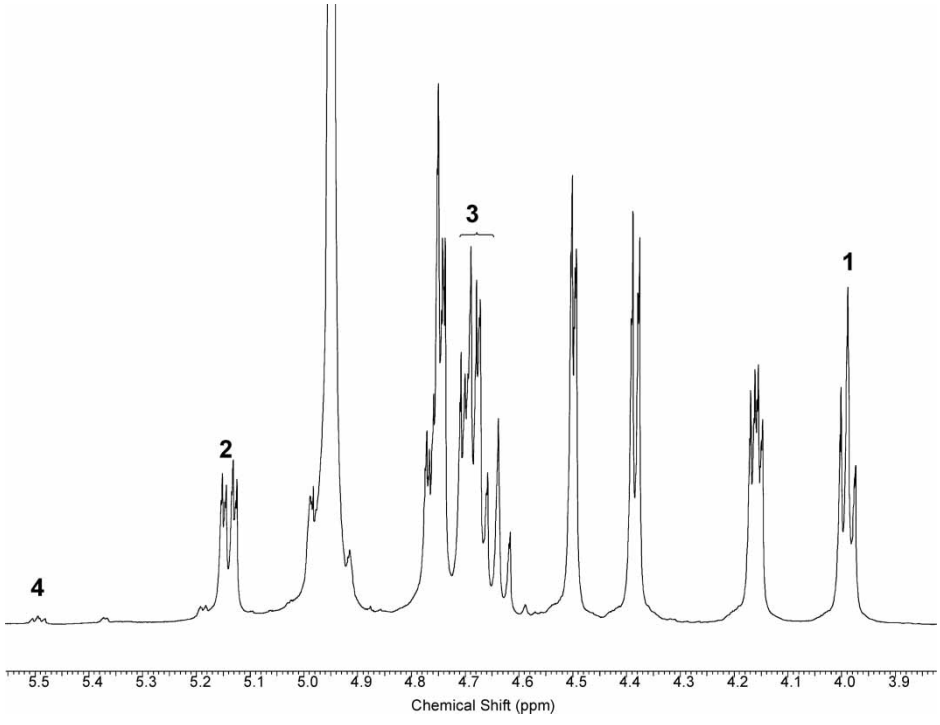

Figure 2: Portion of ^{1}H NMR spectrum of equilibrated sample showing the region in which signals for D-glucaro-6,3-lactone (**3**) (4.69–4.76 ppm) appear and the signals chosen to represent **1**, **2,** and **4**: 4.00, 5.15, and 5.49 ppm, respectively.

remained unchanged out to 60,000 sec. During this period **1** appeared and very slowly increased in quantity. Although it was not possible to measure directly the amount of **3** present, estimation of the mass balance indicated that a similar amount of **3** and **1** was present. The addition of increasing amounts of acid accelerated the rate of attainment of equilibrium as well as changing the relative amounts of products (Fig. 3b). Times to equilibrium (seconds $\times$ 10^{-4}) were 6.9, 6.2, 5.9, 4.6, 3.6, and 2.8 for 0 to 1.5 molar equivalents as indicated above; this trend appears to be linear with the reciprocal of acidity. Once the molar equivalent of added acid exceeded 0.5, the major product was D-glucaric acid, **1**, with **2** and **3** present in lesser amounts, the latter always being less than the former in contrast to previous reports.[10] The dilactone, **4**, was present in trace amounts and did not show any increase during the period of the experiment.

Under neutral conditions **4** disappeared far more rapidly than **2** (Fig. 4a) with the formation of the monolactones **2** and, by consideration of mass balance, **3**. D-Glucaric acid also formed, albeit more slowly, because it must arise from one or another of the monolactones. Once again the addition of

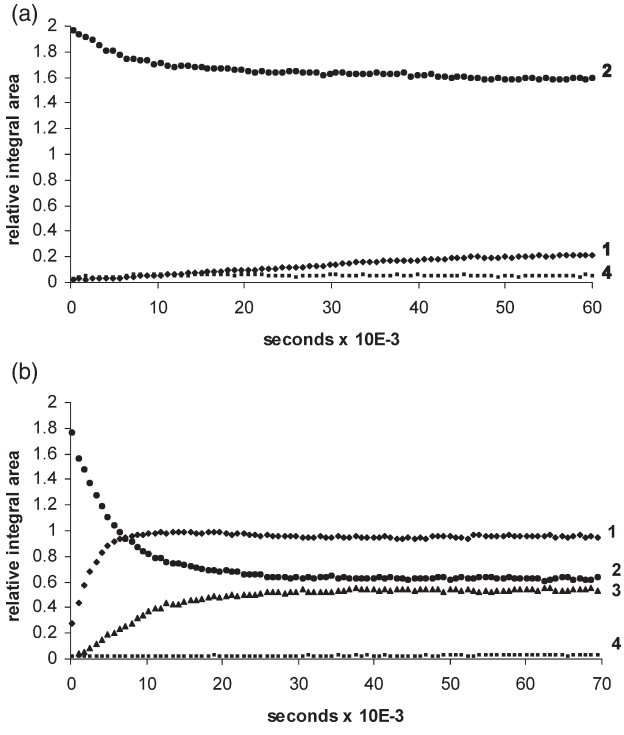

Figure 3: (a) Equilibration of D-glucaro-1,4-lactone (**2**) at 300K in D_2O (data is mean of duplicate determinations; **1** = D-glucaric acid, **4** = D-glucaro-1,4:6,3-dilactone); (b) Equilibration of D-glucaro-1,4-lactone (**2**) at 300 K in D_2O with 1.5 molar equivalents of DCl added (data is mean of duplicate determinations; **1** = D-glucaric acid, **3** = D-glucaro-6,3-lactone, **4** = D-glucaro-1,4:6,3-dilactone).

increasing amounts of acid accelerated the attainment of equilibrium with very rapid loss of **4** (Fig. 4b). Times to equilibrium (seconds $\times$ 10^{-3}) were also linear with the reciprocal of acidity and were 10, 6.8, and 4.9 for 0.5, 1.0, and 1.5 molar equivalents as indicated above; the system did not attain equilibrium during the course of the experiment in the absence of acid. In the presence of acid, D-glucaro-6,3-lactone (**3**) formed more rapidly than D-glucaro-1,4-lactone (**2**) and then declined to an equilibrium value less than **2**. Because **3** is formed by opening of the 1,4-lactone ring of **4**, the result shown in Figure 3b indicates that the 1,4-lactone ring is more reactive to nucleophilic attack than the 6,3-lactone ring, as has been reported previously under melt thermolysis[12] and aminolysis [13] conditions.

The figures reveal that the reaction rates are obviously accelerated by hydrogen ion catalysis. The figures also reveal that the equilibrium constants vary according to the concentration of acid; this has also been observed for the γ-butyrolactone system and possibly relates to differential degrees of protonation at different pHs for the different lactones and acids that are present. The

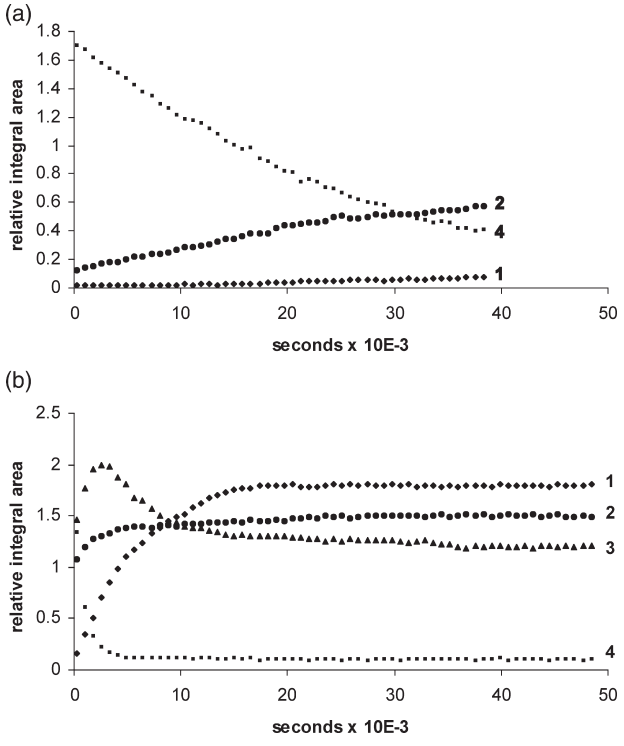

Figure 4: (a) Equilibration of D-glucaro-1,4:6,3-dilactone (**4**) at 300 K in D_2O (data is mean of duplicate determinations; **1** = D-glucaric acid, **2** = D-glucaro-1,4-lactone); (b) Equilibration of D-glucaro-1,4:6,3-dilactone (**4**) at 300 K in D_2O with 1.5 molar equivalents of DCl added (data is mean of duplicate determinations; **1** = D-glucaric acid, **2** = D-glucaro-1,4-lactone, **3** = D-glucaro-6,3-lactone).

acid-catalyzed hydrolysis of γ-butyrolactone, an unstrained five-membered ring, occurs at low values of hydrogen ion concentration and is pseudo-first order with a rate constant directly proportional to the hydrogen ion concentration.[14] As indicated below, equilibrium constants have been calculated only for 1.0 and 1.5 molar equivalents of acid (0.43 and 0.65 M and 0.48 and 0.72 M DCl for **2** and **4,** respectively). In the γ-butyrolactone it was found that ~13% change in equilibrium constant and less than 1% change in hydrolysis rate constant occurred when acid concentration changed from 0.485 M to 0.996 M.[14] Thus, we deem it unlikely that there will be acidity effects upon equilibrium constants for such small changes in acidity and only minor medium effects upon rate and equilibrium constants since all the species involved are highly polar and exist in equilibrium. Such small changes would likely be subsumed into experimental error.

For the reactions in which 1.0 or 1.5 molar equivalents of DCl were added, equilibrium constants, K_1–K_4, for the equilibria shown in Figure 1 were

calculated from experimental equilibrium data such as is shown in Figures 3 and 4. The following relationships must be met because the principle of microscopic reversibility[15] requires each step to reach equilibrium individually and ΔG_r^0 must be zero for the cycle of reactions:

$$K_1 = \frac{[1]_{eq}}{[2]_{eq}} = \frac{k_1}{k_2}$$

$$K_2 = \frac{[3]_{eq}}{[1]_{eq}} = \frac{k_3}{k_4}$$

$$K_3 = \frac{[4]_{eq}}{[3]_{eq}} = \frac{k_5}{k_6}$$

$$K_4 = \frac{[2]_{eq}}{[4]_{eq}} = \frac{k_7}{k_8}$$

$$K_1K_2K_3K_4 = \frac{[1]_{eq}[3]_{eq}[4]_{eq}[2]_{eq}}{[2]_{eq}[1]_{eq}[3]_{eq}[4]_{eq}} = \frac{k_1\,k_3\,k_5\,k_7}{k_2\,k_4\,k_6\,k_8} = e^{-\Delta G_r^0/RT} = 1$$

The experimental equilibrium constants were calculated from the concentration of each species at the end of the experiments and are given in Table 2. The values for K_1 and K_2 agree within 9% and 14%, respectively, between experimental sets but the agreement for K_3 and K_4 is less good, which is likely to be due to the difficulty in integrating very small peaks to measure the concentration of **4**.

Approximate starting values of the rate constants k_2, k_3, k_4, k_6, and k_7 for simulation were obtained by dividing the initial rate of growth of a species by the initial concentration of the species from which it is derived; this method is based on the assumption that in the initial phase of reaction, reverse reactions are unimportant because the concentration of product is so small. Starting values for the remaining rate constants were obtained by consideration of the appropriate equilibrium constants.

Table 2: Equilibrium constants derived from experimental data.

Starting material	Molar equiv. DCl	K_1	K_2	K_3	K_4
D-glucaro-1,4-lactone (**2**)	1.0	1.50	0.48	0.13	11.02
	1.0	1.31	0.50	0.16	9.70
	1.5	1.54	0.62	0.04	23.64
	1.5	1.48	0.49	0.06	25.10
D-glucaro-1,4:3,6-dilactone (**4**)	1.0	1.31	0.64	0.10	12.02
	1.0	1.34	0.63	0.08	14.05
	1.5	1.18	0.70	0.09	14.09
	1.5	1.26	0.65	0.09	13.39

During the simulations, pairs of rate constants were systematically varied to obtain the best possible fit while retaining the ratio as defined by the equilibrium constant. Comparisons between experimental and final simulated data are shown in Figures 5 and 6 for **2** and **4** as the respective starting materials. The final adjusted rate constant values and calculated equilibrium constants are given in Table 3 and the latter reproduce the experimental equilibrium constants in Table 2 rather closely. The simulated value of $K_1K_2K_3K_4 = 1.08$ is in good agreement with the thermodynamic value of one.

Although the fit to experimental data is not perfect, it provides very strong, qualitative support for the chosen mechanism and also provides an explanation for some previous observations. It has been reported[10] that the reciprocal transformation between **2** and **3** occurs via **1** rather than **4** because **1** is the major species present at equilibrium and **4** was not detected except at elevated temperatures. The current results indicate that, especially in the case of **3** as starting material, the relatively rapid equilibration between **3** and **4** would suggest a significant contribution via the dilactone, **4**. This was borne out by simulating the equilibration using **3** as the starting material. The simulation (Fig. 7) showed that **4** rises rapidly to a maximum before declining to its equilibrium value. This would be difficult to detect under experimental conditions employed here or in reference [10].

The ratio of the fluxes between **3** and **2** via **1** and **4** is initially less than 1.0 (Fig. 8) and at equilibrium rises to just above one as the concentration of **4** passes through its maximum and declines. The calculated ratio does not

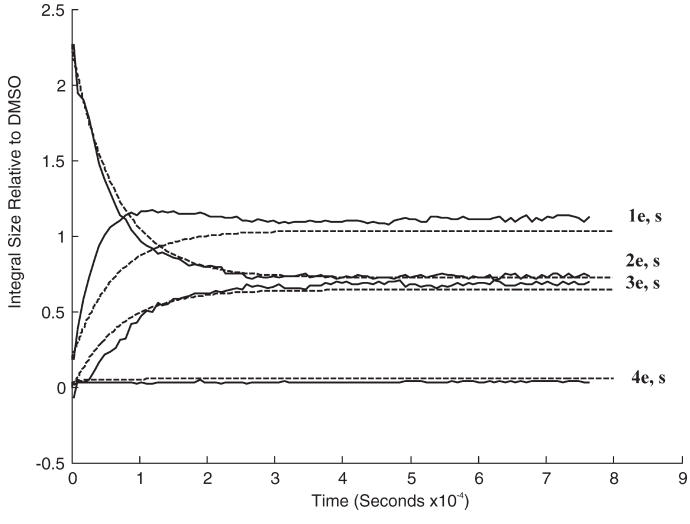

Figure 5: Simulated versus experimental data for D-glucaro-1,4-lactone (**2**) plus 1.5 molar equivalents of DCl (solid line (e) = experimental data, dotted line (s) = simulated data).

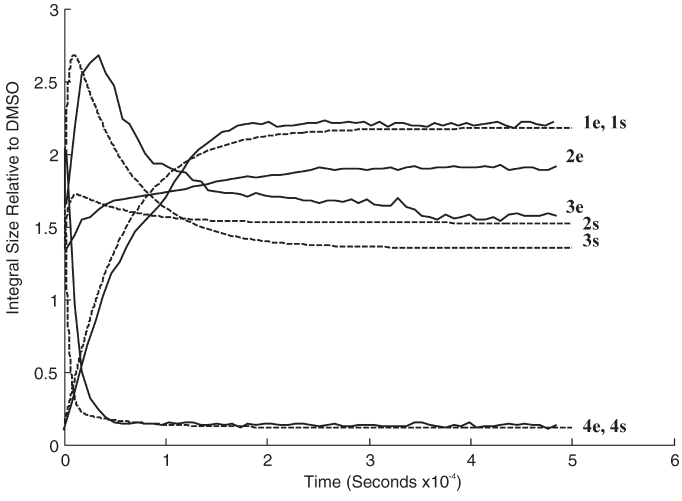

Figure 6: Simulated versus experimental data for D-glucaro-1,4:6,3-dilactone (**4**) plus 1.5 molar equivalents of DCl (solid line (e) = experimental data, dotted line (s) = simulated data).

quite reach 0/0 at equilibrium because the approximate rate constant values used do not precisely satisfy microscopic reversibility. This indicates that a significant proportion of exchange between **3** and **2** occurs via **4** even though the latter is present only in very small quantity.

The rapid mutarotation of **4** has been attributed[9] to the instability of the 1,4-lactone ring; similarly, greater reactivity of the 1,4-monolactone compared to the 6,3-monolactone has been reported elsewhere.[12,13] The current results support this because, when **4** is the starting material, **3** rises rapidly to a maximum as a result of the opening of the 1,4-ring and then declines to its

Table 3: Final rate constants and calculated equilibrium constants for the equilibration of D-glucaric acid lactones at 300 K.

Rate constant	Final value from modeling (s^{-1})	Equilibrium constant	Calculated value
k_1	7.04×10^{-5}	K_1	1.45
k_2	4.84×10^{-5}		
k_3	5.52×10^{-5}	K_2	0.634
k_4	8.70×10^{-5}		
k_5	1.74×10^{-4}	K_3	0.088
k_6	1.97×10^{-3}		
k_7	6.64×10^{-4}	K_4	13.2
k_8	5.01×10^{-5}		

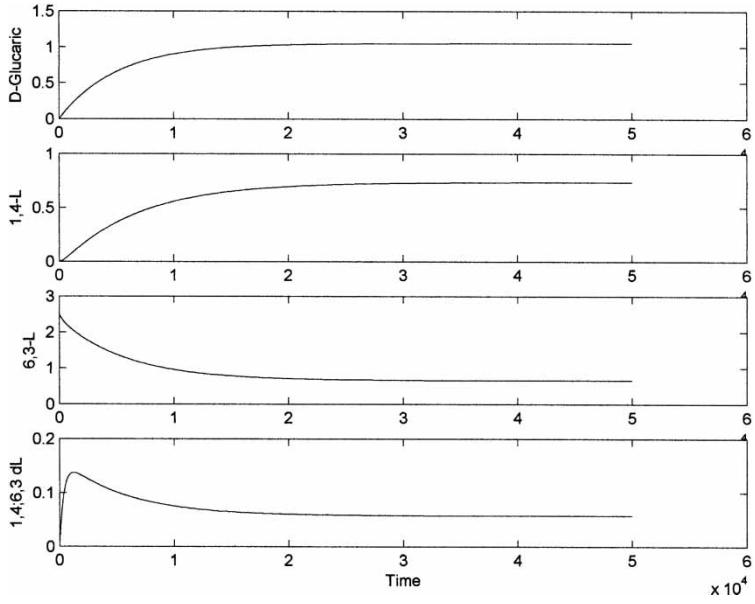

Figure 7: MATLAB simulation of equilibration commencing from D-glucaro-6,3-lactone (**3**) using mass-action rate expressions derived from Figure 1, rate constant values given in Table 3, and initial scaled [**3**] = 2.5.

equilibrium concentration; correspondingly, the value of k_6 is much greater than the value of the other rate constants. The observation that **3** is formed more rapidly from **1** than is **2**[11] is not borne out by the current data in which k_2 and k_3 have fairly similar values; however, the reported study was undertaken under neutral conditions, whereas the current rate constants were derived from a study in acidic conditions and may therefore differ.

EXPERIMENTAL

Materials

D-Glucaro-1,4-monolactone dihydrate, deuterium oxide (99.9 atom%, glass distilled), deuterium chloride (35% w/w, 99 atom%), dimethyl sulfoxide (99.9% purity, spectrophotometric grade), and Dowex 50WX8 hydrogen form resin (50–100 mesh) were obtained from Sigma-Aldrich. Monopotassium glucarate was prepared by a standard method.[16]

D-Glucaro-1,4:6,3-dilactone (**4**) was prepared as follows: To monopotassium glucarate (20.0 g, 0.086 mol) in distilled water (250 mL) was added Dowex 50WX8 hydrogen form resin (70 mL) and the mixture shaken on a radial shaker (4 h) during which time the monopotassium glucarate dissolved. The

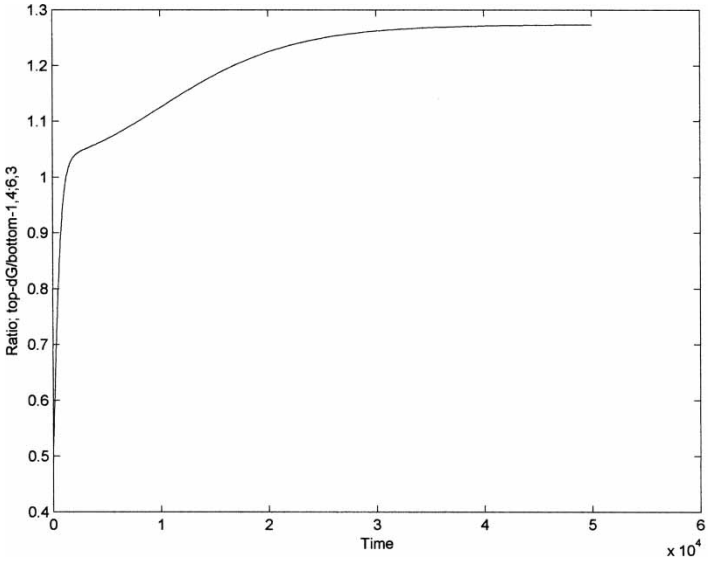

Figure 8: Plot of the ratio of flux between D-glucaro-6,3-lactone (**3**) and D-glucaro-1,4-lactone (**2**) via D-glucaric acid (**1**) (top-dG) and via D-glucaro-1,4:6,3-dilactone (**4**) (bottom-1,4:6,3). The calculation was carried out using the simulated concentrations given in Figure 7 and the relationships top-dG = k_4(**3**) − k_3(**1**) + k_2(**1**) − k_1(**2**) and bottom-1,4:6,3 = k_5(**3**) − k_6(**4**) + k_7(**4**) − k_8(**2**).

resin was removed by filtration and the filtrate concentrated to a syrup under reduced pressure. The syrup was heated under vacuum (90°C, 12 h), during which time it was transformed into an amber-colored glass. The glass was dissolved in 1,4-dioxane and **4** precipitated by the addition of dichloromethane. The crude product was recrystallized from 3:1 1,4-dioxane: dichloromethane.

NMR Spectroscopy

Assignments of the spectra of **1**–**4** in D_2O were carried out using a Bruker DRX400 400 MHz NMR spectrometer fitted with an inverse probe; ^1H, ^{13}C, COSY, HSQC, HMBC, SELTOCSY, and SELNOESY experiments were carried out.

Kinetics measurements were carried out using a Bruker Avance AC300 300 MHz NMR spectrometer operating at 300 K. The spectrometer was shimmed and tuned on a sample of D_2O before this was replaced by the tube containing the sample. In each set of experiments 50 to 100 ^1H spectra were recorded (128 scans) for each sample with a 5-min delay between spectra. Spectra were referenced to the DMSO singlet (2.71 ppm) and manually integrated relative to the DMSO signal in the first experiment. The integral of

the DMSO signal in the first spectrum in each set was assigned the value 1.0000. The absolute value of the integral for the DMSO signal in subsequent experiments ranged from 0.97 to 1.03. Sets of spectra were carried out in duplicate for the addition of each of 0, 0.1, 0.21, 0.325, 0.43, or 0.65 M DCl to **2** and 0.12, 0.24, 0.36, 0.48, or 0.72 M DCl to **4** as starting material.

Sample Preparation

Starting material (50 mg, 0.26 mmol for **2** and 0.29 mmol for **4**) was added to deuterium oxide (0.6 mL) in a vial.

The appropriate amount of DCl and a drop of DMSO were added before the solution was mixed and transferred to a 5-mm NMR tube.

Modeling of Kinetics

MATLAB (The MathWorks Inc., Natick, Mass.) software was used for kinetic simulation of the NMR data.

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