

A Kinetic Study of the Fructopyranose–Fructofuranose Interconversion at Normal and Elevated Pressure over an Extended pH Range

BJØRN ANDERSEN, FINN GRØNLUND and H. C. JØRGENSEN

Chemical Laboratory IV, University of Copenhagen, Universitetsparken 5, DK-2100 Copenhagen Ø, Denmark

Kinetics of fructose mutarotation in aqueous solution was followed at pressures from 1 to 1200 bar (1 bar = 10^5 Pa) over a pH range from 1.5 to 7 using addition of HCl or NaOH to avoid buffer catalysis. At all pressures the observed first order rate constant was better described by the expression $k = k_{\text{H}^+}c_{\text{H}^+} + k_{\text{H}_2\text{O}} + k_{\text{OH}^-}(c_{\text{OH}^-})^{1/2}$ than by the classical linear relation. Each of the three rate constants was decomposed into a forward and a reverse rate constant, and the corresponding six activation volumes were calculated. For hydrogen ion catalysis the values were -0.9 and -5.6 $\text{cm}^3 \text{mol}^{-1}$ respectively, while both water and hydroxide ions gave about -8.5 and -13.4 $\text{cm}^3 \text{mol}^{-1}$ for the forward and reverse reaction. These values are discussed in conjunction with the corresponding values for glucose mutarotation.

In a previous kinetic study of glucose mutarotation, a case of α - β -pyranose anomerisation, we found that the rate increased with pressure at constant pH corresponding to an activation volume of about -10 $\text{cm}^3 \text{mol}^{-1}$.¹ This was explained in terms of the concerted reaction model proposed by Swain and others.^{2,3}

The present work deals with fructose mutarotation which is a pyranose–furanose interconversion. While this reaction differs from the former with respect to enthalpy, activation energy, and pH sensitivity,⁴ investigations on deuterium isotope effects in the two reactions⁵ support the idea that both proceed via acyclic intermediates, and that the rate determining steps are similar in both cases. In order to see how far the

analogy goes, we have determined the activation volume in fructose mutarotation. Mutarotation as well as most carbonyl addition reactions is complicated by the fact that three reactions have been shown to take place simultaneously: one catalyzed by acids, one by bases, and a spontaneous one,^{6–9} the relative amounts depending on pH. Therefore three empirical rate constants were extracted at each pressure which characterize the overall mutarotation process. A detailed analysis may well prove the latter to consist in a series of steps as found in the case of thiosugars.¹⁰

EXPERIMENTAL

Reaction solutions were made up from doubly distilled water, either pure or with addition of HCl or NaOH in sufficient quantity to obtain the desired pH value. This seems a reliable procedure since continuous measurement showed no change in pH beyond the detection limit (0.01 unit) from the moment the solution was prepared to long after completion of the reaction. Catalysis by buffers, most of which are active as opposed to NaCl, is avoided, and corrections due to the change in buffer K_a with pressure become superfluous. Before use the solvent was thermostatted to (25.00 ± 0.05) °C. A thermostatted 100 cm^3 volumetric flask containing 10.00 g of D(-)-fructose (Merck, extra pure) was half filled with solvent and agitated; timing was started at this moment. When the sugar had dissolved completely the solution was deaerated by suction and

solvent was added to the mark. An aliquot was now quickly transferred to the polarimeter tube by a syringe.

The reaction was followed using a Zeiss Lichtelektrisches Polarimeter, either with a standard 10 cm tube or a high pressure tube 6.54 cm long, both thermostatted with circulating water at (25.00 ± 0.05) °C. The wavelength was 546 nm and the optical rotation was measured to better than 0.005° . Readings could be started 2–3 min after mixing at 1 bar, and 5–6 min after mixing when the high pressure cell was used; they were taken at intervals from 5 s upwards, and continued until completion of the reaction.

The high pressure was produced by a 10 kbar generator and transmitted to the polarimeter tube by a pressure liquid which was separated from the reaction mixture by a floating piston. The pressure was measured by a manganin cell calibrated by Harwood Engineering. Except for the latter, the apparatus has been described previously.¹ The sudden increase in pressure at the beginning of an experiment may be expected to produce a transient temperature rise. This must decay quite rapidly, however, since we have found no indication that the reaction proceeds faster in the beginning than later.

In calculating the parameters of the equation

$$\alpha(t) - \alpha(\infty) = [\alpha(0) - \alpha(\infty)] \exp(-kt)$$

the method of least squares for the nonlinear case was adopted rather than the usual semilogarithmic plot. The calculations consist in varying $\alpha(0)$, $\alpha(\infty)$ and k until a minimum is found for the sum of squares

$$S = \sum_i [\alpha(t_i)_{\text{obs}} - \alpha(t_i)_{\text{calc}}]^2$$

The average scatter of the observed values from the calculated curve amounts to a few millidegrees. Precision in k values was 1 per cent or better. $\alpha(0)$ was found to be (-16.24 ± 0.13) degrees and $\alpha(\infty)$ (-10.69 ± 0.01) degrees (10 g/100 cm³, 10 cm, 546 nm, 25 °C, 1 bar).

RESULTS

Preliminary experiments in which acetate, phthalate, and tris buffers were used to fix pH showed a catalytic effect of the buffer unnoticed by Isbell and Pigman,⁴ and were therefore discarded. In contrast to this addition of HCl and NaOH is not objectionable since the presence of NaCl in concentrations up to 0.1 mol dm⁻³ does

Table 1. First order rate constant k for D(-)-fructose mutarotation in water at 25 °C, 1 atm as a function of pH.

pH	$10^3 k/s^{-1}$
1.56	14.53
1.58	14.29
1.96	7.31
1.99	7.38
2.25	5.63
2.25	5.61
2.55	4.49
2.56	4.53
3.03	3.51
3.05	3.42
3.36	3.23
3.36	3.22
3.41	3.10
3.42	3.04
4.14	3.05
4.15	3.00
4.63	3.16
4.65	3.09
4.86	3.28
5.05	3.48
5.25	3.63
5.27	3.69
5.45	3.75
5.84	4.59
5.86	4.40
5.91	4.43
6.02	4.72
6.26	5.13
6.62	5.75
6.68	6.07
6.78	6.76
7.09	8.37
7.36	10.26

not influence the rate measurably.

Kinetics at ambient pressure. The results of a series of runs at 25.00 °C, 1 atm are given in Table 1 and Fig. 1a in which the rate constant k is given as a function of pH. The plot closely resembles that published by Isbell and Pigman.⁴ Inspection shows that a curve passing through the experimental points is not symmetrical as it should be if k is a sum of three terms: one linear

in c_{H^+} , one linear in c_{OH^-} , and a constant. All previous discussions concerning specific acid and base catalysis in fructose mutarotation rest upon this assumption. To investigate this apparent anomaly, we tried to fit the parameters in the following relationship

$$k = k_{\text{H}^+}(c_{\text{H}^+})^a + k_{\text{H}_2\text{O}} + k_{\text{OH}^-}(c_{\text{OH}^-})^b \\ = k_{\text{H}^+}(c_{\text{H}^+})^a + k_{\text{H}_2\text{O}} + k_{\text{OH}^-}(K_w/c_{\text{H}^+})^b \quad (1)$$

to our data, again using the method of least squares. The following results were obtained:

$$k_{\text{H}^+} = 0.437 \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$$

$$k_{\text{H}_2\text{O}} = 2.95 \cdot 10^{-3} \text{ s}^{-1}$$

$$k_{\text{OH}^-} = 14.90 \text{ dm}^{3/2} \text{ mol}^{-1/2} \text{ s}^{-1}$$

$$a = 0.96$$

$$b = 0.50$$

This indicates that our data (and as our recalculation has shown, also those of Isbell and Pigman) support a relationship of the form (2) for fructose.

$$k = k_{\text{H}^+}c_{\text{H}^+} + k_{\text{H}_2\text{O}} + k_{\text{OH}^-}\sqrt{c_{\text{OH}^-}} \quad (2)$$

This finding is admittedly surprising. To check it, we tried to fit our data to the assumed linear relationship, this time keeping both exponents constant, $a=b=1$, and varying the three catalytic constants. The minimum sum of squares (ten times larger than before) was found with

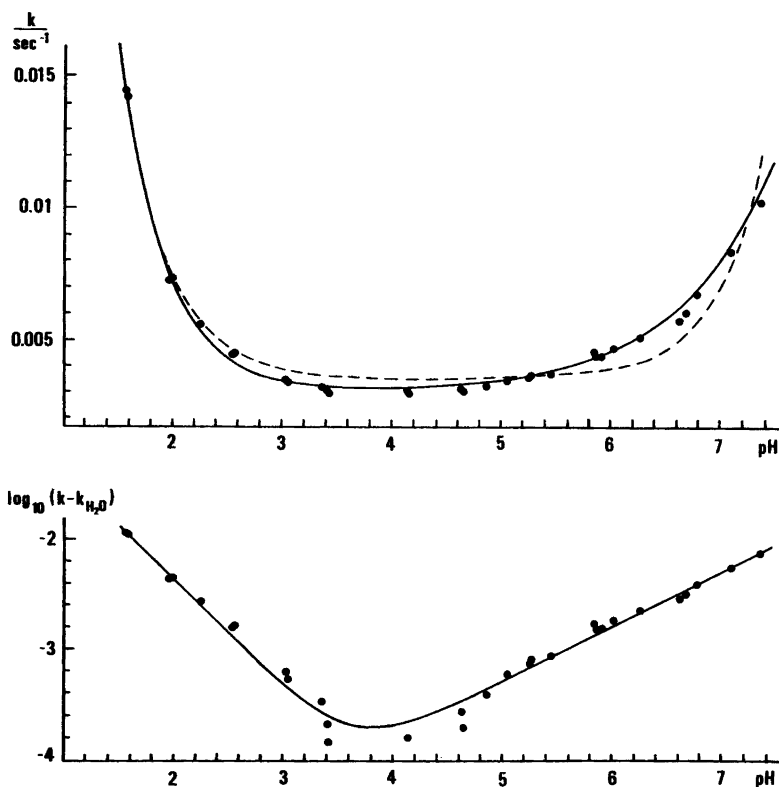


Fig. 1. a(top) Plot of the first order rate constant k as a function of pH at 1 atm. The solid curve is based on a square root relation, the dashed one on a linear relation between k and c_{OH^-} . b(bottom) Doubly logarithmic plot based on the same data as above. Here the logarithm (base 10) of k , corrected for the constant contribution from water catalysis $k_{\text{H}_2\text{O}}$, is given as a function of pH at 1 atm.

$$k_{\text{H}^+}=0.395 \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$$

$$k_{\text{H}_2\text{O}}=3.54 \cdot 10^{-3} \text{ s}^{-1}$$

$$k_{\text{OH}^-}=34.3 \cdot 10^3 \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$$

For comparison, two curves have been drawn in Fig. 1a based on the two sets of parameters. A glance will show that the square root expression (2) fits the data better than the linear expression (1) with $a=b=1$.

This conclusion is further supported by Fig. 1b which contains a doubly logarithmic plot of the form $\log_{10}(k-k_{\text{H}_2\text{O}})=f(\text{pH})$. Equation (1) shows that such a plot should be linear in the acid and basic ranges with slopes $-a$ and b respectively. The curve calculated from equation (1) with $a=1$, $b=1/2$ fits the experimental data well except near the minimum where the difference $k-k_{\text{H}_2\text{O}}$ is so small as to be quite sensitive to slight errors in k .

There can be little doubt, then, that the observed rate constant k for fructose at 25 °C, 1 atm follows an equation of the form (2). This statement seems to be valid at high pressure also (see below).

At this stage it was of interest to see whether glucose follows the same pattern in mutarotation. We repeated the measurements and calculations described above, with glucose as the substrate. However, a linear relationship was found, *i.e.* diagrams of the type of Fig. 1 were perfectly symmetrical. It may be concluded, therefore, that while hydroxide ions catalyze mutarotation of both sugars, the mechanism seems to be different.

Kinetics at high pressure. The rate constant k was measured at pressures up to 1200 bar at each of seven pH values between 1.88 and 6.18. The results are presented in Table 2 together with 1 bar values calculated from eqn. (2). For each pH the results were smoothed and k values computed at 0, 400, 800, 1200 bar. At each of these pressures the data were analyzed in the manner described above, and as the exponent b ranged from 0.45 to 0.55 we proceeded to decompose k according to eqn. (2) at all four pressures. The resulting values are found in Table 3.

Each of the three rate constants k_i ($i=\text{H}^+$, H_2O , OH^-) thus found may be considered as the sum k_i+k_{-i} of a forward (pyranose→furanose) rate constant and a reverse (furanose→pyranose) rate constant, leading to an equilibrium mixture

Table 2. First order rate constant k for D(-)-fructose mutarotation in water at 25 °C as a function of pressure P at different pH. Values at 1 bar (in parentheses) are calculated from eqn. (2).

pH	P/bar	$10^3 k/\text{s}^{-1}$
(1.88	1	8.60)
1.89	363	10.09
1.87	662	10.10
(2.12	1	6.23)
2.12	466	8.76
2.13	664	8.92
2.12	932	9.43
2.11	1284	11.01
(2.51	1	4.33)
2.51	345	5.51
2.51	728	6.48
2.51	970	6.94
2.51	1172	7.58
(3.01	1	3.46)
3.01	575	4.58
3.01	868	5.26
3.01	1150	5.73
3.01	1246	6.08
(4.19	1	3.21)
4.19	360	3.77
4.20	578	4.13
4.20	792	4.56
4.17	868	4.80
4.18	886	4.88
4.22	1061	5.11
4.18	1247	5.28
4.20	1268	5.21
(5.15	1	3.58)
5.18	405	5.04
5.14	622	5.86
5.18	792	5.81
5.12	1068	6.49
5.14	1245	7.02
6.18	1	4.90
6.09	255	5.80
6.28	648	7.08
6.23	919	7.64
6.13	1205	8.92

of pyranose and furanose. Since c_{H^+} does not enter the equilibrium expression explicitly, the latter is independent of pH. This implies that the

Table 3. Individual rate constants for D(-)-fructose mutarotation in water at 25 °C and 0, 400, 800, 1200 bar.

P/bar	$k_{H^+}/\text{mol}^{-1}\text{dm}^3\text{s}^{-1}$	k_{H_2O}/s^{-1}	$k_{OH^-}/\text{mol}^{-1/2}\text{dm}^{3/2}\text{s}^{-1}$
0	0.453	0.00 295	15.36
400	0.480	0.00 386	19.06
800	0.515	0.00 465	23.02
1200	0.557	0.00 533	27.27

Table 4. Forward (\bar{k}_i) and reverse (\bar{k}_i) individual rate constants for D(-)-fructose mutarotation at 25 °C and 0–1200 bar.

P/bar	$\bar{k}_{H^+}/\text{mol}^{-1}\text{dm}^3\text{s}^{-1}$	$\bar{k}_{H_2O}/\text{s}^{-1}$	\bar{k}_{H_2O}	$\bar{k}_{OH^-}/\text{mol}^{-1/2}\text{dm}^{3/2}\text{s}^{-1}$	\bar{k}_{OH^-}	K	
0	0.140	0.313	$0.91 \cdot 10^{-3}$	$2.04 \cdot 10^{-3}$	4.75	10.6	0.448
400	0.141	0.339	$1.13 \cdot 10^{-3}$	$2.73 \cdot 10^{-3}$	5.60	13.5	0.416
800	0.143	0.372	$1.29 \cdot 10^{-3}$	$3.36 \cdot 10^{-3}$	6.40	16.6	0.385
1200	0.146	0.411	$1.39 \cdot 10^{-3}$	$3.94 \cdot 10^{-3}$	7.14	20.1	0.354

Table 5. Activation volumes of forward (\bar{V}_i^\ddagger) and backward (\bar{V}_i^\ddagger) reactions of D(-)-fructose mutarotation.

Catalyst (i)	$\Delta\bar{V}_i^\ddagger/\text{cm}^3\text{mol}^{-1}$	$\Delta\bar{V}_i^\ddagger/\text{cm}^3\text{mol}^{-1}$
H ⁺	-0.87	-5.64
H ₂ O	-8.70	-13.53
OH ⁻	-8.41	-13.22

ratio k_i/k_{-i} must have the same value in all three reactions, namely that of the equilibrium constant at the said pressure. To find K as a function of pressure, linear regression was applied to 36 measurements of the rotation $\alpha(\infty)$ of the equilibrium mixture in the range 1 to 1200 bar, giving $\alpha(\infty)/\text{degree} = -10.69 - 1.18 \cdot 10^{-3} \text{ P/bar}$, and this was corrected for compression using Grindley and Lind's values.¹¹ Assuming the rotation of pyranose and furanose to be $\alpha_p = -16.24$ degrees and $\alpha_f = +1.7$ degrees,¹² K was computed as $(\alpha_p - \alpha(\infty))/(\alpha(\infty) - \alpha_f)$, see Table 4. All rotations are given for 10 g/100 cm³, 10 cm, 546 nm, 25 °C.

Finally the forward and reverse rate constants for each of the three reactions, computed from k_i and K are given in Table 4, while Table 5 contains the corresponding volumes of activation $\Delta\bar{V}_i^\ddagger$ and $\Delta\bar{V}_i^\ddagger$ found in the usual manner.

DISCUSSION

Our calculations are based on pH measurements at 1 atm and the water dissociation constant K_w , equally at 1 atm. At higher pressure, K_w and other protolysis constants which may possibly influence pH take different values. Since we have no detailed knowledge of the reactions that determine pH, we have not been able to correct for this. The effect of such corrections would be additive contributions to the activation volumes.

The process of mutarotation involves the action of an acid and a base on the saccharide. In the spontaneous reaction in aqueous solution where water molecules perform both functions the activation volumes found in fructose mutarotation (-8.7 and -13.53 cm³ mol⁻¹) are comparable to those reported in glucose mutarotation

(-11.7 and $-10.8 \text{ cm}^3 \text{ mol}^{-1}$). Of the four values cited, three are supposed to refer to the opening of a pyranose ring (α - and β -glucose, α -fructose) while the fourth, $-13.53 \text{ cm}^3 \text{ mol}^{-1}$, corresponds to the opening of a furanose ring. The negative values are readily explained by electrostriction if three neutral reactants, the saccharide and two water molecules, react to form a neutral activated complex plus one hydrogen ion and one hydroxide ion.

In the acid range, the activation volumes in fructose mutarotation are numerically smaller by about $8 \text{ cm}^3 \text{ mol}^{-1}$. In this case the reactants are the saccharide, a hydrogen ion and a water molecule, and may in a similar way be supposed to form a neutral activated complex, a water molecule, and a hydroxide ion respectively. No net formation of ions occurs in this case so no electrostriction effect may be expected.

In the basic range where fructose mutarotation is catalyzed by hydroxide ions, the activation volumes cannot be interpreted before the elementary processes have been stated. This presents a problem because of the square root relationship. The simplest way to explain it is to assume a dissociation equilibrium of the type



where A is a compound present in constant concentration and X is a nucleophilic agent capable of catalyzing the mutarotation. If so, then

$$[X] = K([A][\text{OH}^-])^{1/2} = K' [\text{OH}^-]^{1/2}$$

and the rate of the mutarotation reaction would be

$$\begin{aligned} v &= k[\text{saccharide}][\text{H}_2\text{O}][X] \\ &= k'[\text{saccharide}][\text{OH}^-]^{1/2} \end{aligned}$$

Note that the same type of rate equation would be obtained if two active species X and Y, both catalyzing the reaction were formed from one OH^- ion. We have not been able so far to assign an identity to the anonymous species A and X, but the question is of some importance since the anomaly described here in fructose mutarotation is reported to occur also in the kinetics of epoxide ring opening, and therefore deserves further investigation.

REFERENCES

1. Andersen, B. and Grønlund, F. *Acta Chem. Scand. A* 33 (1979) 275.
2. Swain C. G. *J. Am. Chem. Soc.* 72 (1950) 4578.
3. Swain, C. G., Di Milo, A. J. and Cordner, J. P. *J. Am. Chem. Soc.* 80 (1958) 5983.
4. Isbell, H. S. and Pigman, W. W. *J. Res. Natl. Bur. Stand.* 18 (1937) 141.
5. Isbell, H. S. and Wade, W. R. *J. Res. Natl. Bur. Stand. Sect. A* 71 (1967) 137.
6. Hudson, C. S. *J. Am. Chem. Soc.* 29 (1907) 1571.
7. Lowry, T. M. and Smith, G. F. *J. Chem. Soc.* (1927) 2539.
8. Brønsted, J. N. and Guggenheim, E. A. *J. Am. Chem. Soc.* 49 (1927) 2554.
9. Bell, R. P. *Advan. Phys. Org. Chem.* 4 (1966) 1.
10. Grimshaw, C. E., Whistler, R. L. and Cleland, W. W. *J. Am. Chem. Soc.* 101 (1979) 1521.
11. Grindley, T. and Lind, J. E. *J. Chem. Phys.* 54 (1971) 3983.
12. Andersen, B. and Degn, H. *Acta Chem. Scand.* 16 (1962) 215.

Received June 6, 1983.