The Mutarotation of Glucose in Water–Methanol Mixtures—Acetate Ion Catalysis

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The rate of mutarotation of glucose has been studied polarimetrically in water–methanol mixtures with dielectric constants ranging down to about 40 at two temperatures, and the effect of acetate ion as a catalyst determined. The constants are compared with those previously obtained and the catalysts H_2O, AcOH, AcO^- and H^+ are compared. The non-ionic catalysts show very little effect with change of solvent, in accord with theory. The ionic catalysts show an increase as the dielectric constant is lowered, agreeing qualitatively with theory if it is assumed that acid and base attack at opposite ends of the glucose dipole. The H^+ ion is the most effective catalyst measured because it operates with the lowest entropy of activation. The measurements indicate that the reaction is kinetically second rather than third order, but permit a third order mechanism with water the third molecule.

Previous publications from this Laboratory[2] have presented data on the effect of varying proportions of methanol and water as a solvent upon the rate of mutarotation of glucose using various catalysts. Similar results are now presented for the effect of a different catalyst, acetate ion, and an attempt is made to correlate the results of the several investigations.

Experimental

Reagent grade absolute methanol was distilled from CaO and the density determined with a Westphal balance. Reagent grades of AcOH, NaOH, NaCl and HCl were used, and solutions made up with the laboratory supply of distilled water. A stock buffer solution was prepared from carbonate-free NaOH and glacial AcOH and the final concentration checked by titration. The buffer was 0.499 M in AcONa and 0.495 M in free AcOH. Pure alpha glucose was prepared by the method of Hudson and Dale,[3] washed with EtOH and dried in a vacuum desiccator for at least 12 hours.

Solutions were prepared by mixing weighed quantities of MeOH, H_2O and buffer in a volumetric flask. About 20 ml. of the mixture was then transferred to an erlenmeyer flask, stoppered and placed in a thermostat at the temperature planned for the run. A quantity of alpha glucose sufficient to make an approximately 3% solution was added after temperature equilibrium was attained, dissolved by swirling, and the solution immediately transferred to the polarimeter tube. In most of the runs at 35°, the final acidity was checked with a Beckman pH meter in order to be sure that the H^+ concentration was low enough for its catalytic effect to be negligible.

Optical rotations were measured in a Schmidt and Haensch polarimeter graduated to one minute of arc. Temperature was controlled by pumping water from the thermostat through the jacket of the polarimeter tube, and measured by a thermometer placed in the glucose solution itself. It was constant during a run to 0.05°. The time–rotation measurements were carried out in a darkened room by setting the analyzer prism and noting the time at which a match in the fields occurred as read from the sweep second hand of a stop watch. Readings were taken over one-half to one hour at approximately one-minute intervals. The equilibrium rotation was measured from 4 to 24 hours later, by which time the reading was within 0.1 minute of arc from the final rotation.

Following the method of Lowry,[4] time in minutes was plotted against $\log (a - a_\infty)$ where a and a_∞ represent the rotations at time t and at infinity, respectively. The slope of the resulting line, when multiplied by -2.303, gives the specific rate constant, k, in min.$^{-1}$. This constant is actually the sum of the constants for the forward and the reverse reactions, and might be separated into its components if the equilibrium constants were measured for each temperature and each solvent. Calculations made from such

(1) This paper is taken from a thesis submitted by B. A. Thumm in partial fulfillment of the requirements for the Ph.D. degree in the Graduate School of Arts and Sciences of Duke University.

(2) H. Dyas and D. G. Hill, THIS JOURNAL, 64, 236 (1942); J. J. Giuliano and D. G. Hill, ibid., 68, 2359 (1946).

(3) C. S. Hudson and J. K. Dale, ibid., 39, 320 (1917).

(4) T. M. Lowry, J. Chem. Soc., 75, 211 (1899).

data in an earlier paper showed that the effects of solvent and of temperature upon the two individual constants were not significantly different from the effects upon their sum.

Results

The mutarotation of glucose is a pseudo-first order reaction, showing general acid and base catalysis. If the mechanism is truly bimolecular, the measured first order constant is made up of the sum of a number of constants multiplied by the respective concentrations. Of the several constants in this equation, that for H^+ (actually H_3O^+) was evaluated at lower temperatures by Dyas and Hill, and an approximate value for that for AcOH by Giuliano and Hill. The latter determined the dissociation of acetic acid in the solvents used, so all concentrations may be considered known. In calculating the individual rate constants, the concentration of acetate ion for a series of runs in a given buffer and medium was plotted against the measured rate constant. Since the solvent composition and C_{H^+} were constant, their catalytic effect was included in the intercept, and a straight line obtained with slope

$$k = k_{MeOH}C_{MeOH} + k_{H_2O}C_{H_2O} + k_{H^+}C_{H^+} + k_{AcOH}C_{AcOH} + k_{AcO^-}C_{AcO^-}$$

$$k_c = k_{AcO^-} + (C_{AcOH}/C_{AcO^-}) k_{AcOH}$$

where k_c is defined by the above equation. By successive approximations starting from Giuliano and Hill's value for k_{AcOH}, a constant for AcO^- and an improved value for AcOH were obtained. The values given for k_{H^+} by Dyas and Hill at lower temperatures were smoothed by plotting $\log k_{H^+}$ against $1/D$; then, assuming constant activation energy over the temperature range, smoothed values were calculated for k_{H^+} at the present temperatures.

Using the improved constants for AcO^- and H^+, the data of Giuliano and Hill were replotted, giving much straighter lines when observed k was plotted against concentration of free AcOH. A more certain value for the intercept, $k_0 = k_{H_2O} \cdot C_{H_2O} + k_{MeOH}C_{MeOH}$ was obtained. The recalculated values for all the constants are given in Table I, in which it has been assumed, as in previous work, that the catalytic effect of MeOH is so small that k_0 may be set equal to $k_{H_2O}C_{H_2O}$. Times are in minutes. The dielectric constants for water–methanol mixtures are interpolated from the work of Albright and Gosting,[5] and given here for reference. Also included for comparison are values in

(5) P. A. Albright and L. J. Gosting, THIS JOURNAL, 68, 1061 (1946).

TABLE I

CATALYTIC COEFFICIENTS FOR MUTAROTATION

T, °C.	D	MeOH, %	k_0	k_0	k_{H_2O}	k_{AcOH} [c]	k_{H^+} [d]	k_{AcO^-}	k_{H_2O} (third)
35	74.9	0		0.0605[a]	0.0011	0.032[b]	1.98	0.44	0.00002
	57.7	40.0	0.531	.026	.0009	.034	2.4	.50	.00003
	49.0	59.3	.594	.017	.0008	.031	2.9	.56	.00004
	42.2	75.2	.668	.011	.0009	.033	3.5	.64	.00007
45	71.5	0		.144[a]	.0026	.076[b]	5.2	1.21	.00005
	54.6	40.1	1.35	.059	.0019	.084	6.5	1.36	.00006
	46.4	59.2	1.49	.039	.0020	.071	7.9	1.43	.00009
	39.8	75.0	1.73	.024	.0020	.071	9.7	1.66	.00017

[a] Kendrew and Moelwyn-Hughes.[6]   [b] Smith and Smith[7] recalculated for 35 and 45°.   [c] Recalculated from Giuliano and Hill.   [d] Recalculated from Dyas and Hill.

pure water for k_0 and k_{AcOH} calculated from the data of Kendrew and Moelwyn-Hughes[6] and from Smith and Smith.[7] Since our temperature was not very different from theirs, the calculation based on the Arrhenius equation should be valid.

An estimate has been made of the precision of the experimental results in terms of the deviation from a least squares straight line in the plots of log $(a - a_\infty)$ against time, using the method given by Birge.[8] The most probable error to be expected in each constant is given in Table II.

TABLE II

PROBABLE ERROR IN SECOND ORDER RATE CONSTANTS

T, °C.	k_{H_2O}	k_{AcOH}	k_{H^+}	k_{AcO^-}
35	0.00002	0.002	0.02	0.01
45	.00006	.005	.06	.03

Duplicate runs were made in a number of cases. The average difference in the gross first order constant between duplicates was 3.3%, the maximum difference being 5.4%.

The effect of added electrolyte was investigated by measuring the rate of mutarotation at 35° in 40% MeOH catalyzed by HCl both with and without added NaCl. The added electrolyte at an ionic strength of 0.14 M increased the rate constant from 0.470 to 0.481, Since the most concentrated solution used in the rate studies had an ionic strength of less than 0.1 M, the effect of changes in ionic strength is within the probable error of the experiments. The rates given may be considered essentially those at zero ionic strength. No test was made of the effect of electrolyte upon the base-catalyzed reaction. Only a slight salt effect is expected for reactions such as mutarotation in which at least one of the reactants is uncharged.

Discussion

Rates have been presented for the mutarotation reaction in solvents of varying dielectric constant as catalyzed by either of two neutral acids, H_2O and AcOH, by a strong positively charged acid, H_3O^+, and by a strong negatively charged base, AcO^-. It is to be expected that the dielectric constant should have only a very small effect upon the rates for the molecular catalysts, which prediction is borne out by the data.

The logarithm of the rate constant for the ion dipole reactions has been plotted against the re-

ciprocal of the dielectric constant in Fig. 1. These plots have positive slope as required by the Laidler–Eyring[9] equation for reactions in which dipole and ionic strength terms may be neglected, the slope for H^+ catalysis being the steeper since it is the smaller ion. The increase of log k_{H^+} with increas-
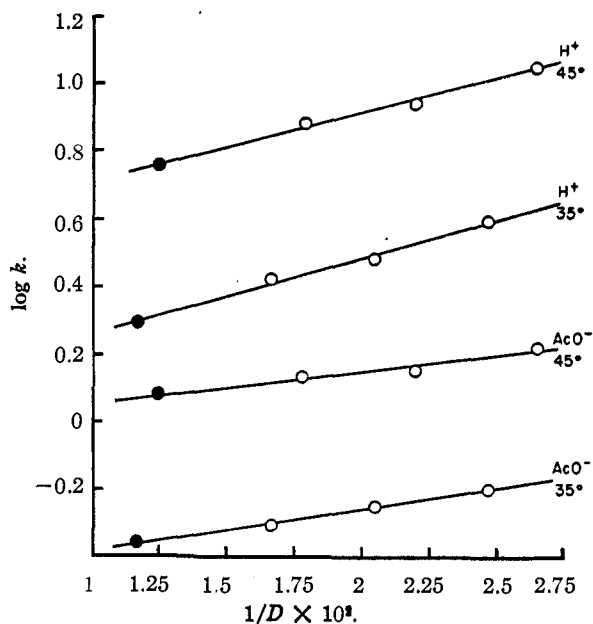

Fig. 1.

ing $1/D$ is also predicted by the Amis–Jaffe[10] equation. This equation, however, predicts the opposite slope for acetate ion catalysis unless it may be assumed that the negative acetate ion attacks the opposite end of the glucose dipole. It seems entirely reasonable to assume that an acid catalyst attacks the negative end of the dipole in the glucose molecule, while a base attacks the positive end. It is known from the work of Bronsted and Guggenheim[11] and that of Lowry and Richards[12] that both acid and base must be present for mutarotation. It has been assumed in this work that the second catalyst is water, and that its part in the reaction is rapid and not rate controlling. The two catalysts may act consecutively, with the

(6) J. C. Kendrew and E. A. Moelwyn-Hughes, Proc. Roy. Soc. (London), A176, 352 (1940).

(7) G. F. Smith and M. C. Smith, J. Chem. Soc., 1413 (1937).

(8) R. T. Birge, Phys. Rev., 40, 207 (1932).

(9) K. J. Laidler and H. Eyring, Ann. N. Y. Acad. Sci., 39, 303 (1940).

(10) E. S. Amis and G. Jaffe, J. Chem. Phys., 10, 598 (1942).

(11) J. N. Bronsted and E. A. Guggenheim, THIS JOURNAL, 49, 2554 (1927).

(12) T. M. Lowry and E. M. Richards, J. Chem. Soc., 127, 1385 (1925).

step in which the ring is opened demanding the presence of the stronger acid or base. An alternative explanation is discussed below.

Arrhenius activation energies have been calculated from the average rate constants for the molecular catalysts and from the smoothed values in the usual manner. They are given in Table III in kilocalories both for constant composition (ΔE) and for constant dielectric constant (ΔE_c).

TABLE III

ARRHENIUS ACTIVATION ENERGIES-CONSTANT COMPOSITION

MeOH, %	ΔE_{H_2O}	ΔE_{AcOH}	ΔE_{H^+}	ΔE_{AcO^-}
0	17.1	15.7	18.3	17.6
40			18.3	17.9
60			18.4	18.0
75			18.6	18.2

Constant Dielectric Constant

D	$\Delta E_{c_{H_2O}}$	$\Delta E_{c_{AcOH}}$	$\Delta E_{c_{H^+}}{}^a$	$\Delta E_{c_{AcO^-}}$
50	17.1	15.7	17.5	17.4
80			17.9	17.5

^{a} Values taken from work of Dyas and Hill[2] at 20 and 29.2°.

The energies given in Table III for H^+ catalysis differ slightly from those given by Dyas and Hill, since smoothed values for the rate constants were used in the present paper. The same remark applies to the values in Table IV. The energies given for AcOH differ from those of Giuliano and Hill because of the improved values for the rate constants.

TABLE IV

THERMODYNAMIC QUANTITIES

T, °C.	MeOH, %	H_2O	AcOH	H_3O^+	AcO$^-$
Free energies of activation (kcal./mole)					
35	0	24.9	22.7	20.1$_5$	21.0$_8$
	40			19.9$_9$	20.9$_9$
	60			19.8$_7$	20.9$_2$
	75			19.7$_4$	20.8$_5$
45	0	25.2	22.9	20.1$_5$	21.2$_4$
	40			19.9$_9$	21.1$_7$
	60			19.8$_7$	21.0$_1$
	75			19.7$_4$	20.9$_5$
Heats of activation (kcal./mole)					
40	0	16.7	15.40	18.0	17.3
(mean)	40			18.1	17.6
	60			18.1	17.7
	75			18.3	17.9
Entropies of activation (cal./mole/deg.)					
40	0	−27	−24	−7	−12
(mean)	40			−6	−11
	60			−6	−10
	75			−5	−10

ΔE_c is expected to vary for ionic reactants with the magnitude of the dielectric constant. Amis[13]

(13) E. S. Amis and F. C. Holmes, THIS JOURNAL, 63, 2231 (1941).

has shown that a completely electrostatic explanation of the variation would demand that the difference be given by

$$\Delta(\Delta E_c) = \frac{69.1 Z \mu \Delta D}{D_1 D_2 r^2}$$

where $\Delta(\Delta E_c)$ is the change in ΔE_c from a medium of one dielectric constant to another. If the radius of glucose is assumed to be 2 Å. and its moment 2 debye units, both of which are reasonable values, $\Delta(\Delta E_c)$ should be 0.26 kcal. for either catalyst. The average value of $\Delta(\Delta E_c)$ approximates this value, so that it seems probable that the effect is largely electrostatic. The experimental determination of $\Delta(\Delta E_c)$ is subject to such large error that the differences between catalysts may not be significant.

The free energies, heats and entropies of activation are given in Table IV. The first are calculated from the Eyring equation, the heats from the Arrhenius activation energies and the entropies from the other two.

The order of increasing heats of activation for the several catalysts is $AcOH < H_2O < AcO^- < H^+$. This order is far from that expected if it were assumed that the better catalysts were effective by reason of a smaller activation energy. The entropies of activation must be considered to compensate for the heats and to place the free energies of activation in their natural order.

The entropy of activation becomes less negative in the order of increasing catalytic strength, $H_2O < AcOH < AcO^- < H^+$, the negative sign indicating that the activated complex possesses a higher degree of order than the reactants. It is difficult to explain the order as representing increased solvation in the activated complex as has often been assumed, since it would seem that the greater solvation should be observed with the charged complex resulting from the ionic catalysts, which is contrary to the facts. Other factors than solvation may be involved.

In a recent paper Swain[14] has proposed a termolecular mechanism for the mutarotation of glucose. It seemed that our results offer a test for third order kinetics, since the concentration of water as a catalyst has been varied nearly fourfold. The last column in Table I gives "constants" calculated as second order in water, or third order over all. A greater variation is found than in the second order constants shown in column 5 of the same table. Similar calculations were made from the data of Worley and Andrews,[15] and again the second order assumption gives better constants than the third. It seems therefore, that however probable a third order mechanism, the rate governing step is of second order.

(14) C. G. Swain, ibid., 72, 4578 (1950).

(15) F. P. Worley and J. C. Andrews, J. Phys. Chem., 32, 307 (1928).