The Acid–Base-Catalyzed Mutarotation of α-D-Tetramethylglucose in Mixed H_2O–D_2O Solvents[1]

H. H. Huang, R. R. Robinson, and F. A. Long[2]

Contribution from the Department of Chemistry, Cornell University, Ithaca, New York. *Received December 17, 1965*

Abstract: The rate of the acid- and base-catalyzed mutarotation of α-D-tetramethylglucose has been studied at 25° in mixed H_2O–D_2O solvents for the catalysts acetate ion, hydronium ion, and water and in pure H_2O and D_2O for acetic acid. The ratios of rate coefficients in D_2O and H_2O, k_D/k_H, are 0.449, 0.746, 0.279, and 0.406, respectively. These values are very close to the corresponding ratios for the mutarotation of ordinary glucose and for the hydration and dehydration of acetaldehyde, suggesting similar mechanisms. Generalized Gross–Butler equations have been developed for a number of types of transition states expressing k_n/k_H, where k_n is rate coefficient in a solvent of deuterium atom fraction n, in terms of n and of fractionation factors ϕ for the exchangeable hydrogens in reactants and transition state. The experimental data can be fitted fairly well by these equations using the conventional mechanism for the mutarotation; however, some of the necessary fractionation factors are difficult to interpret in light of ordinary acid–base data. Cyclic synchronous mechanisms, involving two or three solvent water molecules, fit the data about as well and lead to plausible fractionation factors.

The theory of solvent isotope effects in mixtures of light and heavy water, first discussed by Gross and Butler and their co-workers,[3-8] and reviewed by Purlee,[9] has been developed further by Gold,[10] Swain and Thornton,[11,12] and in more generalized form by Salomaa, Schaleger, and Long.[13,14]

The equations derived by Salomaa, Schaleger, and Long for acid–base equilibria take account of the exchange between hydrogen and deuterium in the solvent, in reactants, and in the products. A fractionation factor ϕ is defined which characterizes the exchange equilibrium of a given labile hydrogen in the substrate and the deuterium of the solvent, and is the equilibrium constant for the equilibrium

$$SH + {}^1\!/_2D_2O \rightleftarrows SD + {}^1\!/_2H_2O \qquad (1)$$

The fractionation factor for the equilibrium

$${}^1\!/_3H_3O^+ + {}^1\!/_2D_2O \rightleftarrows {}^1\!/_3D_3O^+ + {}^1\!/_2H_2O \qquad (2)$$

defined as l has long been a source of study and its value is known to be very close to 0.67 at 25°.[15] However, less is known about the more general fractionation factor ϕ.

For the equilibrium

$$H_iA + H_2O \rightleftarrows H_3O^+ + H_{i-1}A^- \qquad (3)$$

in mixtures of light and heavy water, Salomaa, Schaleger, and Long derived the equation

$$K_H/K_n = \frac{(1 - n + n\phi_i)^i}{(1 - n + nl)^3(1 - n + n\phi_{i-1})^{i-1}} \qquad (4)$$

where K_H/K_n is the ratio of experimentally observed equilibrium constants in water and water containing an atom fraction n of deuterium, ϕ_i is the fractionation factor for the labile hydrogens in H_iA, and ϕ_{i-1} is the fractionation factor for the labile hydrogens in $H_{i-1}A^-$. It should be noted that if the i hydrogens in H_iA are not equivalent, then each hydrogen will have its own characteristic fractionation factor, and similarly for the hydrogens in $H_{i-1}A^-$.

The generalized equations were also applied to kinetics, by using transition-state theory, and are of the same form as those derived for equilibria. For the experimentally determined ratio k_n/k_H (the rate constant observed in water containing atom fraction n of deuterium, divided by the rate constant observed in H_2O), there will be a term $(1 - n + n\phi)$ in the denominator for each exchangeable hydrogen in the reactants and a term $(1 - n + n\phi)$ in the numerator for each exchangeable hydrogen in the transition-state complex. The exchangeable hydrogens in the transition state are of two types: those that remain in position during reaction and those that are being transferred from one reactant to the other, *i.e.*, involved in a proton transfer.

In some measure the value of ϕ reflects the acidity of a particular type of hydrogen atom in the molecule. Thus for a monobasic acid, the ratio of the equilibrium constants in H_2O and D_2O is given by

$$K_H/K_D = \phi/l^3 \qquad (5)$$

It is generally true that in a given class of acids the ratio K_H/K_D increases as the acid strength decreases.[19,20] Hence the stronger the acid, the smaller will be the value of ϕ. The physical significance of the fractionation factor for hydrogen being transferred in the transition state is less clear.

---

[1] This work was supported by a grant from the Atomic Energy Commission.

[2] To whom requests for reprints should be sent.

[3] P. Gross, H. Steiner, and F. Krauss, *Trans. Faraday Soc.*, **32**, 877 (1936).

[4] P. Gross and H. Wischler, *ibid.*, **32**, 879 (1936).

[5] P. Gross, H. Steiner, and H. Suess, *ibid.*, **32**, 883 (1936).

[6] J. C. Hornel and J. A. V. Butler, *J. Chem. Soc.*, 1361 (1936).

[7] W. J. C. Orr and J. A. V. Butler, *ibid.*, 330 (1937).

[8] W. E. Nelson and J. A. V. Butler, *ibid.*, 958 (1938).

[9] E. L. Purlee, *J. Am. Chem. Soc.*, **81**, 263 (1959).

[10] V. Gold, *Trans. Faraday Soc.*, **56**, 255 (1960).

[11] C. G. Swain and E. R. Thornton, *J. Am. Chem. Soc.*, **83**, 3884 (1961).

[12] C. G. Swain and E. R. Thornton, *ibid.*, **83**, 3890 (1961).

[13] P. Salomaa, L. L. Schaleger, and F. A. Long, *ibid.*, **86**, 1 (1964).

[14] P. Salomaa, L. L. Schaleger, and F. A. Long, *J. Phys. Chem.*, **68**, 410 (1964).

[15] Values of l ranging between 0.67 and 0.71 have been observed.[16-18] We have used the value 0.67; however, calculations using l = 0.71 have little effect on our conclusions.

[16] K. Heinzinger and R. E. Weston, *J. Phys. Chem.*, **68**, 744 (1964).

[17] V. Gold, *Proc. Chem. Soc.*, 141 (1963).

[18] A. J. Kresge and A. L. Allred, *J. Am. Chem. Soc.*, **85**, 1541 (1963).

[19] A. O. McDougall and F. A. Long, *J. Phys. Chem.*, **66**, 429 (1962).

[20] R. P. Bell, "The Proton in Chemistry," Cornell University Press, Ithaca, New York, 1959, p 189.

One purpose of this investigation was to obtain more information on the validity of the generalized Gross equations relating to kinetics and to compare for different transition states the predictions made for rate behavior in H_2O–D_2O with experimental observations. A further point of interest concerns the fractionation factors for hydrogens being transferred and their sensitivity to changes in the transition state.

The mutarotation of glucose has been studied extensively and shows general acid and general base catalysis in H_2O–D_2O mixtures.[21,22] Swain and Thornton[12] considered the reaction in detail and derived equations relating k_n/k_H to n for several possible transition states. However, glucose contains four exchangeable hydrogens in addition to the one at the reactive site: to remove any possible secondary effects due to exchange of these hydrogens, α-D-tetramethylglucose was chosen as the substrate. Its mutarotation was studied in H_2O–D_2O mixtures for water, acetate ion, and hydronium ion catalysis and in the two pure solvents for catalysis by acetic acid.

Experimental Section

Materials. All chemicals used were of reagent grade. Heavy water was supplied by the U. S. Atomic Energy Commission and contained at least 99.6% D_2O. Tetramethylglucose was prepared according to the method described by West and Holden,[23] the samples used for the kinetic runs having melting points ranging from 85 to 99°, depending on the proportion of α isomer present.

For the water reaction, stock buffer solutions in light and heavy water were prepared containing 0.005 *M* sodium acetate and 0.0025 *M* acetic acid. Anhydrous sodium acetate and glacial acetic acid were used in the heavy water buffer solution. Since the concentrations of buffer components were low, the dilution in deuterium content introduced by the added hydrogen of the acetic acid was not significant. Buffered solvent mixtures were made up by mixing the corresponding stock solutions in the pure waters in the ratio required. The ionic strength in these and all other final solutions was maintained at 0.2 by adding the requisite amount of sodium chloride. The percentage composition of D_2O in each solution was determined by weight. For hydronium ion catalysis, stock solutions 0.15 *M* in hydrochloric acid were prepared in both waters. In the case of DCl, the required amount of 12 *N* HCl was pipetted into D_2O. The actual compositions of the acid solutions were then checked by titration against standard alkali. In this case the change in D_2O content caused by added hydrogen was significant although small, and appropriate corrections were applied. Mixed solvents were obtained from the stock solutions of HCl and DCl as in the previous case.

Solutions for acetate ion catalysis were prepared from stock solutions of acetic acid and anhydrous sodium acetate in the pure waters, in which the ratio of acetate ion to acetic acid was kept constant at 10. Dilution of these with the appropriate solvent gave the desired variation in acetate ion content without shifting the pH appreciably from about 5.7. It was assumed that the contribution to catalysis by acetic acid molecules was negligible and this assumption was justified by the experimental results.

Because of the smallness of the catalytic effect, rates for acetic acid catalysis were measured only in the pure solvents H_2O and D_2O. Solutions for these were prepared by keeping the concentration of anion constant and the pH as far as possible above 4. When this was not feasible, the catalytic effect of hydronium ion was not negligible; the concentration of hydrogen ion can, however, be calculated from the composition of the buffer solution and the appropriate correction applied. In all cases, this was found not to exceed 2%.

Polarimetric Measurements. Optical rotations were measured with a Rudolph photoelectric polarimeter operating on a mercury lamp. All kinetic runs were performed at 25 ± 0.02° by circulating water from a thermostat through the polarimeter jacket. Since the angle of rotation at 366 mμ was about three times the value at the sodium D line, the former wavelength was used for all measurements. The average concentration of tetramethylglucose used was 0.025 g/ml.

Results

Rate coefficients have been obtained for the three catalysts L_3O^+, L_2O (where L includes all the isotopically different hydrogens), and OAc^- in mixed solvents, and for AcOH in pure H_2O and AcOD in pure D_2O only. In buffered solutions containing acetate ion and acetic acid, the experimental first-order rate coefficient will be given by the general equation

$$k = k_0 + k_{L_3O^+}[L_3O^+] + k_{OL^-}[OL^-] + k_{OAc^-}[OAc^-] + k_{AcOL}[AcOL] \qquad (6)$$

It is known that in the case of glucose in the pH range 4–6, catalysis by H_3O^+ and OH^- is negligible.[24] The situation for the mutarotation of tetramethylglucose is very similar, and the experiments were therefore designed to adjust to and take advantage of this situation.

All first-order rate constants were determined by Guggenheim's method. Second-order rate coefficients for hydronium ion catalysis were calculated from the relation

$$k_{L_3O^+} = \frac{k - k_0}{[L_3O^+]}$$

and in the case of acetate ion or acetic acid catalysis from the slope of a plot of observed first-order rate constant against concentration of catalyst.

The results are summarized in Tables I to IV. As Table I shows, the isotope effects (k_D/k_H) on the mutarotation of tetramethylglucose are very similar to those for the mutarotation of glucose itself[21] and to those for the hydration and dehydration of acetaldehyde.[25]

Table I. k_D/k_H Ratios for the Mutarotation of Tetramethylglucose and Glucose and the Hydration and Dehydration of Acetaldehyde

	Mutarotation		Hydration of acetaldehyde	Dehydration of hydrate
	TMG	Glucose		
Hydronium ion	0.74_6	0.73_0	0.77	0.71_4
Water	0.27_9	0.26_3	0.27_7	0.25_6
Acetate ion	0.44_9	0.42_0	0.43_4	0.40
Acetic acid	0.40_6	0.38_6	0.40	0.35_7

Discussion

The data of Table I for relative rates in the two pure solvents H_2O and D_2O permit a few preliminary generalizations. The close similarity of rate ratios for mutarotation and for aldehyde hydration and dehydration suggests that the reaction mechanisms are similar. The near identity of the ratios for mutarotation of glucose and of tetramethylglucose indicates that the four "extra" hydroxyl hydrogens of glucose do not contribute a significant secondary isotope effect. Turning to the k_D/k_H values for the tetramethylglucose reaction, a first point to make is that the fractionation

---

(21) W. H. Hamill and V. K. LaMer, *J. Chem. Phys.*, **4**, 3195 (1936).

(22) E. A. Halevi, F. A. Long, and M. A. Paul, *J. Am. Chem. Soc.*, **83**, 305 (1961).

(23) E. S. West and R. F. Holden, *Org. Syn.*, 20, 97 (1940).

(24) R. P. Bell, "Acid Base Catalysis," Oxford University Press, London, 1941, p 60.

(25) Y. Pocker, *Proc. Chem. Soc.*, 17 (1960).

Table II

Catalyst	n	No. of expts	$k \times 10^{4\,a}$	k_n/k_H Obsd	k_n/k_H Calcd
Hydronium	0.000	3	50.9	1.000	
	0.249	3	48.4	0.951	
	0.495	3	45.5	0.894	
	0.749	3	42.5	0.835	
	0.984	3	38.3	0.752	
	1.000	...	38.0	0.746[b]	
Water	0.000	4	3.73	1.000	
	0.248	2	2.72	0.729	
	0.495	3	1.99	0.534	
	0.746	3	1.46	0.391	
	0.996	2	1.04	0.282	
	1.000	...		0.279[b]	
Acetate ion	0.000	4	20.5	1.00	
	0.298	3	17.0	0.829	0.810[c]
	0.497	3	14.6	0.712	0.697[c]
	0.698	3	12.6	0.617	0.591[c]
	0.996	4	9.2	0.445	...
	1.000	...	...	0.447[b]	
Acetic acid	0.000	3	1.60	1.00	
	0.996	3	0.65	0.406	

[a] Units of l. mole^{-1} sec^{-1} except for water catalysis where first-order rate coefficients are given. [b] Extrapolated values. [c] Calculated from eq 7 for $\phi_2 = 0.55$.

Table III. Comparison of k_n/k_H, for $n = 0.5$[a]

ϕ_2	ϕ_3	ϕ_4	ϕ_5	k_n/k_H
1.01	0.60	0.90	0.70	0.552
0.71	0.60	0.90	1.00	0.552
0.700	1.00	0.70	1.00	0.551
0.54	1.00	0.80	1.00	0.558
0.75	0.95	0.80	0.75	0.543
0.81	0.81	0.81	0.81	0.543
0.84	0.75	0.88	0.70	0.543
0.88	0.70	0.86	0.75	0.543
0.74	0.80	0.88	0.75	0.542
0.72	0.95	0.82	0.75	0.544
0.74	0.80	0.76	1.00	0.545

[a] Calculated with different ϕ values from eq 9. $\phi_1 = 1.23$. The experimental k_n/k_H is 0.534.

Table IV. Comparison of Experimental and Calculated k_n/k_H Values at $n = 0.5$ for Two Types of Transition States

	Exptl	Transition state A	Transition state B
	Acetate Ion		
ϕ_2		0.89	0.55
k_n/k_H at $n = 0.5$	0.712	0.675	0.697
	Acetic Acid		
ϕ_2		0.89	0.55
ϕ_3		...	0.907
k_n/k_H at $n = 0.5$		0.638	0.662
	Water		
ϕ_2		0.86	0.55
ϕ_4		...	0.79
k_n/k_H at $n = 0.5$	0.534	0.539	0.557
	Hydronium Ion		
ϕ_2		0.81	0.55
ϕ_3			0.907
ϕ_4			0.742
k_n/k_H at $n = 0.5$	0.894	0.846	0.863

factors for all the reactants are known. Specifically, ϕ_1 for the hydroxyl hydrogen of the glucose itself is 1.23;[26] ϕ_{HOAc} is 1.00; for the hydronium ion l^3 is 0.30 (see eq 5). For the general reaction

$$\text{TMG} + \text{catalyst} = \text{transition state}$$

the rate ratio for the solvents D_2O and H_2O will be

$$\frac{k_D}{k_H} = \frac{\pi\phi_i(\text{TS})}{\phi_1\pi\phi_i(\text{catalyst})}$$

where $\pi\phi_i(\text{TS})$ is the product of all the fractionation factors for the transition state. Since the observed k_D/k_H values for the reaction are all considerably below unity, and since the terms in the denominator are either close to or less than unity, the conclusion is that $\pi\phi_i(\text{TS})$ must be less than unity for all cases. This is particularly obvious for the water-catalyzed reaction where $\pi\phi_i(\text{TS}) = 0.279 \times 1.23 = 0.34$, a strikingly low value.

The experimental rate ratio for catalysis by hydronium ion is roughly three times that for water catalysis. Since for the former a term $1/l^3 = 3.3$ enters the equation, the fractionation factors for both transition states must be closely similar. A similar line of reasoning would predict close similarity in the k_D/k_H ratios for the reactions of acetic acid and acetate ion, as is observed.

For a more detailed analysis of the kinetic data there are two limiting approaches. The first is to assume on the basis of previous work that the transition state for the mutarotation of tetramethylglucose is known and see how well the experimental data fit the generalized equations. The other extreme is to assume the validity of the generalized equations and to use them to distinguish between different transition states. In practice, of course, neither approach is completely justifiable and a compromise must be made. To this end we first consider previous work relating to the mechanism of mutarotation.

Mechanism of Mutarotation of Tetramethylglucose. Much of the evidence discussed in this section was derived for glucose, but is is clear that nearly all will apply for tetramethylglucose. For a reaction to show general acid catalysis as does this mutarotation, there are several possibilities. There may be a fast pre-equilibrium protonation followed by a rate-determining step in which a different proton is removed by the conjugate base of the acid. Another possibility is that the rate-determining step is a slow proton transfer from the general acid followed by fast rearrangement to form products. Such a mechanism has occasionally been proposed for the mutarotation of glucose.[28] For either mechanism, as applied to the glucose reaction, a proton is transferred from the catalyst acid to the ether oxygen in the glucose; ring cleavage takes place; and a proton is abstracted from a hydroxyl group to form an open-chain aldehyde.[29] The two mechanisms differ in their timing and in their transition states. For the pre-equilibrium mechanism the slow step must involve a synchronous breaking of the ether linkage and abstraction of a proton by the conjugate base, whereas in the mechanism with slow proton transfer tne events after the slow step, *i.e.*, the breaking of the ether link-

---

[26] This is obtained from eq 5 using the literature value of K_H/K_D = 4.1 for the ratio of ionization constants for tetramethylglucose,[27] and the value of $l = 0.67$.

[27] Y. Pocker, *Chem. Ind.* (London), 968 (1960).

[28] S. W. Benson, "The Foundations of Chemical Kinetics," McGraw-Hill Book Co., Inc., New York, N. Y., 1960, p 560.

[29] J. M. Los, L. B. Simpson, and K. Weisner, *J. Am. Chem. Soc.*, **78**, 1564 (1956).

age and the formation of the aldehyde, are irrelevant to the observed kinetics.

Evidence that was once thought to favor the slow proton transfer, namely that $(k_D/k_H)_{H^+}$ is less than unity for the glucose reaction but greater than unity for enolization of acetone, has been shown by Challis, Long, and Pocker to be entirely consistent with a pre-equilibrium mechanism.[30] This is because, in the case of glucose, the hydrogen of the hydroxyl group which is removed in the slow step is in labile equilibrium with the deuterium in the solvent. A consideration of the relevant equilibria and rate constants for the individual steps of the glucose reaction then shows that the pre-equilibrium mechanism is in accord with the over-all k_D/k_H ratio.

A third possibility is a concerted or synchronous mechanism, involving simultaneous protonation of the ether oxygen and removal of the hydroxylic proton. Two hydrogens are transferred and the transition state may be cyclic. This type of mechanism has been proposed for the mutarotation of glucose by Swain and Brown,[31] who found that 2-hydroxypyridine is enormously more effective as a catalyst than a mixture of phenol and pyridine, even though 2-hydroxypyridine is a weaker base than pyridine and a weaker acid than phenol.

Mechanistic possibilities for general base catalysis parallel these three. There may be (a) slow proton removal accompanied by ring opening; (b) pre-equilibrium proton removal followed by slow attack of a general acid; (c) a concerted mechanism, perhaps with a cyclic transition state.

In the discussion so far, no mention has been made of possible solvent participation. It is easy to envisage water molecules acting as bridges between the glucose molecule and the acid or base catalyst.[32] Such water molecules will be hydrogen bonded into the structure, and, as in the case of the hydronium ion in water, the proton may be transferred by a synchronous making and breaking of hydrogen bonds. For the water-catalyzed reaction, water must act as an acid or a base and the questions are whether or not this is accomplished in a synchronous manner, perhaps *via* a cyclic transition state, and how many water molecules are involved. Similar questions may be asked about the hydronium ion and acetate ion catalyzed reactions.

The considerable similarity in the kinetic data for the glucose mutarotation and the hydration and dehydration of acetaldehyde (see, for example, Table I) suggests that the mechanistic information on the latter reaction has relevance to the mutarotation reaction. Bell and Darwent[33] conclude for the acid- and base-catalyzed hydration and dehydration reactions that the slow steps cannot be simply bimolecular and that instead the reaction must be termolecular, involving a water molecule in addition to the catalyst acid or base species. Their analysis does not, of course, preclude either the presence of further water molecules or the formation of a cyclic transition state.

One of the characteristics of the dehydration reaction is that it has been studied for a large number of catalysts, which have a very wide range of acid strengths, and shows remarkably linear Brønsted plots.[34] Eigen[35] has advanced reasons for expecting that, with acid- and base-catalyzed reactions in which there is a large change in the acid or base strengths of the catalysts, the typical Brønsted plot should show some curvature. This is a consequence of the fact that the relative slopes at the point of intersection of the potential energy curves of the substrate S–H bond, and the catalyst B–H bond, will not be the same where the acid strength of BH is changed drastically. He reconciles the observed linearity by postulating a mechanism involving a cyclic transition state with water molecules bridging between the substrate and the catalyst. In this way protons are transferred to and from the catalyst at a site effectively removed from the substrate by several water molecules. Thus, drastic changes in the potential energy curves are minimized.

Ahrens and Strehlow[36] consider that with a pre-equilibrium mechanism for acid catalysis of the aldehyde hydration reaction the concentration of the protonated aldehyde is extremely small. From studies in acetaldehyde–water mixtures in which the acidity function changes by a whole unit, while the observed rate decreases by only 40%, they conclude that there is strong evidence against a pre-equilibrium mechanism. The pK_B of acetaldehyde in water is estimated by them to be about -8. This means that the second-order rate constant for the second step; namely, the reaction of the protonated species with base is slightly larger than the theoretical maximum for a diffusion-controlled reaction. On these grounds the authors prefer a concerted mechanism.

From these considerations we conclude that the aldehyde reactions almost surely proceed by concerted mechanisms, probably by a cyclic transition state which includes one or more solvent water molecules. By analogy the same mechanism is a likely possibility for the glucose mutarotation. In the detailed analysis of the data for tetramethylglucose, then, we shall explicitly consider and compare the consequences of transition states with no inclusion of solvent molecules (except, of course, a single molecule for catalysis by water itself), and with deliberate inclusion of two water molecules,[37] *i.e.*, sufficient to permit easy formation of a cyclic transition state. Inclusion of larger numbers of water molecules than two does not sharply modify any of the conclusions and is therefore explicitly discussed in only one instance.

The Acetate Ion Catalyzed Reaction. An interesting qualitative feature of the k_n/k_H *vs.* n data is the approximately linear plot obtained (Figure 1). The simplest transition state that can be envisaged for this reaction is the removal of a proton from the hydroxyl group with

---

[30] B. C. Challis, F. A. Long, and Y. Pocker, *J. Chem. Soc.*, 4679 (1957).

[31] C. G. Swain and J. F. Brown, *J. Am. Chem. Soc.*, **74**, 2534, 2538 (1952).

[32] C. A. Bunton and V. J. Shiner, *ibid.*, **83**, 3214 (1961).

[33] R. P. Bell and B. de B. Darwent, *Trans. Faraday Soc.*, **46**, 34 (1950).

[34] R. P. Bell and W. C. E. Higginson, *Proc. Roy. Soc.* (London), A197, 141 (1959).

[35] M. Eigen, *Angew. Chem.*, 75, 489 (1963).

[36] M. L. Ahrens and H. Strehlow, *Discussions Faraday Soc.*, in press.

[37] Two water molecules are the minimum required to satisfy the condition that the hydrogen bands in the cyclic transition state are linear. A six-membered cyclic transition state with one water molecule bridging between the hydroxyl group and the ether oxygen does not satisfy this condition. We have, however, made calculations for transition states with only one water molecule in addition to the catalyst. Not surprisingly, the results are intermediate between those for inclusion of none and two water molecules.

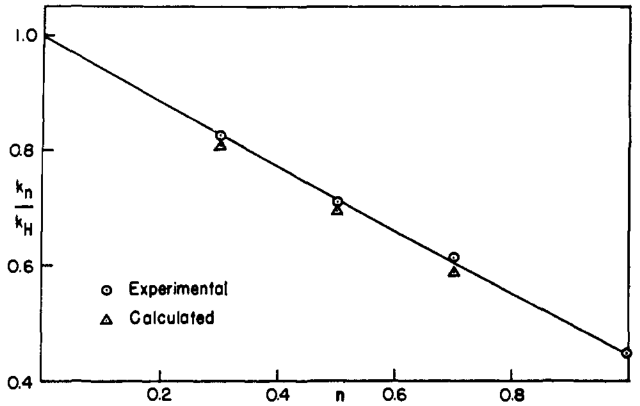
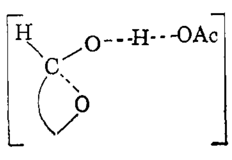
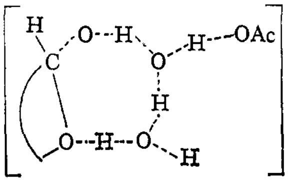


Figure 1. Relative rate of acetate ion catalyzed mutarotation of α-D-tetramethylglucose *vs.* atom fraction *n* of deuterium in mixed H_2O-D_2O solvents. Calculated points are from eq 7 with ϕ_2 = 0.55 for the single exchangeable proton in the transition state.



Ia



Ib

simultaneous ring cleavage (Ia below). In this case, the generalized equations are of the form

$$k_n/k_H = \frac{(1 - n + n\phi_2)}{(1 - n + n\phi_1)} \quad (7)$$

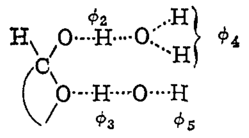
where ϕ_1 is the fractionation factor of the hydrogen in tetramethylglucose and ϕ_2 the fractionation factor of the hydrogen being transferred in the transition state. As noted earlier, ϕ_1 is known to be 1.23. Hence from the value of k_D/k_H, ϕ_2 can be obtained (0.55) and these values can be used in eq 7 to calculate k_n/k_H. The results, given in Table III, are plotted in Figure 1 and the agreement with the experimental values is good. From the form of eq 7 it may be seen that a completely linear plot of k_n/k_H *vs.* *n* would be expected if ϕ_1 had a value of unity. Furthermore, even a modestly smaller value of ϕ_1 leads to better agreement with experimental data. Thus at $n = 0.5$ using $\phi_1 = 1.15$, k_n/k_H(calcd) is 0.706 compared with the calculated value of 0.697 for $\phi_1 = 1.23$ and with the experimentally observed value of 0.712. Taking account of the experimental errors in k_n/k_H and K_H/K_D and the determination of *l*, the generalized equation applied to the transition state I gives a very satisfactory agreement with experiment. This agreement is for the simplest mechanism and has the merit that there are no adjustable parameters. The chief difficulty is that the calculated value of ϕ_2 = 0.55 is very low, lower than even the fractionation factor of 0.67 for the very acidic protons of hydronium ion.

Consider next a cyclic synchronous mechanism with two water molecules in the transition state (structure IB; an alternative incorporates the acetate ion in the ring). In this case there will be five hydrogens in the transition state, each having its own fractionation factor. As a first approximation these may be considered to be the same; the generalized equation then takes the form

$$k_n/k_H = \frac{(1 - n + n\phi_2)^5}{(1 - n + n\phi_1)} \quad (8)$$

Using the experimental value of ϕ_1 as before, ϕ_2 is calculated to be 0.89. The calculated value for k_n/k_H at $n = 0.50$ is then 0.675 compared with the observed value of 0.712 at $n = 0.698$ k_n/k_H(calcd) is 0.577 compared with the observed value 0.615. The agreement between calculation and experiment is poorer than before. From the form of eq 8 it is obvious that k_n/k_H in this case cannot be a linear function of *n*. However, the difference between calculated values of k_n/k_H for eq 7 and 8 is still not especially large.

The Water-Catalyzed Reaction. One can use as a generalized transition state for the water-catalyzed reaction



The generalized equation for this transition state is

$$k_n/k_H = \frac{(1 - n + n\phi_2)(1 - n + n\phi_3)(1 - n + n\phi_4)^2(1 - n + n\phi_5)}{(1 - n + n\phi_1)} \quad (9)$$

One or the other of the water molecules can be excluded from our consideration by making the appropriate fractionation factors unity. For example, use of $\phi_3 = \phi_5 = 1$ effectively excludes the water attached to the ether oxygen. Furthermore some obvious hydrogen bond linkages produce a cyclic transition state. Values of fractionation factors for hydrogens in different acids vary between 0.67, which is the value of *l*, the fractionation factor of the hydronium ion, to 1.3, which is observed for hydrogen in some very weak hydroxylic acids. In the above transition state it would be expected that apart from the actual hydrogen being transferred, the fractionation factors will change from their ground-state values only in a way that reflects their changing acidity. k_D/k_H and ϕ_1 are known; hence, in eq 9 there are three variables which can be treated as adjustable parameters. Using a computer, k_n/k_H was hence calculated for values of *n* at which the experimental observations were made and for all values of ϕ_5 between 0.7 and 1.0 in intervals of 0.05, for values of ϕ_3 between 0.6 and 1.20 in intervals of 0.05, and for values of ϕ_4 between 0.7 and 1.0 in intervals of 0.02. Those sets of fractionation factors which gave values of k_n/k_H close to the experimental values were examined more closely. Several features emerged from this analysis.

First, there is no clearly unique set of fractionation factors which alone describes the experimental data. There are many such combinations. This is illustrated in Table III. At the same time, many other combinations are clearly eliminated from consideration. Secondly, other combinations may be eliminated by a strict adherence to the physical significance of fractionation factors. For instance, the transition state in this case is uncharged; consequently, very low fractionation factors, indicative of acidity comparable to that of the hydronium ion, should be avoided. Thirdly, even though there are three adjustable parameters, it was impossible to obtain values of k_n/k_H at $n = 0.5$ lower than 0.540. Finally, if ϕ_3, ϕ_4, and ϕ_5 are taken to be close to unity, implying "waterlike" protons, then ϕ_2 again assumes implausibly low values.

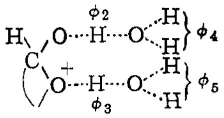
This general treatment clearly permits consideration of a cyclic transition state. A simple approach here is to assume all hydrogens equivalent. As noted in Table III, use of $\phi_2 = \phi_3 = \phi_4 = \phi_5 = 0.81$ leads to a value of k_n/k_H for $n = 0.5$ of 0.543 which is close to the minimum obtainable for this group of factors. A slightly more sophisticated treatment would be to distinguish between the three H-bonded hydrogens which are essential to give a cyclic transition state and the other two hydrogens. However, the general character of the results of Table III makes it very doubtful that this can lead to significantly better-fitting values of k_n/k_H. We conclude that a cyclic transition state with two water molecules is satisfactory but not at all required.

For a transition state involving three water molecules, again assuming that the fractionation factors of the hydrogens involved are the same

$$k_n/k_H = \frac{(1 - n + n\phi_2)^7}{(1 - n + \phi_1)}$$

Since $k_D/k_H = 0.279$ and $\phi_1 = 1.23$, ϕ_2 must be chosen as 0.86. Using these values, at $n = 0.248$, k_n/k_H(calcd) = 0.736 [k_n/k_H(obsd) = 0.729]; at $n = 0.5$, k_n/k_H(calcd) = 0.539 [k_n/k_H(obsd) = 0.534]; and at $n = 0.746$, k_n/k_H(calcd) = 0.396 [k_n/k_H(obsd) = 0.39]. This represents a better fit of the k_n/k_H data than any of those of Table III, but even so the improvement is hardly beyond experimental error.

The Hydronium-Catalyzed Reaction. In a manner similar to the previous case, a generalized transition state for this reaction can be written as



The relevant general equation is

$$k_n/k_H = \frac{(1 - n + n\phi_2)(1 - n + n\phi_3)(1 - n + n\phi_4)^2(1 - n + n\phi_5)^2}{(1 - n + n\phi_1)(1 - n + nl)^3} \qquad (10)$$

A term $(1 - n + nl)^3$ appears in the denominator to account for the hydronium ion. The value of k_D/k_H for this reaction is 0.746. In spite of this larger value, the product of the factors for the transition state must again be much less than unity. This is especially apparent for the case of minimal solvent participation, *i.e.*, where ϕ_4 and ϕ_5 are both assumed to be unity. Then, since $\phi_1 = 1.23$ and $l = 0.67$

$$k_D/k_H = \frac{\phi_2\phi_3}{1.23 \times 0.30}$$

$\phi_2\phi_3 = 0.275$ which implies quite small values for either ϕ_2 or ϕ_3 or both.

For more detailed study of the influence of fractionation factors, ϕ_5 was taken to be unity and then the values of k_n/k_H were calculated for several values of n with systematic variation of the other three fractionation factors using the same computer program as was used for the water reaction.

It was again found that the experimental data could be well fitted to several sets of values of the fractionation factors. The calculated values of k_n/k_H were in fact less sensitive to changes in fractionation factors then those for the water reaction. In view of this generally good fit, explicit results of the calculations are not tabulated. As only one example, for $\phi_2 = 0.43$, $\phi_3 = 0.90$, and $\phi_4 = 0.84$, k_n/k_H at $n = 0.5$ calculates to be 0.890, whereas the experimental value is 0.896.

A cyclic transition state with only two waters in addition to the catalyst species H^+, and with the simplifying assumption of all hydrogens are equivalent, leads to

$$k_D/k_H = \frac{(1 - n + n\phi_2)^6}{(1 - n + n\phi_1)(1 - n + nl)^3}$$

From the k_D/k_H value, ϕ_2 calculates to be 0.81. Then for $n = 0.5$ $k_n/k_H = 0.846$ compared to an observed value of 0.896. This is not especially good agreement, but a somewhat better one can be obtained by not treating all hydrogens as equal.

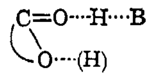
Increasing the number of the water molecules in the transition state does not lead to better agreement with experiment. Thus, if three water molecules plus H^+ are utilized and the hydrogens in the transition state are assumed equivalent, the equation for k_n/k_H is like the above with an eight power term in the numerator on the right. The required value of ϕ_2 becomes 0.85 and the calculated k_n/k_H at $n = 0.5$ is 0.826. This is still more distant from the observed than that for two water molecules. We conclude that again a cyclic mechanism is satisfactory but offers no advantages in data fitting.

Acetic Acid Catalysis. Because of the low contribution of the acetic acid catalyzed term to the over-all reaction, it is difficult to obtain results of the necessary accuracy for this catalyst. The rate constants for the acetic acid catalyzed reaction in the two pure solvents gave a ratio k_D/k_H of 0.41. For a conventional pre-equilibrium transition state with a proton on the ether oxygen and acetate ion attack on the hydroxyl hydrogen, *i.e.*, a protonated version of transition state Ia, one obtains

$$k_D/k_H = \frac{\phi_2\phi_3}{\phi_{HOAc}\phi_1}$$

where ϕ_3 refers to the proton being transferred to the ether oxygen. Since ϕ_1 is 1.23 and ϕ_{HOAc} is 1.00, this leads to $\phi_2\phi_3 = 0.50$, again implying low values for ϕ_2 or ϕ_3 or both. No data are available for k_n/k_H for tetramethylglucose. We can, however, estimate from the results for glucose that k_n/k_H at $n = 0.5$ would lie in the range 0.61 to 0.67. It then turns out that a value within this range is easily obtained either from the conventional transition state (protonated Ia) or from a cyclic transition state with two added water molecules.

Comparison of Different Mechanisms. It is apparent from the preceding discussion that k_n/k_H ratios offer no unambiguous choice between the mechanisms. Table IV summarizes the predictions made for a cyclic transition state (A) with two water molecules and the catalyst species, and a transition state (B) of the type below where the (H) refers to a proton present only for acid catalysis.



To obtain Table IV several assumptions were made for the fractionation factors of the transition states. For the cyclic states all hydrogens were assumed equivalent in each case. For the conventional states (B), a sort of stepwise assignment was used. In all cases, 0.55 was used for ϕ_2, *i.e.*, the value obtained from k_D/k_H for acetate ion catalysis. For acetic acid this then leads to $\phi_3 = 0.707$, a value which in turn was accepted for the hydronium ion reaction. These are not necessarily the best values in every case; they do, however, give a consistent set of factors.

In terms of data-fitting there is no strong preference for one kind of transition state relative to the other. The B-type is perhaps slightly preferable for acetate ion and hydronium ion catalyses but slightly poorer for the water reaction. A possibly more significant point is that the B-type seems almost inescapably to lead to ϕ_2 values which are so low as to make interpretation of them very difficult in terms of equilibrium acid–base data and behavior. A different kind of comment is that, even with the simplified approach of equivalent hydrogens, the cyclic transition states are reasonably satisfactory, a result which then permits other kinds of evidence to be adduced in their support.

The Chromium(II) Reductions of Some Cobalt(III) Aquoammine Complexes[1]

Roderick D. Cannon and Joseph E. Earley

Contribution from the Department of Chemistry, Georgetown University, Washington 7, D. C. 20007. *Received September 28, 1965*

Abstract: The rate of Cr(II) reduction ($\mu = 1$, $NaClO_4$) of *cis-* and *trans*-diaquo- and -aquoamminebis(ethylenediamine)cobalt(III) ions has been found to follow the rate law $R = k[\mathrm{Co(III)}][\mathrm{Cr(II)}][\mathrm{H}^+]^{-1}$. The temperature dependence of the acidity constants of the substrates has been measured. Second-order rate constants at 25° (M^{-1} sec^{-1} $\times 10^{-6}$) and energies of activation (kcal/mole) for the reduction of the hydroxo complexes are: aquo complexes, *cis* 0.79, 6.4; *trans* 2.6, 2.6; ammine complexes, *cis* 0.20, 6.2; *trans* 0.22, 2.4. The small effect of *trans* H_2O relative to the effect noted in similar Fe(II) systems has been interpreted on the basis of less reorganization within the binuclear complex for the Cr(II) reduction. The variation of activation energies for the Cr(II) reductions may be interpreted on the same basis or as an effect on the formation of the binuclear complex.

Reduction of Cr(III) or Co(III) by Cr(II) usually proceeds *via* a binuclear transition state M(III)–X–Cr(II) if the trivalent complex contains a group, X, capable of binding two metals at once.[2] The dependence of the rate of reduction on the nature of the groups present in the transition state has been examined in some detail.[2–5] This paper is concerned with the influence of the nonbridging ligands of the trivalent ion.

In 1956, Orgel proposed[6] that the field strength of the ligand *trans* to the bridging group should be a dominating factor. This followed from the assumption that the incoming electron enters the nonbonding d_{z^2} orbital, the energy of which would be expected to be more seriously affected by variation in field strength of the *trans* ligands than by a similar variation for the *cis* ligands. More recently[2,5] it has been emphasized that outward motion of the *trans* ligand should lower the energy of the d_{z^2} orbital and thereby facilitate electron transfer.

We now report the kinetics of Cr(II) reduction of the ions *cis-* and *trans*-$\mathrm{Co(en)_2(H_2O)_2}^{+3}$ and *cis-* and *trans*-$\mathrm{Co(en)_2(NH_3)H_2O}^{+3}$,[7] the object being to observe the effect of H_2O and NH_3 in both stereochemical positions relative to the bridge.

Experimental Section

***trans*-Hydroxoaquobis(ethylenediamine)cobalt(III) Perchlorate (tO).** This was prepared by a modification of the method of Basolo and Steninger.[8] A 15-g portion of *trans*-dichlorobis(ethylenediamine)cobalt(III) chloride[9] was heated in 15 ml of water for a few minutes and passed through Amberlite IRA-400 (hydroxide form). The effluent, not exceeding 30 ml was made just acid with 72% perchloric acid, and treated with pyridine (5 ml). The solid was purified twice by dissolving in the minimum quantity of 1 *N* perchloric acid and titrating to pH 3.5 with 10 *N* NaOH,[10] yield 4.7 g. The *cis* salt is not precipitated under these conditions.

Anal. Calcd for $[\mathrm{Co(en)_2(H_2O)(OH)}](\mathrm{ClO_4})_2$: C, 11.6; H, 4.60; N, 13.6. Found:[11] C, 12.0; H, 4.83; N, 13.5.

---

[1] Presented in part before the Chemical Society of Washington, College Park, Md., May 1965.

[2] H. Taube, *Advan. Inorg. Chem. Radiochem.*, **1**, 1 (1959).

[3] Effect of bridging groups: J. P. Candlin, J. Halpern, and O. L. Trimm, *J. Am. Chem. Soc.*, **86**, 1019 (1964).

[4] Nonbridging ligands on Cr(II): (a) J. B. Hunt and J. E. Earley, *ibid.*, **82**, 5312 (1960); (b) R. D. Cannon and J. E. Earley, to be published.

[5] P. Benson and A. Haim, *J. Am. Chem. Soc.*, **87**, 3826 (1965).

[6] L. E. Orgel in "Quelques Problemes de Chimie Minerale," Institute Solvay, Brussels, 1956, p 289.

[7] Complexes will be called cO, tO, cN, tN, or generally, $\mathrm{ROH_2}^{+3}$ or ROH^{+2}; en is ethylenediamine.

[8] F. Basolo and D. H. Steninger, *J. Am. Chem. Soc.*, **72**, 5748 (1950).

[9] J. C. Bailar and C. L. Rollinson, *Inorg. Syn.*, **2**, 222 (1946).

[10] W. Kruse and H. Taube, *J. Am. Chem. Soc.*, **83**, 1280 (1961).

[11] Analyses by Schwarzkopf Microanalytical Laboratory, Inc.