Kinetics of the Mutarotation of α-D-Tetramethylglucose in Aqueous Dioxan and Dimethyl Sulphoxide Solution

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The kinetics of the mutarotation of α-D-tetramethylglucose have been studied by following their optical rotations in solution of water in dioxan and in dimethyl sulphoxide, over a wide range of water concentrations, with and without the addition of catalysts. The results in both solvents suggest that in the ' uncatalysed ' reaction the transition state contains one molecule of glucose and two molecules of water in a cyclic hydrogen-bonded structure; in the pyridine-catalysed reaction one molecule of water may be replaced by a molecule of the base. The balance of evidence suggests that the reaction takes place by an intimate step-wise mechanism rather than a synchronous process.

THE mutarotation of glucose and the reversible hydration of acetaldehyde are special cases of the general reaction (1).[1] Both reactions are catalysed by acids and

$$R^1R^2CO + R^3OH \rightleftharpoons R^1R^2C(OH)OR^3 \qquad (1)$$

bases. The fact that the k_H/k_D values for various catalysts for these reactions are virtually identical[2] strongly suggests that they proceed by similar mechanisms. For the reversible hydration of carbonyl compounds, Eigen,[3] using kinetic arguments based partly on estimates of the absolute rates of the individual processes, has proposed a concerted mechanism involving a hydrogen-bonded transition state which includes two or more water molecules. In n.m.r. studies[4] on proton exchange between carboxylic acids and water and methyl alcohol, it has been found necessary to postulate cyclic transition states containing several solvent molecules. In a more direct study on the hydration reaction of 1,3-dichloroacetone[5] in which the kinetic effect of varying the concentration of water dissolved in a non-reactive solvent was investigated, Bell and his co-workers conclude that in the uncatalysed reaction, the transition state is cyclic and contains one molecule of ketone and three molecules of water; in the catalysed reaction a molecule of triethylamine or benzoic acid can replace one or two molecules of water respectively. It is also suggested that the reaction takes place by the step-wise transfer of three protons rather than by their synchronous motion. The mutarotation of tetramethylglucose proceeds at a reasonably convenient rate in a 40% solution of water in dioxan. As one of the classic examples of a reaction which undergoes general acid–base catalysis, it is important that its reaction mechanism be fully understood. The present investigation seeks to provide direct evidence as to the number of water molecules in the transition state by a kinetic approach analogous to that used for 1,3-dichloroacetone.

EXPERIMENTAL

α-D-Tetramethylglucose was prepared and purified according to the method described by West and Holden[6] and repeatedly recrystallised until the m.p. was at least 97 °C. Dioxan was purified by refluxing over molten sodium until it remained bright followed by fractional distillation, b.p. 101.5°. Dimethyl sulphoxide (DMSO) was purified by fractional vacuum distillation of commercial DMSO under dried nitrogen.[7]

Pyridine, purified by double distillation of the AnalaR product over sodium hydroxide had b.p. 115°, n_D^{20} 1.510 2 (lit.,[8] b.p. 115.3°, n_D^{20} 1.510 20). The perchlorate was prepared by the direct addition of 60% perchloric acid to a solution of pyridine in ethanol in the required proportion, and the salt recrystallised repeatedly from ethanol until it had m.p. 289—290° (lit.,[9] 289—290°).

The reaction solutions were *ca.* 0.27M in glucose and in the case of the catalysed reactions were prepared from appropriate buffered stock solutions containing the requisite amount of salts to maintain the pH in the range 4—6. This was necessary to suppress any contribution from hydronium or hydroxide ion catalysis to the overall kinetics.[10] In the case of the runs without added catalysts, traces of HCl were added for the same reason. The pH of each mixed solution was checked with a pH-meter before being used.

The reactions were followed by the change in optical rotation, using a Bellingham and Stanley polarimeter with a sodium lamp light source. All kinetic runs were performed at 25 ± 0.02°.

All reactions followed a first-order course and velocity constants were determined graphically either by using the infinity reading or by Swinbourne's procedure.[11]

The equation for the general acid–base catalysed mutarotation of tetramethylglucose in buffered aqueous solutions containing a series of acids HA_j and a series of bases B_n, may be written as (2) where k_{obs} is the overall velocity

$$k_{obs} = k_{H_2O} + k_{H_3O^+}[H_3O^+] + k_{OH^-}[OH^-] + \Sigma_j k_{HA_j}[HA_j] + \sum_n k_{B_n}[B_n] \qquad (2)$$

constant, k_{H_2O} is the velocity constant of the ' spontaneous ' water reaction and the summations are for all the acid and base species present in the system, these being characterised by catalytic velocity constants. It is known that in the pH range 4—6, catalysis by hydrogen and hydroxide ions is negligible.[10] Thus, in the presence of a base B and its

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[1] R. P. Bell, *Adv. Phys. Org. Chem.*, 1966, **4**, 1.

[2] H. H. Huang, A. N. H. Yeo, and L. H. L. Chia, *J. Chem. Soc.* (*B*), 1969, 836.

[3] M. Eigen, *Discuss. Faraday Soc.*, 1965, **39**, 7.

[4] (*a*) E. Grunwald, C. F. Jumper, and S. Meiboom, *J. Amer. Chem. Soc.*, 1963, **85**, 522; (*b*) E. Grunwald and S. Meiboom, *ibid.*, p. 2047; (*c*) Z. Luz and S. Meiboom, *ibid.*, p. 3923.

[5] R. P. Bell, J. P. Millington, and J. M. Pink, *Proc. Roy. Soc.*, 1968, **A303**, 1.

[6] E. S. West and R. F. Holden, *Org. Synth.*, 1940, **20**, 97.

[7] H. L. Schlafer and W. Schaffernicht, *Angew. Chem.*, 1960, **72**, 618.

[8] D. P. Biddiscombe, B. A. Coulson, R. Handley, and E. F. G. Herington, *J. Chem. Soc.*, 1954, 1957.

[9] J. G. Pritchard and F. A. Long, *J. Amer. Chem. Soc.*, 1957, **79**, 2365.

[10] J. N. Brønsted and E. A. Guggenheim, *J. Amer. Chem. Soc.*, 1927, **49**, 2554.

[11] E. S. Swinbourne, *J. Chem. Soc.*, 1960, 2317.

conjugate acid BH^+ in the pH range 4—6, equation (2) becomes (3). When the reaction is carried out in a mixed

$$k_{obs} = k_{H_2O} + k_B[B] + k_{BH^+}[BH^+] \qquad (3)$$

solvent consisting of water and dioxan, this equation should be modified to (4), the catalytic effect of dioxan being negligible.

$$k_{obs} = k_{H_2O}[H_2O]^n + k_B[H_2O]^{n_1}[B] + k_{BH^+}[H_2O]^{n_2}[BH^+] \qquad (4)$$

For the reaction without added catalyst, this expression simplifies to (5). Thus, a plot of log k_{obs} *versus* log $[H_2O]$

$$k_{obs} = k_{H_2O}[H_2O]^n \qquad (5)$$

should give a value of n, which may be interpreted as the number of water molecules associated with the transition state. It was found that for solutions of water in both dioxan and dimethyl sulphoxide expressed on the molarity scale, such plots were linear within experimental errors giving values of n close to 2 [Figures 1(a) and (b)]. If the exponent n is considered to have the integral value 2, the value of k_{H_2O} may be determined by least squares. The rate law is then given by the equations (6).

$$k_{obs} = \begin{cases} 1.02\ [H_2O]^2 \times 10^{-7}\ (H_2O \text{ in dioxan}) \\ 0.97\ [H_2O]^2 \times 10^{-7} \\ \qquad (H_2O \text{ in dimethyl sulphoxide}) \end{cases} \qquad (6)$$

For the pyridine-catalysed reaction, the rate expression (at pH 4—6) is given by (7) with the last term dropping out

$$k_{obs} = k_{H_2O}[H_2O]^2 + k_B[\text{pyridine}][H_2O]^{n_1} + k_{BH^+}[\text{pyridine perchlorate}][H_2O]^{n_2} \qquad (7)$$

since the pyridinium ion has no measurable catalytic effect.[2] Assuming the exponent for the term [pyridine] is one, equation (7) may be written as (8). Thus, a plot of

$$k_c = k_{obs} - k_{H_2O}[H_2O]^2/[\text{pyridine}] = k_B[H_2O]^n \qquad (8)$$

log k_c *versus* log $[H_2O]$ should yield the apparent kinetic order with respect to water.

Attempts were also made to study the effect of acetate ion, benzoate ion, and benzoic acid as catalysts, using sodium salts to buffer the solutions. However, the results obtained in these cases were erratic, caused probably by solubility difficulties and the smallness of the benzoic acid catalytic effect. Solubility difficulties also limited the range over which acetate ion catalysis could be studied.

DISCUSSION

It is generally accepted that the mutarotation reaction involves two proton transfers at different sites of the substrate molecule,[12-15] the reaction scheme being formulated either as a series of consecutive steps, or in terms of a concerted mechanism in which the transition state contains two catalyst molecules, one acid and one base. The concerted type of mechanism first proposed by Lowry [16] and later accepted by Brønsted and Guggenheim,[10] was further supported by Swain and Brown who found that 2-hydroxypyridine is overwhelmingly more effective as a catalyst than a mixture of phenol and

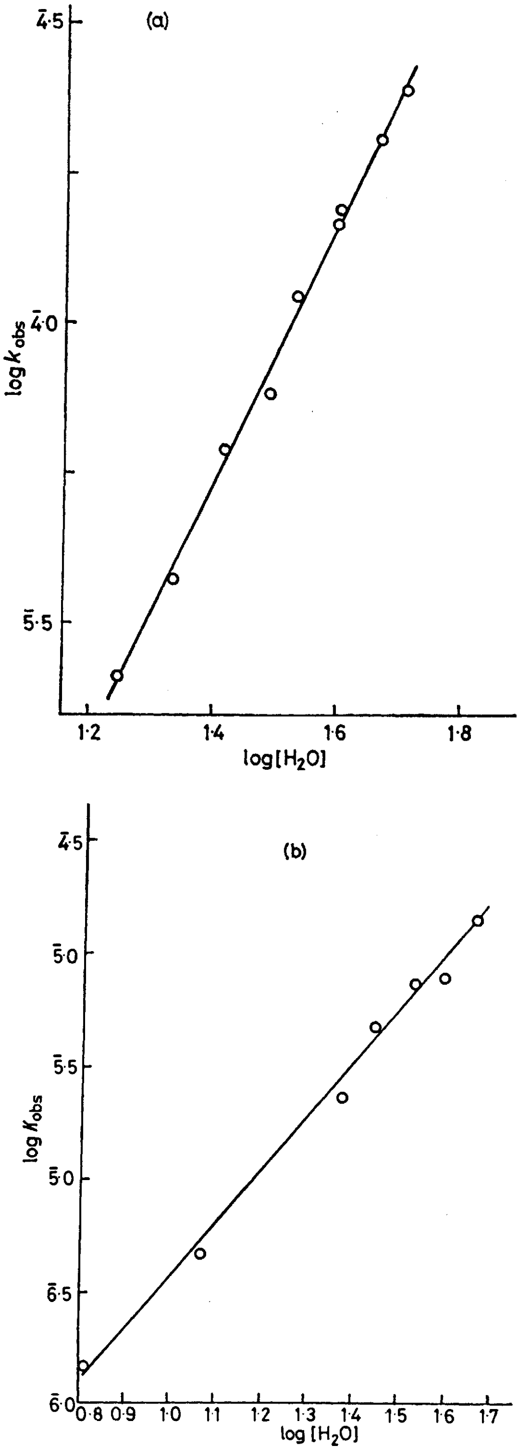

FIGURE 1 (a) Plot of log k_{obs} *versus* log $[H_2O]$. Water in dioxan (without catalyst). (b) Plot of log k_{obs} *versus* log $[H_2O]$. Water in dimethyl sulphoxide (without catalyst)

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[12] S. W. Benson, 'The Foundation of Chemical Kinetics,' McGraw-Hill, New York, 1960, p. 560.

[13] J. M. Los, L. B. Simpson, and K. Weismer, *J. Amer. Chem. Soc.*, 1956, **78**, 1964.

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

[15] C. G. Swain and J. F. Brown, *J. Amer. Chem. Soc.*, 1952, **74**, 2534, 2538.

[16] T. M. Lowry and I. J. Faulkner, *J. Chem. Soc.*, 1925, **127**, 2883.

pyridine, even though it is a weaker base than pyridine and a weaker acid than phenol.[17]

Studies [18] on the acid–base catalysed mutarotation of α-D-tetramethylglucose in mixed H_2O–D_2O solvents have shown that although the experimental data can be fitted fairly well by the generalized Gross–Butler equations using the conventional consecutive mechanism for the mutarotation, some of the necessary fractionation factors were difficult to interpret in the light of ordinary acid–base data. On the other hand cyclic concerted mechanisms, involving two or three solvent water molecules, fit the data about as well and moreover, lead to plausible fractionation factors. Of particular interest [2] is the observation that for the series of the base catalysts, pyridine, 2-picoline, 4-picoline, and 2,6-lutidine, a pronounced steric effect was found for the last member. To explain this, it was necessary to postulate a cyclic transition state in which the attacking base is relatively close to the reaction centre possibly associated with one water molecule. The overall evidence for a cyclic transition state is therefore quite strong.

TABLE 1

Collected velocity constants. C_w molarity of water; observed velocity constants k_{obs} in s^{-1}; C_{py} molarity of pyridine; $k_c = [k_{obs} - k_{H_2O}C_w^2]/C_{py}$

Dioxan solution									
No catalyst									
C_w	17.62	21.50	25.95	30.60	33.74	39.15	39.35	45.37	50.08
$10^5 k_{obs}$	2.588	3.744	6.174	7.652	11.13	14.59	15.44	20.29	24.46
Catalyst pyridine; buffer mixture: pyridine–pyridine perchlorate									
C_w	1.46	2.99	4.83	7.46	9.92	16.85	19.04	22.76	28.48
	33.04	37.74	39.67	44.77	49.73	52.21	55.55		
C_{py}	0.8140	0.397	0.2169	0.1880	0.1008	0.1110	0.1070	0.1101	0.1070
	0.1094	0.1128	0.1126	0.1062	0.1107	0.1129	0.2016		
C_{salt}	0.0310	0.0044	0.0064	0.0280	0.0060	0.0195	0.0203	0.0333	0.0340
	0.0368	0.5999	0.0508	0.0547	0.0962	0.1001	0.2000		
$10^5 k_{obs}$	2.12_0	1.88_6	2.02_2	3.29_7	2.97_6	7.38_7	8.94_8	12.96	21.38
	30.03	46.11	49.90	69.22	98.12	109.09	175.0		
$10^5 k_c$	2.580	4.596	8.237	14.58	19.76	40.42	49.07	69.70	122.4
	172.7	280.0	300.6	459.3	658.5	720.0	715.0		
Dimethyl sulphoxide solution									
No catalyst									
C_w	6.40	11.67	23.61	28.08	33.66	39.33	45.73		
$10^5 k_{obs}$	0.140	0.465	2.345	4.798	7.533	8.080	14.29		
Catalyst pyridine; buffer mixture: pyridine–pyridine perchlorate									
C_w	1.67	2.89	4.48	4.98	5.96	7.90	11.36	15.59	22.11
	26.43	36.72							
C_{py}	0.816	0.1025	0.0999	0.0980	0.1007	0.0984	0.0994	0.1814	0.1004
	0.1007	0.1070							
C_{salt}	0.0314	0.0661	0.0656	0.0636	0.0646	0.0587	0.0507	0.0051	0.0526
	0.0506	0.0514							
$10^5 k_{obs}$	1.47_8	0.460	0.831	0.891	1.26_7	1.636	2.897	5.37_4	9.063
	13.64	31.84							
$10^5 k_c$	1.778	3.673	6.306	6.561	9.057	10.28	16.17	16.220	41.58
	66.55	171.6							

The observed velocity constants are listed in Table 1. The apparent kinetic orders with respect to water were determined by linear regression and are collected in Table 2.

For the mutarotation reactions with no added catalyst, Table 2 shows that the orders with respect to water in both solvents are close to 2. It is interesting that this order of 2 is observed for concentrations of water in two non-reactive solvents as dissimilar in structure and dielectric constant as dioxan and dimethyl sulphoxide, starting from *ca.* 8M. It was unfortunate that at lower concentrations of water, the reactions were too slow for results of the necessary accuracy to be obtained. At these (still relatively high) concentrations of water, deviations from the laws of dilute solutions have been observed (for dioxan); but it is probable that as the water concentration increases, the activity coefficient of the glucose molecule varies similarly to f_w, the activity coefficient of water; and that the activity coefficient of the transition state varies similarly to f_w^2, since their non-ideal behaviour arises mainly from hydrogen bonding to other water molecules.

TABLE 2

Apparent orders with respect to water

Catalyst	Solvent	n	n_1
None	Dioxan	2.20 ± 0.05	
Pyridine	Dioxan		1.17 ± 0.05 (2.88 ± 0.08)
None	Dimethyl sulphoxide	2.32 ± 0.05	
Pyridine	Dimethyl sulphoxide		1.02 ± 0.06 (2.83 ± 0.08) [a]

[a] Numbers in parentheses are values of n_1 for the high water concentration range.

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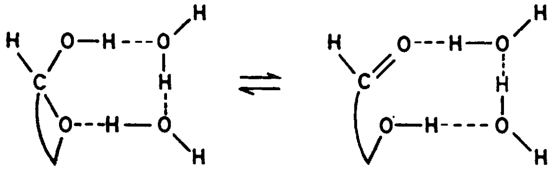
[17] C. G. Swain and J. F. Brown, *J. Amer. Chem. Soc.*, 1952, **74**, 2541.

[18] H. H. Huang, R. R. Robinson, and F. A. Long, *J. Amer. Chem. Soc.*, 1696, **88**, 1866.

The apparent order of two for the water reaction is entirely consistent with the findings on the reversible hydration of 1,3-dichloroacetone [5] and strongly suggests that in the case of tetramethylglucose, the critical stage in the reaction can be shown as (A) where the broken lines represent hydrogen bonds.



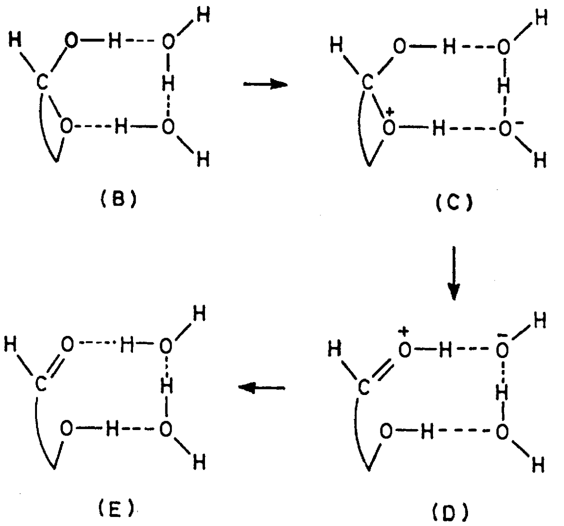
(A)

In this proposal for the transition state for the water-catalysed reaction, the water molecules are hydrogen-bonded to each other and also into the glucose structure. Further, one water molecule must act as an acid while the other functions as a base or *vice versa*. The question now arises as to whether the proton shifts take place synchronously or in a step-wise fashion. Unfortunately attempts to find a sharp experimental criterion for distinguishing between the synchronous and step-wise mechanisms have not been entirely successful. Albery [19] has given a number of reasons for preferring the synchronous mechanism but these have been questioned by Bell and his co-workers.[5] The latter have also made calculations of activation energies for proton transfers by synchronous and step-wise mechanisms based on simple electrostatic models of concerted transition states for the reversible hydration of 1,3-dichloroacetone. Their results indicate that the activation energy for the synchronous mechanism is about twice as great for the step-wise process. Thus they conclude that the latter would be preferred. This conclusion was considered to be further strengthened by the fact that the observed kinetic hydrogen isotope effect for the ' uncatalysed ' reaction is k_H/k_D 2.7. This is a low value whereas a synchronous mechanism should be associated with an abnormally high isotope effect. They also showed that it is possible to write a reasonable step-wise mechanism for the reversible addition of water to carbonyl compounds, in which all the intermediates are normal chemical species.

The mechanism of the mutarotation of glucose for the uncatalysed reaction may be considered in the light of the conclusions derived by Bell and his co-workers. First it is clear that the activation energy argument applies with equal force to the mutarotation and no further comment appears necessary on this point. The second criterion involving the magnitude of the kinetic hydrogen isotope effect, however, may be less certain than desirable. This doubt arises because it seems possible that low kinetic hydrogen isotope effects could be associated with non-linear hydrogen-bonded transition states rather than absence of synchrony. Thus although our value of k_H/k_D (3.6) for the ' uncatalysed ' mutarotation of tetramethylglucose could be considered as being on the low side and consequently used to argue against a synchronous mechanism, this may not be fully justified as cyclic transition states are almost certainly involved here.

Finally it would be interesting to see whether a reasonable step-wise mechanism can be formulated in terms of a cyclic transition state. This can indeed be done by viewing the mutarotation as a transformation of the open-chain aldehyde molecule into the α- or β-D-glucose in its pyranose ring form.

Alternatively, a step-wise mechanism can be written for the reaction of the pyranose ring with a pair of water molecules to form the open-chain aldehyde as in reactions (9) and (10). Here, the water molecule is acting as an acid in sequence (9) and as a base in sequence (10). It should be noted that the individual steps take place within a hydrogen-bonded complex in what has been termed an intimate *step-wise mechanism.*



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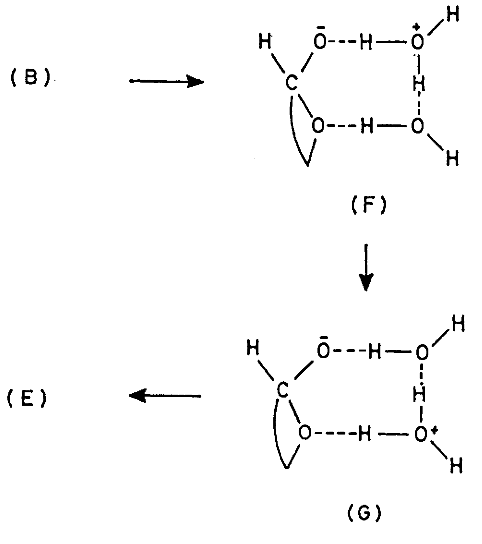

(10)

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[19] W. J. Albery, *Progr. Reaction Kinetics*, 1967, **4**, 355.

Turning to the effect of catalysts, Table 2 shows that when the reaction is catalysed by pyridine, the apparent order with respect to water is one as determined by the slope of the log k_c *versus* log $[H_2O]$ plot over the lower concentration range observed. Over the higher concentration range it increases to three as seen in Figures 2(a) and (b). This result is found for dioxan as well as dimethyl sulphoxide. It seems likely that the value of n_1 in this case depends markedly on the non-ideality of the dissimilar species in solution (that is pyridine, water, glucose, and the transition state) since the observed rate constants will be affected by the different extents to which the activity coefficients of the species cancel over the concentration range. Nevertheless, it seems reasonable to expect the lower value of n_1 to reflect the correct number of water molecules in the transition state. This value of one is of course in accord with the corresponding finding in the case of 1,3-dichloroacetone, that is, it is consistent with the suggestion that the catalyst can replace one of the water molecules in the transition state proposed in the absence of catalyst.

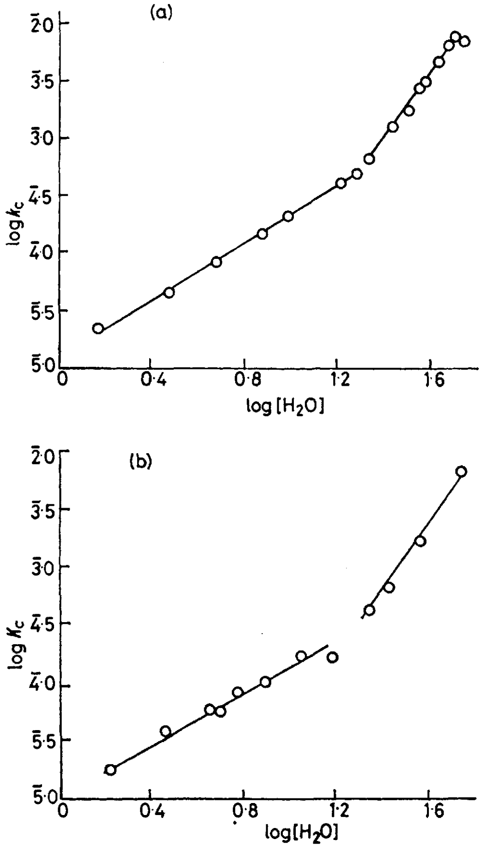
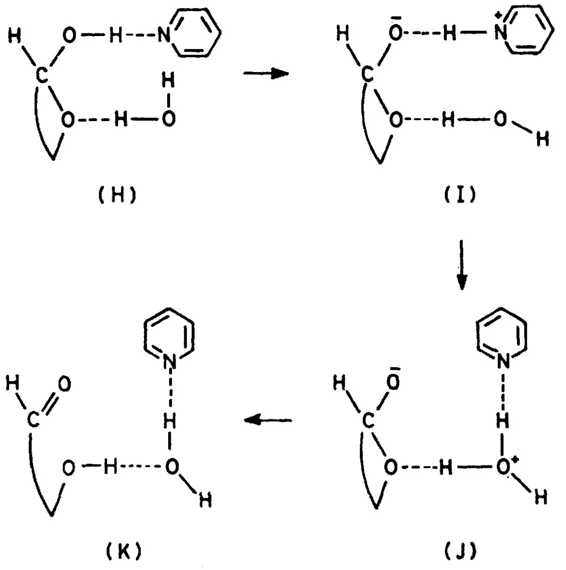


FIGURE 2 (a) Plot of log k_c *versus* log $[H_2O]$ with pyridine as catalyst in water–dioxan mixtures. (b) Plot of log k_c *versus* log $[H_2O]$ with pyridine as catalyst in water–dimethyl sulphoxide mixtures

A step-wise mechanism which is equivalent to the case of catalysis by a tertiary amine for 1,3-dichloroacetone is (11). It does not seem possible to formulate a synchronous mechanism. It should be noted that this step-wise scheme would require the pyridine molecule to come close to at least one reaction centre; this accords well with the experimental observation that 2,6-lutidine displays a strong steric effect.[2] Moreover, a transition state incorporating one water molecule in addition to the pyridine molecule was preferred in the study in H_2O–D_2O solvent mixtures on the ground that this model gave more plausible values of the fractionation factors involved. Thus we conclude that the above step-wise reaction scheme is the most reasonable mechanism we can devise at present for the pyridine-catalysed mutarotation reaction.



We thank Lye Geok Choo and Phua Peck Ling for assistance.

[7/163 *Received*, 31*st January*, 1977]