Simultaneous Proton Transfers Coupled with Heavy Atom Motion in the Transition State of the 2-Pyridone-catalysed Mutarotation of Tetramethylglucose. Primary and Secondary Deuterium Isotope Effects

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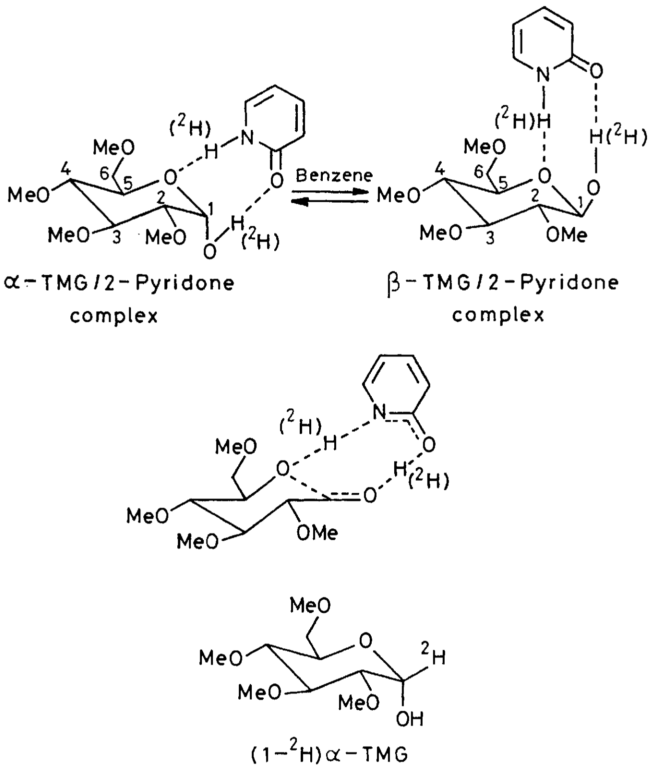
Primary and secondary deuterium isotope effects and calculated primary isotope effects for the 2-pyridone-catalysed mutarotation of tetramethylglucose suggest rate-limiting simultaneous transfer of two protons coupled with considerable heavy atom motion.

Several intricate problems are involved in the elucidation of reaction mechanisms of multiple proton transfer reactions. Among the questions to which answers are needed are the following: Is the multiple proton transfer occurring in an elementary reaction, *i.e.* are the protons transferred simultaneously or by a stepwise mechanism? Are the proton transfers coupled to heavy atom motion in the transition state? Is tunnelling important in the reactions?[1]

To get a deeper understanding of the nature and importance of simultaneous two-proton transfers in bifunctional catalysis we have been investigating a number of reaction systems.[2] In this communication we report results which answer the above questions for the classical 2-pyridone-catalysed mutarotation of tetramethylglucose. Because of the high catalytic activity it was suggested by Swain and Brown to involve simultaneous transfer of two protons.[2b,3] The conclusions in this paper are based upon primary and secondary deuterium isotope effects, the interpretation of which is assisted by calculations.

The reactants 2,3,4,6-tetra-*O*-methyl-α-D-glucopyranose (α-TMG) and 2-pyridone were deuteriated with methan(^{2}H)ol yielding (1-*O*-^{2}H)α-TMG and (*N*-^{2}H)2-pyridone. 0.2 M Solutions of (1-*O*-^{1}H)- and (1-*O*-^{2}H)-α-TMG and 0.1 M solutions of (*N*-^{1}H)- and (*N*-^{2}H)-2-pyridone were prepared with benzene as solvent. Mixtures of equal volumes of each of the two TMG solutions with each of the two 2-pyridone solutions were used in the polarimetric runs, which yielded the experimental points of Figure 1. The precision and accuracy of the k_{obs} values were better than 0.5 and 1.0%, respectively, and the *relative* accuracy of the percentage of ^{2}H was the same (with sign) for the four points and less than 1%. The experimental primary isotope effect $k_{\text{HH}}/k_{\text{DD}}$ is 3.7 [4,5a] which at a first glance appears to be a surprisingly small value for a rate-



Scheme 1

controlling simultaneous two-proton transfer reaction. However, the non-linear relation between the observed rate constants and the percentage of ^{2}H of the mobile hydrogens (Figure 1) is consistent with rate-controlling simultaneous proton transfer.[5b]

If deuterium isotope effects on the association equilibria of TMG and 2-pyridone and ^{2}H fractionation between OH and NH groups are ignored (no fractionation takes place in dimethyl sulphoxide according to ^{1}H n.m.r. spectroscopy), equation (1) is easily derived. X_H and X_D express the mole

$$k_{obs} = k_{HH}\, X_H^2 + (k_{HD} + k_{DH})X_H X_D + k_{DD}\, X_D^2 \qquad (1)$$

fraction of H and D in the mobile hydrogen pool (OH and NH), respectively. Simultaneous two-proton transfer is simulated by the solid curve in Figure 1 assuming $k_{HD} = k_{DH} = (k_{HH}k_{DD})^{\frac{1}{2}}$. The straight, dashed line, on the other hand, results if $k_{HH} = k_{HD}$ and $k_{DD} = k_{DH}$, *i.e.* rate-limiting one-proton transfer is assumed.

The curvature of the solid line in Figure 1 is not significantly changed using equilibrium isotope effects of 1.1 on the association equilibria. Furthermore a fractionation factor as large as 1.3 (deuterium is assumed to prefer the OH over the NH bond) accounts for only 25% of the deviation from linearity at 50 mol % of ^{2}H.

Thus the observations seem to support strongly the conclusion that the two protons are transferred simultaneously.

A possible reason for the small observed primary isotope effect could be that the proton transfers are accompanied by heavy atom motion in the reaction co-ordinate.[6] Therefore primary isotope effects have been calculated using a cut-off model of the present reaction system.[7] For an activated complex in which the protons are 50% transferred and their motion is coupled with only small heavy atom (C and O) motion, a k_{HH}/k_{DD} of 38 is predicted. In contrast, a value of only 3.7 is calculated assuming considerable heavy atom motion coupled to the proton transfers.† The isotope effects on each of the protons transferred is found to be close to $(k_{HH}/k_{DD})^{\frac{1}{2}}$, *i.e.* for the latter case a value of 1.9 is estimated. Furthermore all the models used predict a negligible tunnelling contribution. This model obviously agrees excellently with our experimental results.

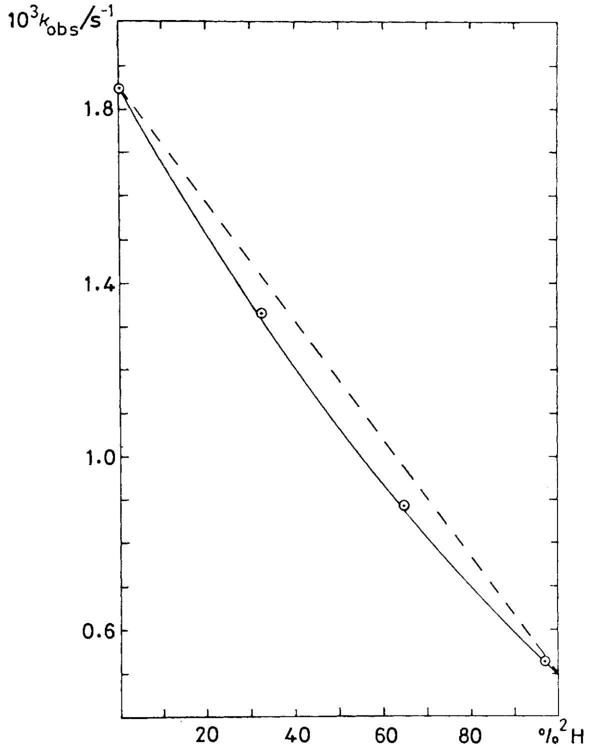


Figure 1. k_{obs} *vs.* ^{1}H/^{2}H composition of the mobile hydrogen pool at 25 °C in benzene solutions, 0.1 mol l^{-1} in TMG and 0.05 mol l^{-1} in 2-pyridone. Encircled dots are experimental points. The solid and dashed lines indicate the expected behaviour of two- and one-proton/deuteron transfers, respectively, in the rate-limiting step.

An experimental test of this hypothesis of considerable heavy atom motion would be the measurement of a secondary isotope effect. Therefore (1-^{2}H)α-TMG was synthesized from TMG which was oxidized in benzene with silver carbonate on Celite to the corresponding lactone. The purified lactone (yield 90%) was reduced with (^{2}H$_6$)diborane. Pure (1-^{2}H)TMG was isolated in 95% yield (based upon the lactone). Recrystallization from dry hexane gave pure α-anomer with a yield of 38% (based upon the lactone). The isotopic purity was determined by ^{1}H n.m.r. spectroscopy to be 98.9% ^{2}H at C-1 (Scheme 1).

A secondary isotope effect of 1.14 ± 0.02 was measured. This value indicates substantial rehybridization of C-1 in the transition state[8] relative to the initial state and points to considerable breaking of the C-O bond of the ring in the activated complex. This secondary isotope effect thus suggests that considerable heavy atom motion is coupled to the simultaneous two-proton transfer in the reaction co-ordinate.

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† Definitions of the assumed couplings of motions of heavy atoms and protons will be presented in detail in a full paper by the authors.

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