Intramolecular Catalysis in the Mutarotation of Aldoses

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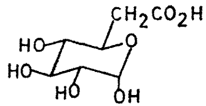
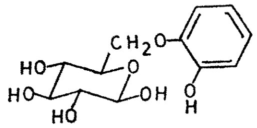
Summary The mutarotations of the anions of 6-deoxy-D-*gluco*hepturonic acid and 6-*O*-(*o*-hydroxyphenyl)-D-glucose are intramolecularly catalysed.

ALTHOUGH many examples of intermolecular general-acid and general-base catalysis of the mutarotation of aldoses have been reported there is only one known example of intramolecular catalysis, *viz.*, that of D-glucose-6-phosphate.[1,2] We now report that the mutarotations of 6-deoxy-α-D-*gluco*hepturonic acid (I) and 6-*O*-(*o*-hydroxyphenyl)-β-D-glucose (II) are intramolecularly catalysed. The rate constants extrapolated to zero buffer concentration, k_0, for the mutarotation of D-glucose and 6-*O*-phenyl-D-glucose are independent of pH between pH 2·0 and 6·89 (see Figure) but the pH–rate profile for the mutarotation of 6-deoxy-D-*gluco*hepturonic acid is sigmoid with $k_0 = (k_{SH} \times 10^{-pH}/K_a + k_S)/(1 + 10^{-pH}/K_a)$; k_{SH} and k_S, the rate constants for the mutarotation of the un-ionised and ionised forms respectively, have values $2{\cdot}48 \times 10^{-4}$ and $4{\cdot}49 \times 10^{-3}$ s^{-1} at 25° and K_a, the apparent dissociation constant, is $5{\cdot}08 \times 10^{-5}$ mol l^{-1}. The value of k_S is about



(I)



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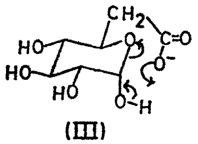

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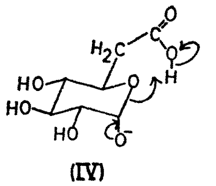

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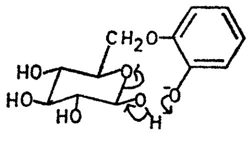

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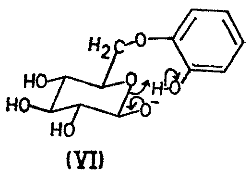

(VI)

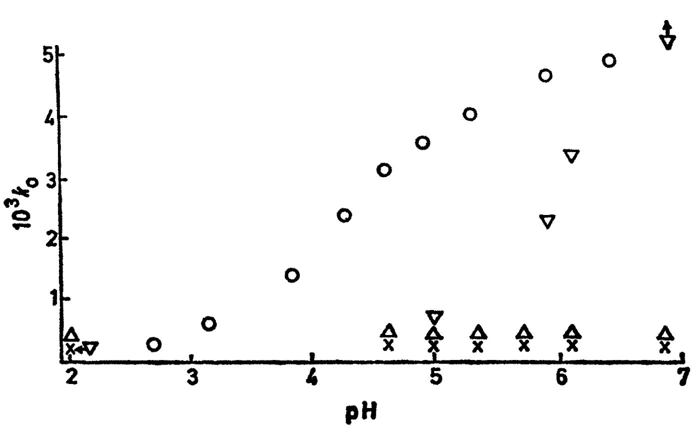

FIGURE. pH–*rate profiles for the mutarotation of some aldoses:* △, D-*glucose;* ×, 6-O-*phenyl*-D-*glucose;* ○, 6-*deoxy*-D-gluco-*hepturonic acid;* ▽, 6-O-(o-*hydroxyphenyl*)-D-*glucose. At* pH 6·8 *the value of* k_0 *for the mutarotation of* 6-O-(o-*hydroxyphenyl*)-D-*glucose is at least* $1{\cdot}1 \times 10^{-2}$ s^{-1}. *Under these conditions the apparent rate of change of rotation was limited by the time constant of the polarimeter and so the apparent rate constant is a lower limit for the rate constant for mutarotation. At* pH 2 *the value of* k_0 *for the mutarotation of* 6-O-*phenyl*-D-*glucose is* $3{\cdot}11 \times 10^{-4}$ s^{-1} *and that for the mutarotation of* 6-O-(2-*hydroxyphenyl*)-D-*glucose is* $3{\cdot}23 \times 10^{-4}$ s^{-1}.

11 times greater than the rate constant for the spontaneous mutarotation of D-glucose (σ_I for $CH_2{\cdot}OH$ and $CH_2{\cdot}CO_2^-$ are respectively 0·05 and 0·01)[3] and five times greater than that for the mutarotation of 6-deoxy-D-glucose (σ_I for CH_3 is $-0{\cdot}05$).[3] The plot of the logarithms of the rate constants for the spontaneous mutarotation of 6-substituted glucoses against σ_I is a fairly good straight line with $\rho = -3{\cdot}2$ and $r = 0{\cdot}943$.[4] The rate constant for the mutarotation of the anion of 6-deoxy-D-*gluco*hepturonic acid estimated from this plot is $5{\cdot}40 \times 10^{-4}$ s^{-1}, 8·3 times less than the experimentally determined value of k_S. These results indicate that the mutarotation of the anion of 6-deoxy-D-*gluco*hepturonic acid is faster than expected on the basis of the inductive effect of the $CH_2{\cdot}CO_2^-$ group and hence the reaction is probably intramolecularly catalysed. The second-order constant for the mutarotation of D-glucose catalysed by a carboxylate ion of pK_a 4·3 was estimated from the results of Schmid and Bauer[5] for the formate- and acetate-catalysed reactions to be $1{\cdot}2 \times 10^{-3}$ l mol^{-1} s^{-1} at 25°. The effective concentration[6] of the internal carboxylate group in the mutarotation of the anion of 6-deoxy-D-*gluco*hepturonic acid is therefore 3·5M. The analogous factor reported by Bailey, Fishman, and Pentchev for the mutarotation of D-glucose-6-phosphate is 2·2M.[2]

A more striking rate enhancement is found in the mutarotation of 6-*O*-(*o*-hydroxyphenyl)-D-glucose (II). In the pH range 2·0—6·89 the pH–rate profile is of the form: $k_0 = k_{spon} + k_{OH} \times 10^{(pH-pK_W)}$ with $k_{spon} = 3{\cdot}23 \times 10^{-4}$ s^{-1} and $k_{OH} = 2{\cdot}28 \times 10^5$ l mol^{-1} s^{-1} and at pH 6·89 k_0 is more than 40 times greater than k_0 for the mutarotation of 6-*O*-phenyl-D-glucose. k_{OH} is 2700 times greater than the rate constant for the hydroxide-ion-catalysed mutarotation of 6-*O*-phenyl-D-glucose. This rate enhancement presumably arises from the rapidity of the mutarotation of the ionised form of 6-*O*-(*o*-hydroxyphenyl)-D-glucose and the rate constant for this reaction is 14·0 s^{-1} (the pK_a is 9·78). The second-order constant for the mutarotation of 6-*O*-phenyl-D-glucose catalysed by phenolate ion (pK_a = 9·98) is 1·24 l mol^{-1} s^{-1} and that for a base of pK_a 9·78 was estimated to be 1·0 l mol^{-1} s^{-1}. The effective concentration of the internal phenolate ion in the mutarotation of 6-*O*-(*o*-hydroxyphenyl)-D-glucose is therefore *ca.* 14M.

The intramolecular catalysis could be general-base catalysis (III) and (V)† or general-acid catalysis (IV) and (VI). Although there is no compelling evidence for either at present we favour intramolecular general-acid catalysis since this appears to be stereochemically more favourable.

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† Analogous mechanisms which involve proton transfer through one or more water molecules and/or which involve water acting as a general-acid catalyst in concert with the intramolecular general-base catalysis are also possible.

[1] J. M. Bailey, P. H. Fishman, and P. G. Pentchev, *J. Biol. Chem.*, 1968, **243**, 4827.

[2] J. M. Bailey, P. H. Fishman, and P. G. Pentchev, *Biochemistry*, 1970, **9**, 1189.

[3] M. Charton, *J. Org. Chem.*, 1964, **29**, 1222.

[4] B. Capon and R. B. Walker, unpublished work.

[5] H. Schmid and G. Bauer, *Monatsh.*, 1965, **96**, 1503.

[6] *Cf.* W. P. Jencks, "Catalysis in Chemistry and Enzymology", McGraw-Hill, New York, 1969, p. 11; B. Capon, "Essays in Chemistry," in the press, submitted June 1970.