Benzamidine-catalysed Mutarotation of 2,3,4,6-Tetra-*O*-methyl-D-glucose

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A comparison of the catalytic powers of benzamidine, n-butylamine, and 1,4,5,6-tetrahydro-2-phenylpyrimidine has shown that the first base is a powerful catalyst for tetra-*O*-methyl-D-glucose mutarotation in benzene. However, the observed high reactivity is not due to a bifunctional action of the catalyst, as benzamidine in the same solvent is also very effective in promoting dehydrohalogenation reactions, the *anti*-stereochemistry of which cannot involve a simultaneous intervention of the acidic and basic functions. Therefore, the catalytic activity is attributed to the basic group only, and the results are explained in terms of a mechanism involving a glucosyloxide–benzamidinium ion pair. The difference in behaviour between the benzamidine and other tautomeric catalysts (*e.g.* 2-pyridone) is discussed.

SEVERAL mechanisms involving acid- or base-catalysed processes are available for the mutarotation of glucose.[1,2] Considerable attention has been attracted by a process involving simultaneous protonation of the hemiacetal oxygen atom and removal of the hydroxylic proton. Originally, a mechanism of this type was proposed by Swain and Brown [3] to explain the catalytic action of 2-pyridone (or 2-hydroxypyridine), which was found to be enormously more effective than a mixture of phenol and pyridine, even though 2-pyridone is a weaker acid or base than either phenol or pyridine. This kind of catalysis was termed polyfunctional [3] and nowadays it is one of the most favoured concepts for explaining mechanistic features of enzyme-catalysed reactions.[4]

Rony *et al.*[5] have reported that exceptionally favourable energetics result when the bifunctional catalyst is represented by a neutral tautomeric system. Benzamidine is such a catalyst and was, together with other tautomeric compounds, included in a list of potential bifunctional catalysts for glucose mutarotation.[5a] Although considerable theoretical [6] and experimental [7-10]

[1] For reviews on mutarotation see B. Capon, *Chem. Rev.*, 1969, **69**, 407; W. Pigman and E. F. L. J. Anet in 'The Carbohydrates,' eds. W. Pigman and D. Horton, Academic Press, New York, 1972, vol. IA, ch. 4.

[2] For recent work see B. Capon and R. B. Walker, *J.C.S. Perkin II*, 1974, 1600; N. M. Ballash and E. B. Robertson, *Canad. J. Chem.*, 1973, **51**, 556; J. H. Fendler, E. J. Fendler, R. T. Medary, and V. A. Woods, *J. Amer. Chem. Soc.*, 1972, **94**, 7288; G. de Wit, A. P. G. Kieboom, and H. van Bekkum, *Tetrahedron Letters*, 1975, 3943.

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

[4] M. L. Bender, 'Mechanisms of Homogeneous Catalysis from Protons to Proteins,' Wiley–Interscience, New York, 1971, ch. 3; W. P. Jencks, 'Catalysis in Chemistry and Enzymology,' McGraw–Hill, New York, 1969, ch. 3.

[5] (*a*) P. R. Rony, *J. Amer. Chem. Soc.*, 1968, **90**, 2824; (*b*) P. R. Rony, W. E. McCormack, and S. W. Wunderly, *ibid.*, 1969, **91**, 4244; (*c*) P. R. Rony, *ibid.*, p. 6090; (*d*) P. R. Rony and R. O. Neff, *ibid.*, 1973, **95**, 2896.

[6] H. M. Niemeyer, O. Goscinski, and P. Ahlberg, *Tetrahedron*, 1975, **31**, 1699.

[7] G. Biggi, F. del Cima, and F. Pietra, *Tetrahedron Letters*, 1971, 2811; *J.C.S. Perkin II*, 1972, 188; F. M. Menger, *J. Amer. Chem. Soc.*, 1966, **88**, 3081.

[8] H. Anderson, C. W. Su, and J. W. Watson, *J. Amer. Chem. Soc.*, 1969, **91**, 482.

[9] (*a*) E. Ciuffarin, L. Senatore, and L. Sagramora, *J.C.S. Perkin II*, 1973, 534; (*b*) E. Ciuffarin, L. Senatore, and M. Vichi, *J.C.S. Chem. Comm.*, 1975, 858.

[10] P. Ahlberg and F. Ladhar, *Chemica Scripta*, 1973, **3**, 31; E. Haruki, T. Fujii, and E. Imoto, *Bull. Chem. Soc. Japan*, 1966, **39**, 852; R. H. De Wolfe in 'The Chemistry of Amidines and Imidates,' ed. S. Patai, Wiley–Interscience, 1975, ch. 8.

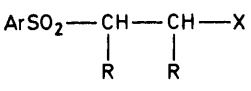
attention has been attracted by amidines in other general acid/base catalysed reactions, the role of their bifunctionality is still controversial. Therefore, it seemed of interest to us to ascertain experimentally the type of catalysis performed by benzamidine in the mutarotation of 2,3,4,6-tetra-*O*-methyl-D-glucose (TMG) in benzene. A comparison between the reactivities of benzamidine and of an amine of similar basicity (*i.e.* n-butylamine) is usually used to diagnose the importance of the bifunctionality in the first system.[7-9] We decided to follow this approach but, aiming at a clear distinction between a basic or a tautomeric catalysis, we compared the results of the mutarotation process with those obtained by using the same pair of catalysts in a reaction which requires only the basic function. An elimination reaction which in benzene follows the *anti*-pathway was chosen, similar processes being under active investigation in these laboratories.[11]

Furthermore, since useful information can be obtained by comparison of the reactivity of benzamidine with the behaviour of cyclic amidines,[8] whose geometry would make a concerted bifunctional catalysis impossible, we have made a kinetic study of the effect of 1,4,5,6-tetrahydro-2-phenylpyrimidine (THPP).

RESULTS

First-order rate constants for the mutarotation k_{ex} ($k_{ex} = k_{forward} + k_{reverse}$) were calculated from linear plots of $\log[(\alpha_0 - \alpha_\infty)/(\alpha_t - \alpha_\infty)]$. The measured values are reported in Table 1. As in previous work, mutarotation reactions in benzene were found to follow a first-order dependence on amine concentration.[5c] When the amount of base was kept constant and the concentration of TMG was changed, the observed variations were similar to those found in previous work,[5d] where amines were also used as catalysts, *i.e.* a decrease in rate coefficient was caused by an increase in concentration of the substrate. Table 1 also lists second-order rate coefficients (k_2) obtained by dividing

(1) X = Br, R = H, Ar = Ph



(2) X = Cl, R = Ph, Ar = *p* - MeC_6H_4

k_{ex} by the base concentration. At variance with the case of 2-pyridone,[3,5] no evidence in favour of a benzamidine–tetramethylglucose complex was obtained from the values of initial and final optical rotations, which in the presence or absence of benzamidine did not differ significantly.

The linearity of the plots used for calculating k_{ex} values suggested that no side reaction, *e.g.* formation of glucosylamine,[12] was occurring during mutarotation. Nevertheless, control experiments were performed in order to ascertain the complete absence of parallel reactions. In fact, TMG was recovered quantitatively from 1 : 1 reacting solutions after complete precipitation and removal of butylamine or benzamidine hydrochloride with an equivalent amount of hydrogen chloride in benzene.

Kinetic data for the dehydrohalogenation of 1-bromo-2-phenylsulphonylethane (1) and *erythro*-1-chloro-1,2-diphenyl-2-*p*-tolylsulphonylethane (2) are listed in Table 2. As in previous work,[11b,d] the reactions followed second-order kinetics (first-order in both substrate and amine). In the case of n-butylamine a slight deviation from linear

TABLE 1

Rate coefficients [a] for the mutarotation of 2,3,4,6-tetra-*O*-methyl-D-glucose (TMG) in benzene

10^4[Base]/M	10^2[TMG]/M	t/°C	$10^3 k_{ex}$/s^{-1}	k_2/l mol^{-1} s^{-1}
Benzamidine [b]				
1.20	1.70	15	1.60	13.30
1.40	1.70	25	3.00	21.50
2.80	1.70	25	6.00	21.60
1.20	1.70	35	4.50	37.20
1.40	4.00	25	1.50	10.60
THPP				
11.40	1.70	25	0.22	0.20
23.00	1.70	25	0.49	0.21
n-Butylamine				
9.40	1.60	25	0.34 [c]	0.36
4.70	1.70	25	0.17	0.37

[a] Average of at least three runs performed at concentrations close to those indicated. Probable error ±2%. [b] By using k_2 values the following values were calculated for the activation parameters: E_a 9.1 ± 0.5 kcal mol^{-1}; $\Delta H^{\ddagger}_{25°}$ 8.5 ± 0.5 kcal mol^{-1}; $\Delta S^{\ddagger}_{25°}$ −24.0 ± 1.5 cal mol^{-1} K^{-1}. [c] A value of 0.91 s^{-1} has been reported [5c] for solutions 2×10^{-3}M in base and 1.1×10^{-1}M in TMG.

behaviour was observed at 60—70% conversion in the second-order plots. However, the scope of this work did not require an investigation of the origin of this deviation.

Control experiments with the *erythro*-chloro-compound (2) showed a stereochemical course identical with that observed with other amines,[11] *i.e.* complete *anti*-elimination.

DISCUSSION

Table 1 indicates that benzamidine is a powerful catalyst for mutarotation. The reactivity ratio between benzamidine and n-butylamine is *ca.* 60 : 1, which seems too high to be attributed to a Brønsted behaviour, in view of the pK_a difference in water (11.6 for benzamidine and 10.7 for n-butylamine).[13] However, in benzene electronic stabilization [8,9a] might play an important role, and the pK_a difference might then be sufficiently large to justify the observed reactivity ratio. Owing to lack of experimental data to support the above hypothesis, we are led to consider an alternative explanation. Thus a transition state of type (a) could be invoked, similar to that considered [1,3,5a] responsible for the powerful action of 2-pyridone.

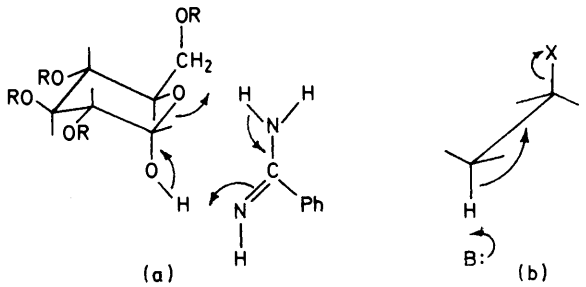
However, the results for the elimination process indicate that benzamidine can be even a thousand times more reactive than n-butylamine in a process where the acidic function is not required. Elimination reactions of sulphonyl halogeno-derivatives have been shown to follow the *anti*-pathway when chloride, bromide, iodide,

[11] (*a*) V. Fiandanese, G. Marchese, F. Naso, and O. Sciacovelli, *J.C.S. Perkin II*, 1973, 1336; (*b*) V. Fiandanese, G. Marchese, and F. Naso, *ibid.*, p. 1538; (*c*) V. Fiandanese, C. V. Maffeo, G. Marchese, and F. Naso, *ibid.*, 1975, 221; (*d*) V. Fiandanese, C. V. Maffeo, F. Naso, and L. Ronzini, *ibid.*, 1976, 1303.

[12] S. Kolka, *Roczniki Chem.*, 1976, **50**, 611; G. P. Ellis and J. Honeyman, *Adv. Carbohydrate Chem.*, 1955, **10**, 104.

[13] D. D. Perrin, 'Dissociation Constants of Organic Bases in Aqueous Solution,' Butterworths, London, 1965.

and tosylate ions are the leaving groups.[11,14] The *syn*-pathway may intrude because of eclipsing effects [11c] or when fluoride ion is the leaving group.[11a] In agreement, in the present investigation the reaction of the *erythro*-chloro-derivative was found to follow the *anti*-pathway.

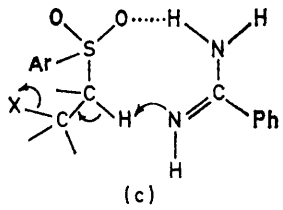


On the basis of stereochemical and kinetic evidence [11] the most likely mechanism for these processes is of the *E2* type (b). High and low degrees respectively of C–H and C–X bond cleavage should be involved in the transition state. However, whatever the timing of the bond ruptures, no interaction can be envisaged between the attacking base and the leaving group when the *anti* course is operating. Consequently, the higher reactivity of benzamidine than of n-butylamine cannot represent evidence in favour of bifunctional catalysis, and electronic stabilization [8,9a] could be advocated to explain the trend observed in both elimination and mutarotation processes.

Comparison of the kinetic data for mutarotations catalysed by benzamidine and 1,4,5,6-tetrahydro-2-phenylpyrimidine reveals that the former is *ca.* one hundred times more reactive than the latter. Once again, considering only mutarotation data, polyfunctional catalysis seems of importance. In fact, the pyrimidine, which in water is more basic (pK_a 12.8) [13] than benzamidine, could be less reactive than the latter because its geometry would not permit the intervention of a transition state of type (a). However, an alternative explanation for the lower reactivity of the cyclic base could involve the operation of steric effects associated with the presence of the methylene groups, the sensitivity of mutarotation to steric factors being well known.[5b,15]

[14] P. S. Skell and J. H. McNamara, *J. Amer. Chem. Soc.*, 1957, **79**, 85; F. G. Bordwell and P. S. Landis, *ibid.*, p. 1593.

The elimination data also support the importance of steric effects in controlling the reactivities of the two amidines. In fact, benzamidine is almost as effective as the tetrahydropyrimidine in promoting dehydrohalogenation of the bromo-sulphone (1), but for the dehydrohalogenation of the *erythro*-chloro-compound (2), where steric crowding is increased because of the presence of two additional phenyl rings, the ratio between the k values for benzamidine and the pyrimidine rises to 50. Furthermore, the observed trend does not seem to indicate that hydrogen bonding between the amidine and the oxygen atom of the sulphone [16] could be important. In principle such an interaction, as depicted in (c), might assist proton abstraction from the substrate. Thus, some doubt could arise as to the validity of the elimination reaction as model of a simple base-promoted process. Fortunately, the similarity in rates of the reactions of the bromo-sulphone (1) with benzamidine and the tetrahydropyrimidine rules out the above hypothesis. Indeed, the geometry of the latter reagent,[8] as also shown by molecular models, does not permit the bidentate action. When the *erythro*-chloro-compound is used benzamidine is more reactive than the pyrimidine, but we have already suggested the intervention of a steric effect in the latter case. If a bidentate action were important for the chloro-compound (2) there would be no reason for the absence of such an action in the case of the bromo-derivative (1).



In conclusion, the foregoing comparisons indicate that the presence of both acidic and basic centres suitably located in a tautomeric system does not represent a sufficient condition for a bifunctional inter-

TABLE 2

Rate coefficients [a] for the amine-promoted dehydrohalogenation of compounds (1) and (2) in benzene

Substrate	10^3[Substrate]/M	Amine	10^3[Amine]/M	t/°C	10^3k_2/l mol^{-1} s^{-1}
(1)	1.20	Benzamidine [b]	2.60	15	710
(1)	1.20	Benzamidine	2.70	25	1 200
(1)	1.20	Benzamidine	2.60	35	1 900
(1)	5.00	THPP	6.50	25	990
(1)	5.00	n-Butylamine	7.50	25	4.10
(1)	5.00	n-Butylamine	16.00	25	4.50
(1)	10.00	n-Butylamine	8.00	25	4.30
(2)	1.20	Benzamidine	2.70	25	2 260
(2)	5.00	THPP	6.50	25	45.00
(2)	5.00	n-Butylamine	7.00	25	2.80

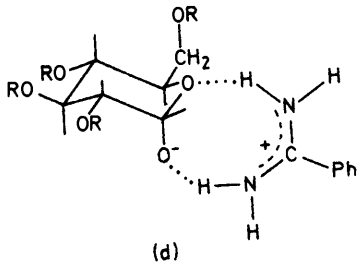
[a] As in Table 1. [b] Activation parameters for this reaction are: $E_a = 8.7 \pm 0.5$ kcal mol^{-1}; $\Delta H^{\ddagger}_{25°} = 8.1 \pm 0.5$ kcal mol^{-1}; $\Delta S^{\ddagger}_{25°} -31.0 \pm 1.5$ cal mol^{-1} K^{-1}.

[15] F. Covitz and F. H. Westheimer, *J. Amer. Chem. Soc.*, 1963, **85**, 1773; H. H. Huang, A. N. H. Yeo, and L. H. L. Chia, *J. Chem. Soc.* (*B*), 1969, 836.

[16] C. J. M. Stirling, *J. Chem. Soc.*, 1964, 5863; R. C. Pink, R. Spratt, and C. J. M. Stirling, *ibid.*, 1965, 5714.

vention in the mutarotation process. In the catalytic system under investigation the high strength and reactivity of the basic centre make irrelevant the advantage accruing from its favourable position relative to the acidic function.

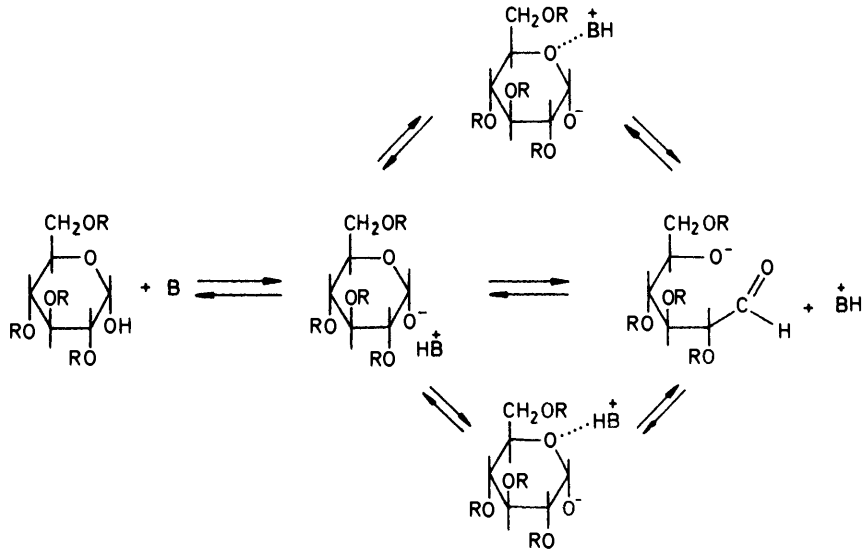
The difference between the two potentially tautomeric catalysts, 2-pyridone and benzamidine, may be better understood by recalling that the rate-determining step of the mutarotation can be represented as a carbonyl-forming elimination.[1-3,5] A concerted mechanism (*E*2 according to the elimination terminology [17]) is usually suggested for the 2-pyridone-catalysed mutarotation,[1,3] although difficulty in establishing the actual timing of bond-breaking and formation has been envisaged.[5c] Owing to the relatively low strength of the basic centre,



(d)

in this concerted mechanism the breakage of the C(1)–O bond is made easier by electrophilic assistance from the acidic centre. When a relatively strong base is used, as in the case of benzamidine or an amine of comparable basicity, the intervention of a stepwise process seems more likely, according to the illustrated Scheme, where for the sake of simplicity only the recyclization to give the α-form is shown. Owing to the nature of the solvent, ion pairs rather than free ions might well be involved, and the reaction could then be regarded as an $(E1cB)_{ip}$ [11b] carbonyl-forming elimination. Several pathways are shown for the ring opening of the intermediate ion pair formed in the pre-equilibrium. One is an uncatalysed route; the others are catalysed by the hydrogen or the positive centre of the ammonium ion.

In the proposed stepwise process, when benzamidine



SCHEME

is used and glucosyloxide–amidinium ion pairs are formed, interaction of oxygen atoms with both NH_2 groups could be envisaged [see (d)]. Our results do not rule out completely such a possibility, but they do emphasize the slight importance of bifunctionality in the catalyst. Indeed, it appears that the conjugate acid formed by protonation of a monofunctional base during the pre-equilibrium step can, if necessary, effectively assist the rate-determining ring opening in the anionic partner.

EXPERIMENTAL

Materials.—2,3,4,6-Tetra-*O*-methyl-D-glucose was prepared according to the procedure of West and Holden,[18] and was purified by vacuum sublimation or by repeated crystallizations from light petroleum (b.p. 30—50 or 75—120 °C). The m.p.s of the samples used were in the range 90—96 °C and $[\alpha]_D^{25}$ values were in the range 115—120°. The specific rotation at infinite time was in the range 90—92°. n-Butylamine was distilled over KOH pellets. Benzamidine was obtained from its chloride (Aldrich) and purified by two vacuum sublimations.[19] 1-Bromo-2-phenylsulphonylethane (1),[11b] *erythro*-1-chloro-1,2-diphenyl-2-*p*-tolylsulphonylethane (2),[11c] and 1,4,5,6-tetrahydro-2-phenylpyrimidine [20] were prepared according to reported procedures. Benzene was distilled twice over sodium.

[17] W. H. Saunders, jun., and A. F. Cockerill, ' Mechanisms of Elimination Reactions,' Wiley, New York, 1973.

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

[19] B. H. Beggs and R. D. Spencer, *Analyt. Chem.*, 1962, **34**, 1590.

[20] G. S. Skinner and P. R. Wunz, *J. Amer. Chem. Soc.*, 1951, **73**, 3814.

Kinetic Experiments.—These were performed by following the optical rotations of reacting solutions contained in a jacketed cell. The polarimeter was a Roussel-Jouan instrument. Elimination reactions and stereochemical control studies were performed as reported in previous papers.[11]

Reactants were quantitatively recovered from solutions 2×10^{-2}M in the case of n-butylamine and 3×10^{-3}M in the case of benzamidine, after the optical rotation had reached the ' infinite ' value. The purity of the recovered TMG was estimated by i.r. analysis (Perkin-Elmer 177 instrument; solvent carbon tetrachloride).

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