Mechanism of Benzidine and Semidine Rearrangements. Part XXVI.[1] Solvent Isotope Effects and Conclusions concerning the Nature of the Proton Transfers

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The solvent isotope effect (k_{D_2O}/k_{H_2O}) for the rearrangement of 2,2'-dimethoxyhydrazobenzene that is of the first order in acid at convenient acidities is 1·9. This suggests, in contrast to conclusions drawn from volumes of activation, that pre-equilibrium protonation occurs. The value for the one-proton catalysed rearrangement of 2,2'-di-iodohydrazobenzene is 2·2.

The two-proton catalysed reactions of 2,2'-dibromo- and 2,2'-dichloro-substituted hydrazobenzenes give values (2·0, 2·3) considerably lower than those previously reported for rearrangements of this order in acid, whereas the value for the 4-chloro-compound (3·0) is intermediate. Evidence that the second proton is transferred in an equilibrium step is not clear-cut in these examples.

THE benzidine rearrangement of hydrazoarenes and its associated reactions may show an order of either one or two in catalysing acid depending on the substrate.[2,3] Two mechanisms [equations (1) and (2)] were suggested for the more usual latter case.[4] The first step that is common to each can hardly be other than an equilibrium

$$B + H^+ \rightleftharpoons BH^+$$

$$BH^+ + H^+ \rightleftharpoons BH_2^{2+} \xrightarrow{s} \text{Products} \qquad (1)$$

$$B + H^+ \rightleftharpoons BH^+$$

$$BH^+ + H^+ \xrightarrow{s} \text{Products} \qquad (2)$$

$$B = \text{Hydrazo-compound}; \quad s = \text{rate-limiting step}$$

proton transfer for the first pK_b of hydrazoarenes can be reasonably estimated[5] to be *ca.* 14, but the status of the second protonation is more difficult to assess. Either a second pre-equilibrium leads to a dication that rearranges to products [equation (1)] or the mono-protonated substrate breaks up on the approach but not complete transfer of the second proton [equation (2)]. Although protonation of the monocation must be hindered by its positive charge, the formation of the dication is unlikely to be rate-limiting. Inability of the second protonation step to reach equilibrium would imply that the rate of breakdown of the dication to rearrangement products is faster than the rate of loss of a proton from it to the solvent: the dication must be an extremely strong acid, and as the latter transfer would require essentially no activation energy, the rearrangement step could hardly be faster.

Mechanisms (1) and (2) correspond to specific and general acid-catalysis respectively. The H_0-dependence and the kinetic form in buffer solutions of representative rearrangements are consistent with the former although general acid catalysis cannot be definitely excluded.[3] However, solvent isotope effects (k_{D_2O}/k_{H_2O}) of 3·5—4·8 for three cases of the two-proton mechanism strongly suggest specific acid catalysis, for current theory requires[6,7] that each pre-equilibrium proton transfer be associated with a solvent isotope effect of 1·4—2·9, whereas rate-determining proton transfer is associated with a value of less than unity.[8-11]

Values of volumes of activation derived from kinetic measurements at high pressure are consistent with mechanism (1) for the rearrangements of hydrazobenzene and its 2,2'-dimethyl homologue[12,13] (two of the three above-mentioned examples) but it was concluded that the second proton transfers in the rearrangements of 2-chloro-2'-methyl and 2,2'-dibromo-substituted hydrazobenzenes[14,15] and the proton transfer in the one-proton rearrangement of 2,2'-dimethoxyhydrazobenzene[16] were probably rate-limiting. The significance of this type of data is however not fully understood.[17]

We here report measurements of solvent isotope effects for the last two substrates and certain others: this approach seems[7] to be the best criterion available to assign the type of acid-catalysis.

RESULTS

Rate constants of reactions in solvents containing 60% (v/v) dioxan and the remainder either water or deuterium oxide but otherwise under identical conditions are recorded in the Table. All rate constants are the mean of 3—5 determinations and have standard deviations of *ca.* ±2%.

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Rates of rearrangements in dioxan–water and dioxan–deuterium oxide

Substrate[a]	Acid (H$^+$ or D$^+$)	T/°C	k_{D_2O}[b]	k_{H_2O}[b]	k_{D_2O}/k_{H_2O}
2,2′-Dibromo-X	4·5N-H_2SO_4	25	4·39	2·20	2·0
2,2′-Dichloro-X	1·00N-$HClO_4$	0	0·0251	00109	2·3
4-Chloro-X	0·60N-$HClO_4$	0	46·5	15·5	3·0
2,2′-Dimethoxy-X	2·3 × 10^{-4}N-$HClO_4$	0	78·3	41·2	1·9
2,2′-Di-iodo-X	0·70N-HCl	25	0·0638	0·029	2·2

[a] X = Hydrazobenzene. [b] Rate constant, $10^4k_{obs}/s^{-1}$ (pseudo first-order).

DISCUSSION

Solvent isotope effects of 2·3, 2·1, and 2·6 had previously been reported for the one-proton catalysed rearrangements of 1,1′-hydrazonaphthalene, 2,2′-dimethylhydrazobenzene, and *N*-(2-naphthyl)-*N*′-phenylhydrazine; whereas values of 3·5, 3·8, and 4·8 were obtained for the two-proton catalysed reactions of 2,2′-dimethylhydrazobenzene, *N*-(2-naphthyl)-*N*′-phenylhydrazine, and hydrazobenzene.[2,3] The conclusion was drawn that both proton transfers were at equilibrium for two-proton catalysed mechanisms in general. Changes of basicity of the substrates resulting from exchange of hydrogen bonded to nitrogen in the deuterium-containing media [18] are unlikely to account for the effects observed.[19]

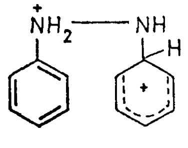
Our results were obtained under kinetically defined conditions.[20-23] The one-proton catalysed reactions of 2,2′-di-iodo- and 2,2′-dimethoxy-substituted hydrazobenzenes exhibit solvent isotope effects indicative of pre-equilibrium proton transfer. The conclusion with respect to the latter compound differs from that derived from the high-pressure studies; and (see opening paragraphs) the present conclusion seems extremely reasonable.

The solvent isotope effect for the 2,2′-dibromo- and 2,2′-dichloro-hydrazobenzenes, whose reactions are both of the second order in acid, are lower than expected for mechanisms involving two pre-equilibrium proton transfers, whereas the value for the 4-chloro-compound is intermediate. These results can be rationalised in three ways.

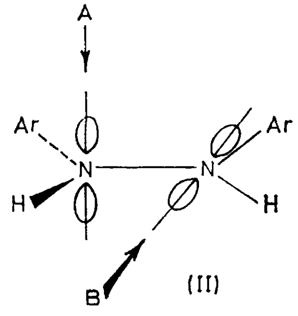
First, pre-equilibrium proton transfer associated with an isotope effect of 2—3 could be followed by a slow proton transfer [mechanism (2)] with an isotope effect of *ca.* 0·7—1. The latter value for the second step would occur if the proton was transferred almost to substrate in the transition state of the slow step.[24-26]

Secondly, mechanism (1) could occur with each pre-equilibrium associated with an isotope effect of *ca.* 1·4. Effects of this magnitude are predicted for this type of reaction by the Bunton–Shiner [24-26] and other theories,[27] but these models are approximate especially when new polar centres are developed in the transition state [28] as is here the case.[2,3] Further, these theories fail to predict the high values for the solvent isotope effects in the two-proton mechanism that have been found experimentally.

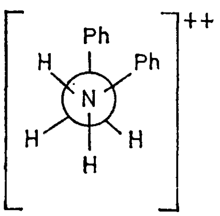
Thirdly, a novel rate-determining proton transfer to the aromatic ring could lead [29] to an intermediate (I) such as has been suggested [30] (although with no supporting evidence) for the sulphanilic acid rearrangement.



(I)



(II)



(III)

It is difficult to account for the pattern of rates and products from the many benzidine rearrangements that have been studied on the basis of the third suggestion, but these patterns are very satisfactorily rationalised on the ' polar transition-state mechanism ' involving mono- or di-protonation on the nitrogen atoms.[2,3] Accordingly, we prefer the first two suggestions. Although no choice can be made between them by use of the present data, the correlation of low isotope effect with low basicity of the anilino-moieties of the substrates (pK_a for aniline, 4·6; 1-naphthylamine, 4·0; 4-chloroaniline, 4·15; 2-chloroaniline, 2·65; 2-bromoaniline, 2·53) does suggest that the second protonation could become rate-limiting for feebly basic substrates.

No other reliable mechanistic criterion appears available, especially as the application of the Nelson–

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Butler theory is now considered to be definitely suspect.[31,32]

The existence of the dications involved in mechanism (1) has never been unambiguously demonstrated,[3] but the mono- and di-cations derived from hydrazobenzenes have been estimated[33] to exist in equilibrium concentrations in the ratio *ca.* $10^{12}:1$. If this estimate is correct the reactivity of the latter species would have to be enormously greater than that of the monocation to permit the observed frequent co-occurrence of the one- and two-proton catalysed routes of rearrangement. The first and second $\mathrm{p}K_a$ values of any hydrazoarene have never been measured and the above estimate was made by analogy with data for protonation of phenylhydrazines and similar compounds. However, inductive electron release from the aromatic residue attached to the protonated nitrogen may reduce the charge on the 'onium centre of the monocation and make diprotonation considerably easier than expected from analogy with other structures. Molecular orbital calculations to attempt to evaluate these possibilities are under way.

Even if the approach or transfer of the proton is less influenced by like-charge repulsion than was thought, the substrate molecule must adopt an apparently unfavourable conformation to permit the aromatic rings to be aligned and the molecule to fold to form the ' polar transition state ' for rearrangement. If, however, the conformation of the ground state were (II) in which the *p*-orbitals of the nitrogens (shown unconjugated to the aromatic π-electrons) were orthogonal (perhaps owing to the influences of anticonjugation[34]), initial protonation from direction A followed by sterically-directed transfer of a second proton from direction B could lead to a dication in the conformation (III) in which the two aromatic rings could easily overlap as the N–N bond cleaved. Other conformations of the diprotonated species would probably be too short-lived with respect to reversion to the monocation to assume a conformation suitable for reaction.

EXPERIMENTAL

Preparation of substrates, kinetic methods, and product analyses have been described,[20-23] with the exception of runs on the 2,2′-dimethoxy-compound which were carried out in Y-tubes with the measurement of initial rates.[2]

Deuteriosulphuric acid (33·76N) was prepared by adding concentrated sulphuric acid (60 ml) to deuterium oxide (25 ml), removing as much water as possible under vacuum, and recycling the process 4 times. The resulting acid was diluted with deuterium oxide to give a solution of appropriate strength. Deuteriated hydrogen chloride and perchloric acid were similarly prepared with care that in the latter case the acid was never concentrated to greater than *ca.* 8N. All deuterium-containing reaction media contained more than 99% atoms excess of label.

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