Aromatic Substitution with Rearrangement. Part V.[1] Base-catalysed Prototropic Rearrangement of 4-Bromo-2,6-di-t-butylcyclohexa-2,5-dienone in Acetic Acid

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The prototropic rearrangement of 4-bromo-2,6-di-t-butylcyclohexa-2,5-dienone to 4-bromo-2,6-di-t-butylphenol has been studied in acetic acid and in aqueous acetic acid under catalysis by added sodium acetate. The kinetic form is consistent with a rate-determining attack of ionic species, including triple ions, on the unprotonated dienone. The reaction is subject to a relatively large primary isotope effect, which varies with the solvent; the maximum value recorded ($k_1^{4\text{-H}}:k_1^{4\text{-D}} = 8{\cdot}8$) was in acetic acid containing 2·6M-water. The reaction is also subject to a small solvent deuterium isotope effect, being slightly faster in deuterioacetic acid than in acetic acid. Measurements of the extent of protonation of *p*-bromo-*NN*-dimethylaniline and of *p*-(*NN*-dimethylamino)azobenzene have been recorded for the solvents used for the kinetic measurements. The mechanistic implications of the observations are discussed.

THE behaviour of bases in acetic acid is complicated by the fact that ionic aggregates, including ion-pairs, ion-triplets, and ion-quadruplets, can make significant contributions to the species present at concentrations in the range in which chemical measurements are customarily made. Bruckenstein and Kolthoff[2] investigated these equilibria by studying the protonation of *p,p'*-bisdimethylaminoazobenzene and of other bases in acetic acid and in aqueous acetic acid to which sodium acetate had been added. They noted an 'abnormal' effect of added water, in that its addition to a solution containing base and its conjugate acid resulted in an increase in the amount of the protonated forms of the base, despite the fact that water is itself a base, and so the reverse behaviour might have been anticipated. They interpreted this result in terms of the equilibria (1)—(4), involving ion-pairs, ion-triplets, and ion-quadruplets. Thus the

$$\mathrm{B} + \mathrm{HOAc} \rightleftharpoons [\mathrm{BH^+\,OAc^-}] \qquad (1)$$

$$[\mathrm{BH^+\,OAc^-}] \rightleftharpoons [\mathrm{BH^+}] + [\mathrm{OAc^-}] \qquad (2)$$

$$[\mathrm{BH^+\,OAc^-}] + [\mathrm{OAc^-}] \rightleftharpoons [\mathrm{OAc^-\,BH^+\,OAc^-}] \qquad (3)$$

$$[\mathrm{BH^+\,OAc^-}] + [\mathrm{H_3O^+\,OAc^-}] \rightleftharpoons [\mathrm{BH^+\,OAc^-\,H_3O^+\,OAc^-}] \qquad (4)$$

addition of water to the medium can result in an increased concentration of acetate ions, with consequent increase in the proportion of ion-triplets and hence [through equilibria (1) and (3)] of the protonated forms of the indicator.

The formation of ion aggregates of this kind is likely to affect the kinetic behaviour of electrolytes in acetic acid. Few measurements have been made, as far as we are aware, of the rates of base-catalysed reactions in this solvent. The rearrangement of 4-bromo-2,6-di-t-butylcyclohexa-2,5-dienone is, however, catalysed by bases as well as by acids,[1,3,4] and it seemed of interest to compare the isotope effects on the rates of these processes. *o*-Nitroaniline, which was the indicator we used for correlation with the rate of acid-catalysed rearrangement,[5] is so nearly completely unprotonated in acetic acid that it could not be used for the more basic solutions used in this work; so we have also made some new measurements of the behaviour of indicators in acetic acid and in deuterioacetic acid containing sodium acetate.

EXPERIMENTAL

Most of the materials and methods have been described in earlier papers.[1,4,5] Solutions of sodium acetate were prepared by dissolving known weights of sodium in anhydrous acetic acid. *p*-Bromo-*NN*-dimethylaniline was prepared by brominating *NN*-dimethylaniline with bromine in a dioxan–water mixture containing potassium hydroxide. The product was washed with water, the dioxan was removed under reduced pressure, and the resulting oil was chromatographed on alumina. Elution with a mixture of benzene and diethyl ether gave the base as white crystals which were crystallised twice from an ethanol–water mixture and then had m.p. 54·5° (lit.,[6] 55°). The basic form of this indicator has characteristic absorption maxima in ethanol, and by our measurements the absorptions had $\lambda_{\text{max.}}$ 312 and 260 nm ($\varepsilon_{\text{max.}}$ 2060 and 19,500 respectively). The protonated form has very small absorption (ε_{A} 87) at 260 nm, determined in acetic acid containing 0·005M-$\mathrm{HClO_4}$. The thermodynamic dissociation constant, $\mathrm{p}K_{\mathrm{BH^+}}$, determined in water,[7] is 4·23. We found that the spectrum of the base in acetic acid had the same shape, and maxima in the same position, as in ethanol, but that the extinction coefficients throughout the absorption curves were markedly different: $\varepsilon_{\text{max.}}$ 870 and 8150 at 312 and 260 nm respectively. The ratios $\varepsilon_{\text{max.}}$(HOAc) : $\varepsilon_{\text{max.}}$(EtOH) are therefore 0·422 and 0·418 respectively. For the more intense band at 260 nm, it seems reasonable to assume that the free base has the same maximum extinction coefficient in acetic acid and in ethanol, and thence to determine the extent of protonation of the base; results are given in Table 1 for the extent of protonation in acetic acid and deuterioacetic acid.

Measurements were made also with *p*-(*NN*-dimethylamino)azobenzene [an AnalaR specimen, used without

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[1] Part IV, P. B. D. de la Mare and A. Singh, *J.C.S. Perkin II*, 1972, 1801.

[2] S. Bruckenstein and I. M. Kolthoff, *J. Amer. Chem. Soc.*, 1956, **78**, 10.

[3] V. V. Ershov and A. A. Volod'kin, *Isvest. Akad. Nauk S.S.S.R. Otdel khim. Nauk*, 1962, 730, 2026; V. V. Ershov, A. A. Volod'kin, and G. N. Bogdanov, *Russ. Chem. Rev.*, 1963, **32**, 75.

[4] P. B. D. de la Mare, O. H. M. El Dusouqui, J. G. Tillett, and M. Zeltner, *J. Chem. Soc.*, 1964, 5306.

[5] P. B. D. de la Mare, A. Singh, J. G. Tillett, and M. Zeltner, *J. Chem. Soc.* (*B*), 1971, 1122.

[6] G. M. Kosolapoff, *J. Amer. Chem. Soc.*, 1953, **75**, 3596.

[7] M. M. Fickling, A. Fischer, B. R. Mann, J. Packer, and J. Vaughan, *J. Amer. Chem. Soc.*, 1959, **81**, 4226.

further purification; m.p. 117·5° (lit.,[8] 117·5—118°)]. Its first protonation is on the azo-nitrogen atom;[9] its basic form has an absorption maximum at 410 nm, and at 514 nm has negligible absorption in ethanol; at the latter wavelength its acidic form has a maximum extinction coefficient, ε_{BH^+} 50,000, determined in acetic acid containing 0·0045M-$HClO_4$. The value of pK_{BH^+} for this indicator is 2·27 in aqueous ethanol,[9] so it must be fully protonated in the above conditions; higher acidities were avoided to minimise the possibility of a second protonation. A good isosbestic point at 462 nm was observed when the spectrum of this indicator was scanned at several low values of the acidity. Table 2 gives the results of the measurements of the extent of protonation with and without sodium acetate in various solvents; all values are relative to the maximum extinction coefficient for the indicator, ε_{BH^+} 50,000, determined as mentioned above.

TABLE 1

Extent of protonation of *p*-bromo-*NN*-dimethylaniline in acetic acid and in deuterioacetic acid at 25°

Solvent	$[H_2O]$/M	[NaOAc]/M	$\log_{10}$ ([BH⁺]/[B])
HOAc			0·148
HOAc		0·0210	0·092
HOAc		0·0320	0·092
HOAc		0·0630	0·092
HOAc		0·105	0·084
HOAc		0·270	0·084
HOAc		0·340	0·084
HOAc	0·45	0·0340	0·20
HOAc	0·45	0·105	0·19
HOAc	0·45	0·170	0·19
HOAc	0·90	0·170	0·26
HOAc	2·60	0·170	0·60
DOAc		0·038	0·01
DOAc		0·095	0·00
DOAc		0·190	$\bar{1}$·99
DOAc		0·285	0·00
DOAc		0·380	0·01
DOAc	2·0 *	0·360	0·26

* D_2O.

TABLE 2

Extent of protonation of *p*-(*NN*-dimethylamino)azobenzene in acetic acid and in deuterioacetic acid at 25°

Solvent	$[H_2O]$/M	[NaOAc]/M	$\log_{10}$ ([BH⁺]/[B])
HOAc			$\bar{1}$·42
HOAc		0·0040	$\bar{1}$·11
HOAc		0·0190	$\bar{1}$·08
HOAc		0·0950	$\bar{1}$·09
HOAc		0·190	$\bar{1}$·13
HOAc		0·285	$\bar{1}$·16
HOAc		0·480	$\bar{1}$·24
HOAc	0·52	0·100	$\bar{1}$·30
HOAc	1·11	0·100	$\bar{1}$·48
HOAc	1·58	0·100	$\bar{1}$·61
HOAc	0·45	0·190	$\bar{1}$·29
HOAc	0·90	0·190	$\bar{1}$·42
HOAc	1·35	0·190	$\bar{1}$·54
HOAc	1·81	0·190	$\bar{1}$·65
DOAc		0·040	$\bar{2}$·99
DOAc		0·100	$\bar{2}$·99
DOAc		0·200	$\bar{1}$·04
DOAc	0·51 *	0·100	$\bar{1}$·22
DOAc	1·12 *	0·100	$\bar{1}$·35
DOAc	1·57 *	0·100	$\bar{1}$·43
DOAc	1·78 *	0·100	$\bar{1}$·49
DOAc	2·24 *	0·100	$\bar{1}$·59

* D_2O.

The rate-measurements were made as described earlier;[1,5] first-order rate-coefficients for the disappearance of the dienone were generally constant over 80—90% of reaction. The product was that of prototropic rearrangement, as was shown by its ^1H n.m.r. and its u.v. spectrum. Results are collected in Table 3.

TABLE 3

Rates of rearrangement of 4-bromo-2,6-di-t-butylcyclohexa-2,5-dienone and its deuterio-derivative in acetic acid and in deuterioacetic acid at 25°

Solvent	H_2O/M	NaOAc/M	$k_1^{4\text{-H}}$/min^{-1}	$k_1^{4\text{-D}}$/min^{-1}	$k_1^{4\text{-H}}/k_1^{4\text{-D}}$
HOAc		0·0210	0·0059	0·00087	6·7
HOAc		0·0219	0·0071		
HOAc		0·0315	0·0086	0·00130	6·6
HOAc		0·0630	0·0186	0·00252	7·4
HOAc		0·0670	0·0191		
HOAc		0·101	0·0304		
HOAc		0·105	0·0330	0·00430	7·7
HOAc		0·155	0·0502		
HOAc		0·243	0·0956		
HOAc		0·270	0·103	0·0130	7·9
HOAc		0·340	0·143	0·0180	7·9
HOAc		0·368	0·184		
HOAc	0·45	0·034	0·0130		
HOAc	0·45	0·105	0·0444	0·0061	7·3
HOAc	0·45	0·170	0·0741	0·0097	7·7
HOAc	0·52	0·100	0·0410		
HOAc	0·90	0·170	0·0976	0·0120	8·1
HOAc	1·11	0·100	0·058		
HOAc	1·58	0·100	0·076		
HOAc	2·60	0·170	0·197	0·0224	8·8
DOAc		0·038	0·0152		
DOAc		0·040	0·0178		
DOAc		0·095	0·0370		
DOAc		0·100	0·0454		
DOAc		0·190	0·0809		
DOAc		0·285	0·135		
DOAc		0·380	0·211		
DOAc	0·51 *	0·100	0·063		
DOAc	1·10 *	0·100	0·084		
DOAc	1·57 *	0·100	0·100		

* D_2O.

DISCUSSION

The values given in Table 1 for the extent of protonation of *p*-bromo-*NN*-dimethylaniline are dependent on the assumption that the free base has the same extinction coefficient in acetic acid as in ethanol, and that all ionised forms of the indicator, including free ions and ion-aggregates, have the same extinction coefficient. These assumptions would normally be thought acceptable, especially in view of the very similar shape of the absorption curves of the indicator in the two solvents over the whole of the spectral range from 330—230 nm. We have noted, however, that there is a significant effect of solvent on the absorption spectrum of *p*-bromo-*NN*-dimethylaniline, the weak maximum at 310 nm observed in ethanol and in acetic acid becoming in water much reduced in intensity and appearing only as a shoulder on the main absorption band, which itself is somewhat reduced in intensity (ε 13,300; an even lower value has been reported [7]). We shall, therefore, base our interpretation mainly on the trends in acidity with change in

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[8] T. W. Campbell, D. A. Young, and M. T. Rogers, *J. Amer. Chem. Soc.*, 1951, **73**, 5789.

[9] M. T. Rogers, T. W. Campbell, and R. W. Maatman, *J. Amer. Chem. Soc.*, 1951, **73**, 5122.

base; these are dependent only on the second of these assumptions. Addition of sodium acetate to the solvent can be seen to result initially in a decrease in the protonating power of the medium as measured by the protonation of this indicator, to a value which remains very nearly constant over a good range of concentration. In the presence of sodium acetate, the addition of water to the medium results in an apparent increase in its power of protonation. This result is in very marked contrast to the behaviour of more basic indicators in acetic acid containing perchloric acid, where the addition of water profoundly reduces the protonating power of the acidic solution (ref. 1, and sources there cited). The result, however, is in good qualitative agreement with the work of Bruckenstein and Kolthoff.[2]

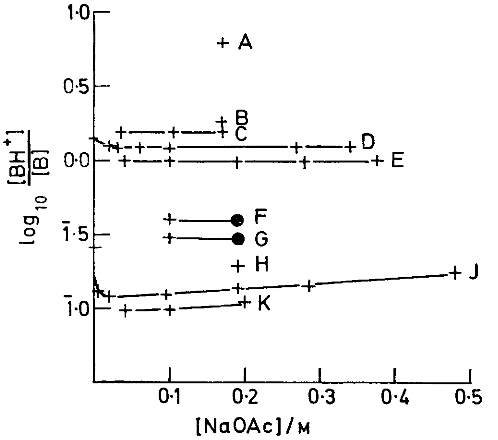

FIGURE 1 Protonation of *p*-bromo-*NN*-dimethylaniline (I) and of *p*-(*NN*-dimethylamino)azobenzene (II) in acetic acid and deuterioacetic acid containing sodium acetate; A, (I),HOAc + 2·6M-H_2O; B, (I),HOAc + 0·90M-H_2O; C, (I),HOAc + 0·45M-H_2O; D, (I),HOAc; E, (I),DOAc; F, (II),HOAc + 1·58M-H_2O; G, (II),HOAc + 1·11M-H_2O; H, (II),HOAc + 0·45M-H_2O; J, (II),HOAc; K, (II),DOAc. Filled circles are interpolated values

Similar phenomena are noted for the protonation of *p*-(*NN*-dimethylamino)azobenzene. In this case, measurements of protonating power are based experimentally on the absorption of the conjugate acid, [BH^+], measured in acetic acid containing perchloric acid. When the concentration of sodium acetate is increased, there is an initial decrease in the protonating power of the medium, followed by a slight increase at the highest concentrations of added base. Added water again increases the acidity. The results are plotted in Figure 1.

It can be seen that the behaviour of the two indicators, though similar, is not quantitatively identical. Differences are no doubt to be expected because the ion-aggregate equilibrium constants are not likely to be the same, especially when (as here) indicators are compared having different types of site for protonation.

In Part III [5] we showed that study of the protonation of *o*-nitroaniline in acetic acid containing perchloric acid [equilibrium probably now [1] best represented as in (5)] shows that the protonating power of the medium is powerfully decreased by the addition of water to the medium; and that the solvent deuterium isotope effect accords both in direction and in magnitude with the corresponding solvent deuterium isotope effect in water containing added mineral acid, the base being more protonated in the deuterium-containing solvent by a factor of *ca.* 4, *i.e. ca.* 0·6 on a logarithmic scale.

$$B + H_2OAc^+ + ClO_4^- \rightleftharpoons [BH^+\,ClO_4^-] + HOAc \qquad (5)$$

The results given in Tables 1 and 2, some of which are plotted in Figure 1, show that the corresponding solvent deuterium isotope on equilibrium (6) is quite different, being in the opposite direction by a factor of *ca.* antilog$_{10}$ 0·1, *i.e. ca.* 1·2.

$$B + HOAc \rightleftharpoons [BH^+\,OAc^-] \qquad (6)$$

Qualitatively, it is easy to see the reason for the direction of this difference; equation (5) indicates that protonation of the base releases acetic acid to the medium; and the lower zero-point energy of DOAc than of HOAc must contribute to the fact that replacement of hydrogen by deuterium in the solvent favours protonation. As far as equilibrium (6) is concerned, however, protonation does not liberate but instead consumes acetic acid; and so now, replacement of hydrogen by deuterium in the solvent is in the reverse direction and disfavours protonation. As far as the quantitative approach is concerned, Isaacs [10] has noted that for the protonation of a tertiary amine as in equation (6), the calculated increase in zero-point energy suggests that protioacetic acid should transfer a proton slightly more strongly than does deuterioacetic acid; and that *NN*-dimethyl-*p*-nitroaniline and *p*-bromo-*NN*-dimethylaniline are protonated slightly more in protioacetic acid than in deuterioacetic acid. We failed to confirm this result; [5] but the transition from the situation represented by equation (5) to that represented by equation (6) is likely to be very

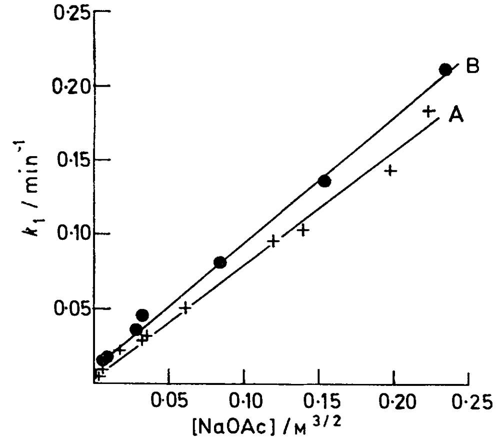

FIGURE 2 Catalysis by sodium acetate of the rearrangement of 4-bromo-2,6-di-t-butylcyclohexa-2,5-dienone in acetic acid and in deuterioacetic acid at 25°: A, HOAc; B, DOAc

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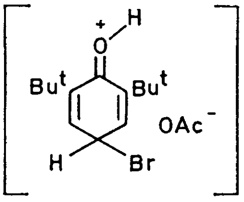
[10] N. S. Isaacs, *Tetrahedron Letters*, 1965, 4553.

sensitive to traces of acidic impurity, and pending further study we think that the situation in the complete absence of added acids or bases is uncertain. Application of Bunton and Shiner's theory [11] to these solvents requires, as Isaacs [10] noted, inclusion of consideration of the details of the hydrogen bonds of all the species concerned, and the necessary information is not available for these bases in acetic acid.

The kinetics of rearrangement of 4-bromo-2,6-di-t-butylcyclohexa-2,5-dienone were first-order in dienone. With added sodium acetate, the rate increased more rapidly than the stoicheiometric concentration of total added salt; Figure 2 shows that the results are well represented by a dependence on $[\mathrm{NaOAc}]^{3/2}$. Although the dienone could be protonated only to a very small extent in this relatively basic medium, it is formally possible that the entity undergoing rearrangement could be the ion pair A. However, the primary deuterium isotope effect for the acid-catalysed rearrangement [1] is in the order $\mathrm{HOAc} > \mathrm{Cl}^- > \mathrm{Br}^-$; it would be expected that an acetate-catalysed rearrangement involving the more nucleophilic acetate ion attacking the protonated dienone would also show a low primary isotope effect. The reverse is true, as is shown in Table **3**; very large primary deuterium isotope effects are found in the acetate-catalysed rearrangement. For this reason, we deduce that the substrate attacked by base is the free dienone, and further discussion depends on this conclusion.



A

The fact that the rate depends on the three-halves power of the total sodium acetate concentration indicates that the most important basic species involved in attack on the substrate is a complexed form of the acetate ion; consideration of equilibria (7) and (8) shows that if the bulk species present in solution is undissociated sodium acetate and/or an ion-pair of the same stoicheiometry, then $[\mathrm{Na(OAc)_2^-}] = \mathrm{const.}[\mathrm{NaOAc}]^{3/2}$. It can be deduced, therefore, that the main base involved in attack on the dienone is $\mathrm{Na(OAc)_2^-}$.

$$\mathrm{Na^+ + OAc^- \rightleftharpoons NaOAc} \qquad (7)$$

$$\mathrm{NaOAc + OAc^- \rightleftharpoons Na(OAc)_2^-} \qquad (8)$$

The fact that the addition of water to the medium results in a small increase in the rate of rearrangement probably results from the fact that the addition of water promotes processes involving ionisation, and so results in an increase in the concentration of any ionic species present, including triple ions. Table **3** shows also that the reaction is subject to a small reverse deuterium solvent isotope effect; the rate is faster in the deuteriated solvent by a factor of *ca.* 1·2. On the present interpretation, this effect could result only from the summation of small secondary influences on the ionic equilibria and on the transition state.

The primary deuterium isotope effect, $k_1^{4\text{-H}} : k_1^{4\text{-D}}$, experimentally increases with concentration of sodium acetate. This change probably arises because the rate at low concentrations of sodium acetate contains a component from a mechanism not involving base catalysis and having a smaller primary isotope effect, as in the acid-catalysed reaction. Evidence for this comes from the non-zero intercept of the plot of rate against $[\mathrm{NaOAc}]^{3/2}$ shown in Figure 2.

The large value of the primary deuterium isotope effect (7·9 at high concentrations of sodium acetate, increased to 8·8 by the addition of 2·6M-water) shows that the C–H bond in the substrate is about half-broken in the transition state, so that nearly all of its zero-point energy has been lost. As noted already, this is in marked contrast with the situation for the acid-catalysed reaction. In the latter, when the proton loss is to HOAc, the value of $k_1^{4\text{-H}} : k_1^{4\text{-D}}$ is 4·2; catalysis by addition of a stronger base reduces the value (for bromide ion, $k_1^{4\text{-H}} : k_1^{4\text{-D}} = 2·5$). So we have argued,[1,5] in accordance with the Hammond postulate,[12] that the C–H bond is less than half broken in the transition states for these acid-catalysed processes, the transition states lying well towards the reactants. The fact that the change from the more reactive protonated substrate to the intrinsically less reactive dienone has apparently resulted in an increase in the extent of bond-breaking in the transition state seems also to be in general accordance with the Hammond postulate.[12]

We thank Miss Susan Nicholson for help with some measurements of u.v. absorption spectra.

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[11] C. A. Bunton and V. J. Shiner, *J. Amer. Chem. Soc.*, 1961, **83**, 42.

[12] G. S. Hammond, *J. Amer. Chem. Soc.*, 1955, **77**, 334.