Diazepines. Part XIX.[1] Kinetics of Addition of Bromine to Position 6 in 2,3-Dihydro-1,4-diazepinium Salts

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Measurements on the aqueous bromination of 2,3-dihydro-1,4,6-trimethyl- and of 2,3-dihydro-6-methyl-1,4-diazepinium perchlorate show that addition of bromine at position 6 is a fast reaction between bromine molecules and dihydrodiazepinium cations, for which the rate constant at 298 K is *ca.* 5×10^6 l mol^{-1} s^{-1}. The activation parameters are consistent with such a reaction. In contrast, bromination at position 6 of 6-bromo-2,3-dihydro-5,7-dimethyl-1,4-diazepinium perchlorate is an equilibrium bromination, proceeding only to a small extent, followed by an equilibrium proton dissociation step, and concluded by rate-determining hydrolyses of the two intermediates. Again, the activation parameters are consistent with the mechanism. Both types of bromination kinetics can be accommodated within a single reaction scheme, the rate-determining steps being different, and possible reasons for the difference are discussed. The influence of mesomerism and other stability effects on the behaviour of 2,3-dihydro-1,4-diazepinium cations towards bromine is discussed.

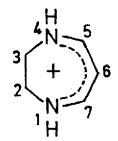
THE 2,3-dihydro-1,4-diazepinium cation (I) contains a mesomeric π-electron system, the stability of which enables it to resist addition by electrophiles, and instead to exhibit *meneidic*, or *regenerative*, properties,[2] for

[1] Part XVIII, E. M. Grant, D. Lloyd, and D. R. Marshall, *Chem. and Ind.*, 1974, 525.

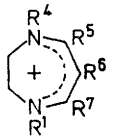
[2] D. Lloyd and D. R. Marshall, *Angew. Chem. Internat. Edn.*, 1972, **11**, 404.

which reason it was formerly described as 'quasi-aromatic.'[3] Electrophilic reactivity is centred, apparently exclusively, at position 6, and hydrogen atoms there are replaced by common electrophilic reagents, although hydrogen atoms at positions 5 and 7 are not.[4,5] Substituents which have been introduced at position 6 in this way include deuterium,[4,6,7] chlorine,[8] bromine,[1,5,6,8-10] iodine,[6,8] and nitro-,[5,11,12] amino- (and derivatives),[12,13] diazo-,[12,13] and arylazo-groups.[14] Protodehalogenation can also take place at position 6.[8]

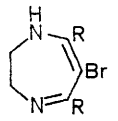
It has been observed, however, that further reaction with bromine is possible when position 6 carries an alkyl [10] or bromine [6,8] substituent. This reaction also takes place at position 6, and consumes one molar proportion of bromine, but when water is used as solvent the isolable product is not a diazepine. Thus, 6-bromo-2,3-dihydro-5,7-dimethyl-1,4-diazepinium (II) salts give 3,3-dibromopentane-2,4-dione, which separates immediately as an oil, while 2,3-dihydro-1,4,6-trimethyl-1,4-diazepinium (III) perchlorate with an excess of bromine rapidly gives a precipitate of a bromine complex of dimethylethylenediamine dihydrobromide.[10] On the other hand, a benzene solution of 6-bromo-2,3-dihydro-5,7-diphenyl-1,4-diazepine base (V; R = Ph) reacts with bromine to give 6,6-dibromo-2,3-dihydro-5,7-diphenyl-1,4-diazepine base (VI; R = Ph).[8] Clearly such non-conjugated, geminally substituted dihydrodiazepines are



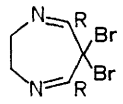
(I)



(II) R^6 = Br, R^5 = R^7 = Me, R^1 = R^4 = H
(III) R^1 = R^4 = R^6 = Me, R^5 = R^7 = H
(IV) R^6 = Me, R^1 = R^4 = R^5 = R^7 = H



(V)



(VI)

rapidly hydrolysed in aqueous solution. The resultant destruction of the normally very stable mesomeric system is so unusual that geminal bromination at position 6 has been examined further. The reaction is an 'addition' in the sense that reaction of bromine with an enol is an addition, the dihydrodiazepine here reacting as an enamine. The reaction is more precisely classified as a substitution in which the leaving group departs, not from the reaction centre, but from a hetero-atom β to the reaction centre.

EXPERIMENTAL

6-Bromo-2,3-dihydro-5,7-dimethyl- (II),[6,9] 2,3-dihydro-1,4,6-trimethyl- (III),[15] and 2,3-dihydro-6-methyl-1,4-diazepinium (IV) [16] perchlorates were used, and were prepared as previously described. Other chemicals were of AnalaR grade.

Kinetic measurements were made by the method of Atkinson and Bell,[17] modified in ways already reported.[10] All rates were measured in dilute aqueous acid solution at 273 or 298 K (±0·05 K). Water for reaction mixtures was distilled, redistilled from alkaline permanganate, treated with bromine, and again distilled. Runs were carried out at least in duplicate, with agreement generally within 2—3%. Corresponding uncertainties in activation parameters are *ca.* $\Delta H^{\ddagger} \pm 1$ kJ mol^{-1}; $\Delta S^{\ddagger} \pm 3$ J mol^{-1} K^{-1}.

RESULTS AND DISCUSSION

It has already been shown [10] that 2,3-dihydro-1,4,6-trimethyl- (III) and 2,3-dihydro-6-methyl-1,4-diazepinium (IV) perchlorate react rapidly with aqueous bromine at position 6, giving products which do not absorb significantly in the u.v. at wavelengths above 200 nm. The u.v. spectra show that the products must be geminally disubstituted at position 6, and the rapidity of formation of dimethylethylenediamine by hydrolysis of the product from (III) supports this, the bromination being an addition which destroys the conjugated system.

The kinetic results for these two reactions are shown, for (III) in Table 1, and for (IV) in Table 2. For both, the constancy of the values of k_{obs} $(1 + K[Br^-])$ shows that the transition state contains a bromine molecule. (Here K is the stability constant of the tribromide ion, and is taken to be 16 l mol^{-1} at 298 K,[18,19] and 20 l mol^{-1} at 273 K.[19,20]) Since tribromide ions are less reactive than bromine molecules,[21] this establishes bromine molecules as the reagent species. The rates are independent of pH, showing that the bulk diazepine species, the dihydrodiazepinium cations, and not differently protonated species, are the effective substrates. [This is also suggested by the similarity of reactivities of (IV), which can form a neutral base, and (III), which cannot.] Thus the reactions appear to involve rate-determining attacks by bromine molecules on dihydrodiazepinium cations.

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TABLE 1

Bromination of 2,3-dihydro-1,4,6-trimethyl-1,4-diazepinium perchlorate

T/K	I/M	[H$^+$]/ M	[Br$^-$]/ M	$10^{-4}k_{obs}$/ l mol^{-1} s^{-1}	$10^{-4}k_{obs}(1 + K[Br^-])$/ l mol^{-1} s^{-1}
298	0·02	0·0001	0·01	465	539
298	0·02	0·001	0·01	471	546
298	0·02	0·005	0·01	463	537
298	0·02	0·01	0·01	479	556
298	0·11	0·01	0·01	475	551
298	0·41	0·01	0·01	474	550
298	0·41	0·01	0·10	189	491
298	0·41	0·01	0·40	65	481
				Mean	531
273	0·02	0·001	0·01	42·5	51·0
273	0·02	0·01	0·01	42·2	50·6
273	0·41	0·01	0·01	41·8	50·2
273	0·41	0·01	0·01	41·9	50·3
273	0·41	0·01	0·04	28·4	51·1
273	0·41	0·01	0·10	16·6	49·8
273	0·41	0·01	0·40	6·0	54·0
				Mean	51·0

K_{273} = 20 l mol^{-1}; K_{298} = 16 l mol^{-1}.

TABLE 2

Bromination of 2,3-dihydro-6-methyl-1,4-diazepinium perchlorate

T/K	I/M	[H$^+$]/ M	[Br$^-$]/ M	$10^{-4}k_{obs}$/ l mol^{-1} s^{-1}	$10^{-4}k_{obs}(1 + K[Br^-])$/ l mol^{-1} s^{-1}
298	0·02	0·01	0·01	352	408
298	0·02	0·005	0·01	356	413
298	0·02	0·001	0·01	348	404
298	0·02	0·0001	0·01	354	410
298	0·11	0·01	0·01	347	402
298	0·41	0·01	0·01	366	424
298	0·41	0·01	0·10	154	400
298	0·41	0·01	0·40	52	385
				Mean	406
273	0·02	0·01	0·01	40·2	48·2
273	0·02	0·0001	0·01	40·0	48·0
273	0·11	0·01	0·01	40·3	48·3
273	0·41	0·01	0·01	39·5	47·4
273	0·41	0·01	0·04	27·3	49·1
273	0·41	0·01	0·10	15·9	47·8
273	0·41	0·01	0·40	5·56	49·9
				Mean	48·4

K_{273} = 20 l mol^{-1}; K_{298} = 16 l mol^{-1}.

The data also show that variation of the ionic strength does not affect the rates. This suggests that in each transition state the bromide ion, which must separate to complete the reaction, has not yet separated to any significant extent, since this separation must increase the polar character of the reacting system. Such an increase in polar character should give rise to a positive primary salt effect, which is not observed. Since the only pre-equilibrium process involved, the dissociation of tribromide ions (a major bromine species in the solutions), shows no marked secondary salt effect at moderate ionic strengths,[18,20] there is no possibility of a primary salt effect being compensated by such a secondary effect, and so concealed.

Thus, the transition states for bromination of both (III) and (IV) by bromine molecules appear to be reached early in the reactions.

The bimolecular rate constants (Tables 1 and 2) are very high, *ca.* 10^6 l mol^{-1} s^{-1}. The values at 273 and 298 K allow calculation of the activation parameters. The entropies of activation, $\Delta S^{\ddagger}_{298}$, are +42 and +4 J mol^{-1} K^{-1} for (III) and (IV) respectively. These small to moderate positive values are similar to values found previously [1,6] for reactions between bromine molecules and dihydrodiazepinium cations, and are to be expected for encounters of this type. The enthalpies of activation ($\Delta H^{\ddagger}$) are correspondingly fairly low, 53 and 37 kJ mol^{-1}, respectively.

Reaction intermediates geminally disubstituted at position 6 are formed readily,[5] so that ready attack by bromine upon (III) and (IV) is understandable, but that attack should proceed to completion and lead to complete destruction of the system is less easy to understand. Further information, however, is provided by the results for the 6-bromo-compound (II).

We have confirmed that the stoicheiometry of the bromination of 6-bromo-2,3-dihydro-5,7-dimethyl-1,4-diazepinium (II) perchlorate corresponds to a mono-bromination reaction (*cf.* ref. 6). The kinetic results are given in Table 3. It has already been shown [6] that

TABLE 3

Bromination of 6-bromo-2,3-dihydro-5,7-dimethyl-1,4-diazepinium perchlorate at 298 K

I/M	[H$^+$]/ M	[Br$^-$]/ M	k_{obs}/ l mol^{-1} s^{-1}	k_{obs}[Br$^-$] [1 + 16[Br$^-$])	k_{calc}[Br$^-$] (1 + 16[Br$^-$])
0·11	0·01	0·1	866	225	223
0·11	0·001	0·1	1463	380	385
0·11	0·001	0·05	3907	351	385
0·11	0·0003	0·1	3190	830	805

at 273 K and I = 0·1 the reaction conforms to equation (1). The present results for 298 K and I = 0·11

$$k[Br^-](1 + 20[Br^-]) = 59 + 0{\cdot}090/[H^+] \quad (1)$$

correspond to the equivalent equation (2). This rate

$$k[Br^-](1 + 16[Br^-]) = 205 + 0{\cdot}18/[H^+] \quad (2)$$

form differs in two ways from that found for (III) and (IV): the kinetic dependence on the bromide ion concentration is different, showing an additional inverse dependence on [Br$^-$], and there is an additional pH-dependent term.

The dependence of reaction rate upon [Br$^-$] might be explained by bromination by Br$^+$, formed by dissociation of bromine, but this is unlikely.[6] The only likely reagent is the bromine molecule. The rate form is then accounted for by a two-step mechanism, in which the first step involves reversible formation of a brominated intermediate and a bromide ion. In a benzenoid *substitution*, the second step is loss of the leaving group from the reaction centre. Loss of a leaving group is possible here, too, if the leaving group is a proton at position 1 (or 4, *i.e.* from NH), but a requirement of the effective reversibility of the first step in a two-step mechanism is that this proton loss should be rate determining. The pH-dependent rate term makes this improbable.

The pH-dependent rate term in equation (1) was earlier [6] explained as a reaction of the dihydrodiazepine base (V; R = Me). The temperature coefficient of such a reaction can be calculated from the rate coefficients in (1) and (2) and the values [16] of the dissociation constant of the bromodihydrodiazepinium cation at the two temperatures. The rate ratio is found to be $k_{273}/k_{298} = 2{\cdot}9$. This, corresponding to a negative activation energy of -34 kJ mol^{-1}, is highly improbable. It must be concluded that the pH-dependent rate term does not arise from prior formation of (V; R = Me) from (II), followed by bromination of (V; R = Me). It is likely, therefore, that it arises from equilibrium bromination of the cation (II), followed by equilibrium proton loss. This renders *rate-determining* proton loss unlikely as an explanation of the pH-independent term.

Both rate terms therefore require a third, rate-determining step. This step must produce a different product, and can only be hydrolysis [Scheme; the

$$H_2Diaz^+ + Br_2 \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} H_2DiazBr^{2+} + Br^- \quad (A)$$

$$H_2DiazBr^{2+} \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} HDiazBr^+ + H^+ \quad (B)$$

$$H_2DiazBr^{2+} \xrightarrow{k_3} \text{hydrolysis products} \quad (C)$$

$$HDiazBr^+ \xrightarrow{k_4} \text{hydrolysis products} \quad (D)$$

SCHEME

substrate H_2Diaz^+ represents (II)—(IV)]. Since the reaction rates were measured by following the disappearance of bromine, the intermediates must be unstable and present only in low proportion (or the hydrolysis rates would not determine the bromination rate). It follows that, in the absence of water, reaction should proceed to a negligible extent, and this should provide a test of the suggested mechanism.

It was found that solutions of 6-bromo-2,3-dihydro-5,7-dimethyl-1,4-diazepinium (II) perchlorate in chloroform or in glacial acetic acid, when treated with a few mole % of bromine, did indeed fail to react to any noticeable extent, much bromine remaining after 9 h. When 2,3-dihydro-5,7-dimethyl-1,4-diazepinium perchlorate (which reacts with bromine by substitution) was then added, the bromine was decolourised immediately. Alternatively, addition of water to the glacial acetic acid solution also caused discharge of the bromine colour within a few seconds, demonstrating the involvement of water in the reaction. It has also been shown [10] that (III) fails to react with bromine in solution in chloroform or glacial acetic acid, but does react readily when water is added to the glacial acetic acid solution. For (III) also, therefore, bromination is contingent upon hydrolysis, though in aqueous solution the bromination step appears to be rate determining (see below) and the hydrolysis relatively fast.

The entropies of activation are consistent with this. For bromination of (II), the pH-independent rate term shows $\Delta S^{\ddagger}_{298} = -76$ J mol^{-1} K^{-1}, while for the pH-dependent term $\Delta S^{\ddagger}_{298} = -105$ J mol^{-1} K^{-1}. These values may be compared with reasonable estimates of the values to be expected for the Scheme. Step (A) is most easily considered as the (hypothetical) sum of the steps (A1) and (A2). The principal effects will be

$$H_2Diaz^+ + Br_2 \rightleftharpoons H_2DiazBr_2^+ \quad (A1)$$

$$H_2DiazBr_2^+ \rightleftharpoons H_2DiazBr^{2+} + Br^- \quad (A2)$$

solvation effects, for in sum the cratic effects of these two steps will cancel.

In (A1) both ions are large and singly charged, and their entropies should be rather similar. Bromine, however, is a small neutral molecule with a negative entropy of solution in water. Data of Hantzsch and Vagt [22] on the partition of bromine between the vapour phase and dilute aqueous solutions less than 10% saturated yield values for the solution process of $\Delta H^{\ominus}_{298} = -30{\cdot}2$ kJ mol^{-1} and $\Delta S^{\ominus}_{298} = -77$ J mol^{-1} K^{-1}. (Data [23,24] on saturated solutions give slightly more negative values for both quantities.) For the present purpose we may take this entropy change as the value of $-\Delta S^{\ominus}_{A1}$ (neglecting the cratic entropy term, which will cancel out).

In (A2) the main effect will be electrostatic. Though the entropy of solvation of Br^- is known, those of the organic ions are not, and a value for $\Delta S^{\ominus}_{A2}$ must therefore be estimated. An approximate calculation based on a simple point-charge-in-continuum electrostatic model [25] appears to be as satisfactory as any other estimation. The entropy change is then given by $\Delta S^{\ominus}_{el} = +42 z_A z_B$ J mol^{-1} K^{-1} where z_A and z_B are the ionic charges on the products. Hence for (A2), $\Delta S^{\ominus}_{el} = -84$ J mol^{-1} K^{-1}. If we again omit the (cancelling) cratic part, the total entropy change estimated for step (A) is $\Delta S^{\ominus}_{A} = \Delta S^{\ominus}_{A1} + \Delta S^{\ominus}_{A2} = (77 - 84)$ J mol^{-1} K^{-1} $= -7$ J mol^{-1} K^{-1}. The experimental value is much more negative than this.

Step (C) is a hydrolysis reaction, and one or more molecules of water might be incorporated. It has been pointed out [26] that incorporation of a molecule of water leads to an entropy reduction averaging *ca.* -76 J mol^{-1} K^{-1}. The total entropy of activation for reaction incorporating one molecule of water might therefore be *ca.* $(-7 - 76) = -83$ J mol^{-1} K^{-1}, which is similar to the observed value for the pH-independent rate term in bromination of (I).

The pH-dependent rate term has a more negative value, which must incorporate a contribution from the entropy of dissociation $\Delta S^{\ominus}_{B}$. It is difficult to estimate this, though somewhat similar diamine dications

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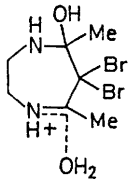
[24] Ref. 23, p. 201.
[25] S. W. Benson, 'The Foundations of Chemical Kinetics,' McGraw-Hill, New York, 1960, ch. XV.
[26] L. L. Schaleger and F. A. Long, *Adv. Phys. Org. Chem.*, 1963, **1**, 1; R. P. Bell, *ibid.*, 1966, **4**, 1.

generally have small positive entropies of dissociation (*e.g.* ethylenediamine, +13 J mol^{-1} K^{-1}). This suggests an estimated activation entropy of perhaps *ca.* −70 J mol^{-1} K^{-1}, more than the observed value. The comparison thus strongly supports the suggestion that water is incorporated in the transition state. It might also be inferred that two molecules of water could be incorporated, since this would cause the entropy of activation to be more strongly negative, as observed. Were this so, it would imply that in this rate process the reaction has progressed further when the transition state is reached, possibly to (VII).



(VII)

Application of the stationary state hypothesis to steps (A) and (C) of the Scheme gives equation (3).

$$k_{obs} = k_1k_3/(k_{-1}[Br^-] + k_3) \quad (3)$$

This conforms to the observed kinetics for the pH-independent bromination of (II) if $k_{-1}[Br^-] \gg k_3$, *i.e.* if k_3 is rate determining, as suggested. Similarly for the pH-dependent reaction of (II) steps (A), (B), and (D) give equation (4) which has the observed kinetic form when

$$k_{obs} = \frac{k_1k_2k_4}{k_2k_4 + k_{-1}(k_4[Br^-] + k_{-2}[Br^-][H^+])} \quad (4)$$

k_4 is sufficiently small and so is rate determining, *i.e.* equation (5) obtains.

$$k_{obs} = k_1k_2k_4/k_{-1}k_{-2}[Br^-][H^+] \quad (5)$$

The same Scheme can account for reaction of (III) and (IV) also, if step (B) [and also step (D)] is negligible, when equation (3) applies. This satisfies the observed kinetics for (III) and (IV) when $k_{-1}[Br^-] \ll k_3$, *i.e.* when bromination is rate determining, implying that brominated (III) and (IV) will be debrominated by bromide ions less readily than will brominated (II) [the cation of (VI; R = Me)], or that they will be hydrolysed more rapidly, or both. Certainly (III) and (IV) should be more open to hydrolytic attack because they are less substituted. [For the same reason, the unsubstituted diazepine (I) is difficult to prepare in aqueous conditions, for although its equilibrium stability is high, it is hydrolysed rapidly when conditions favour hydrolysis.[16]]

These hydrolysis reactions, whether preceded by bromination or not, appear to show instability in 2,3-dihydro-1,4-diazepinium cations. The hydrolytic brominations of (III) and (IV), too, are very fast, with low enthalpies of activation. This is not inconsistent with their meneidic character, however, because amongst the products are β-dicarbonyl compounds, which are themselves markedly stabilised meneidic systems. Modest stability towards hydrolysis under aqueous conditions does not preclude greater stability in resisting addition reactions when hydrolysis cannot occur, *i.e.* meneidic character.

In aprotic solvents 6-substituted dihydrodiazepinium cations do not react significantly with bromine, whereas the bases do, suggesting that the cations are more strongly meneidic than the bases. This is associated with the more symmetrical mesomeric structure in the cations, which also gives rise to high pK values (*cf.* amidines, guanidine, *etc.*). Measurements of pK values show [27] that while in aqueous solution the cations have resonance energies of *ca.* 80 kJ mol^{-1}, the bases have resonance energies *ca.* 34 kJ mol^{-1} less. In aprotic solvents such as benzene the bases may be even less stabilised, possibly owing to the absence of hydrogen bonding (in *N*-unsubstituted compounds), and so may undergo addition of bromine more readily.

[4/1737 *Received*, 19*th August*, 1974]

[27] H. P. Cleghorn, D. Lloyd, and D. R. Marshall, *Adv. Heterocyclic Chem.*, 1974, **17**, 1.