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[^{2}H] LABELLING STUDIES ON THE MECHANISM OF ELECTROCYCLIC AROMATIC SUBSTITUTION BY THE DIAZO-GROUP

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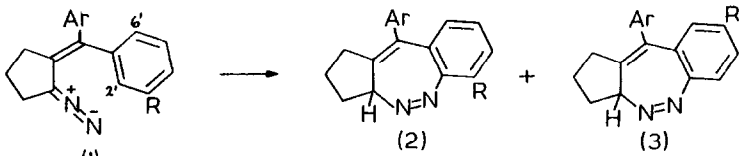
Abstract: A primary deuterium isotope effect has been observed in the cyclisation of diazo-compounds (1) selectively deuteriated at the ring closure sites.

We have recently reported on the directive effects of meta substituents (R) in the synthesis of 1,2-benzodiazepines (2) and (3) from β-aryl-α,β-unsaturated diazoalkanes (1).[1]

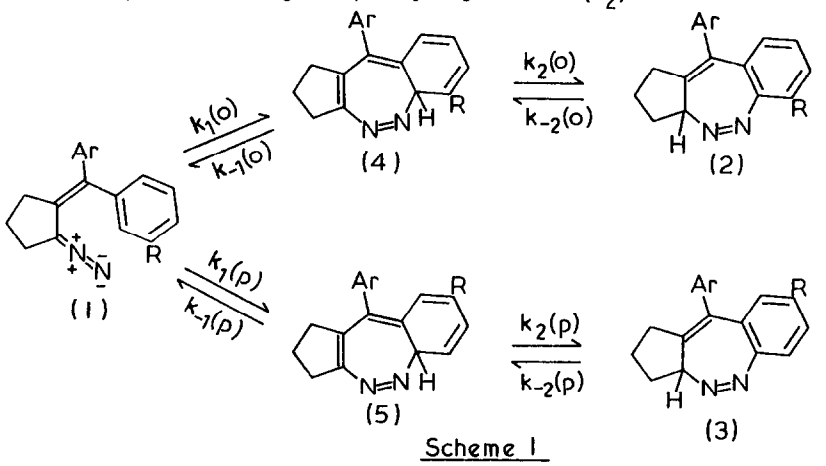


(1) [Ar = m-C_6H_4R] (2) (3)

(a), R = Me $\frac{[2a]}{[3a]}$ = 4·3

Under conditions where the product ratio is under kinetic control (80°C) both +I and +M substituents (R=Me, Et, OMe, OEt) favour the more hindered isomer (2) while a -I group (R=CF_3) favours (3). We are interested in the origin of this directive effect and initiated this study using deuteriated substrates to find out more about the basic mechanism of the reaction.

The reaction is overall an aromatic substitution in which hydrogen is replaced by an azo-group, and it was proposed[1,2] that it occurs in two steps (Scheme 1), an 8π electrocyclic ring closure (k_1) followed by a [1,5] sigmatropic hydrogen shift (k_2).

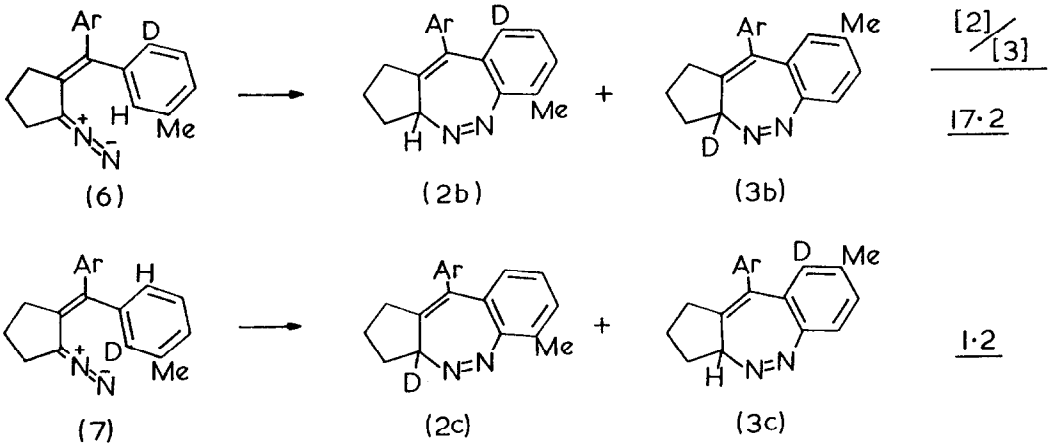


Scheme 1

A priori the substituent directive effect could be exerted in either or both of these steps.

If we make the reasonable assumption that the second step (k_2) is irreversible ($k_{-2}=0$) under 'kinetically controlled' conditions then two extreme situations can be visualised: (i) slow non-reversible cyclisation ($k_{-1}=0$) followed by a fast hydrogen shift (k_2), the product ratio would then depend only on the k_1 (o): k_1 (p) ratio; and (ii) a reversible cyclisation step ($k_{-1}\neq 0$), in this case the product ratio would be affected by both k_1 and k_2.

To determine whether the first step is reversible or not we have carried out experiments using both substituted and unsubstituted diazo-compounds [1, R=Me and R=H], selectively deuteriated at ring closure sites in the aryl rings. In the first of these we examined the effect on the product ratio (2)/(3) of deuteriation at the position <u>para</u> (6') to the methyl substituent. In the cyclisation of this compound (6), if mechanism (i) applies i.e. a slow rate-determining cyclisation step followed by a fast ^1H or ^2H migration then the product ratio should be unaffected by the presence of deuterium but if the first step is reversible then the product ratio will depend to some degree on k_2 and operation of the primary isotope effect should result in a diversion of the reaction path in favour of cyclisation at the non-deuteriated site.

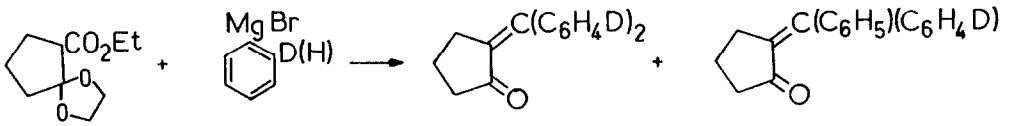


In the event the (2)/(3) ratio did change, from 4.3:1 in the non-deuteriated case to 17.2:1 from (6).[2] The total yield (isolated) of benzodiazepines from (6) was 67% compared to 74% from the non-deuteriated substrate so it is clear that the presence of deuterium has resulted not only in a decrease in the yield of (3) but an almost corresponding increase in the yield of (2). To confirm this result the analogous diazocompound (7) deuteriated at the alternative ring closure site (2') was generated; in this case the (2)/(3) ratio decreased to 1.2:1 and the total benzodiazepine yield was 78%. In these experiments the diazo-compounds contained <u>ca</u> 88% and 85% respectively of dideuteriated species (two equivalent aryl rings). If the product ratios are corrected for presence of monodeuteriated species[3] they become 20.5 and 1.1 respectively which represent changes in the product ratio by factors of 4.8 and 3.9 due to deuteriation.

These results are consistent with the operation of a fast pre-equilibrium between the diazo-compound and the intermediates (4) and (5), Scheme 1, and show that the relative rates of the sigmatropic shifts in the second step are important in determining the product ratio. Thus the directive effects of the substituents (R) could be due in large part to their

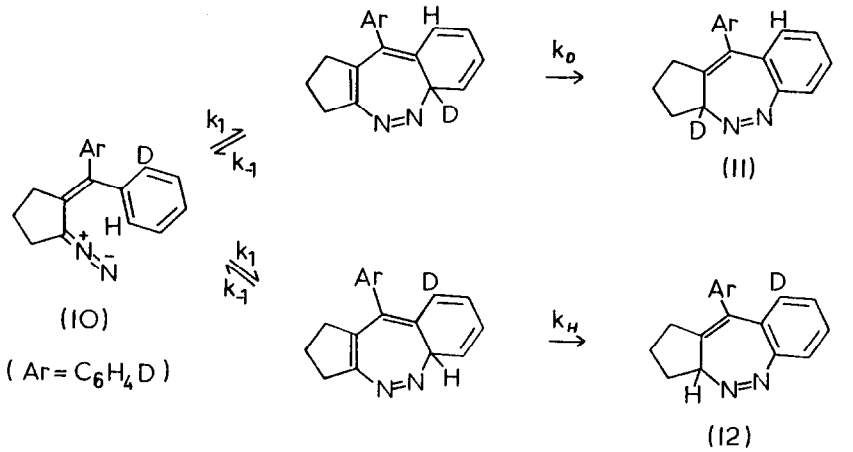
effects on the relative rates of the hydrogen migrations, this effect either accentuating or opposing any directing effect exerted in the cylisation step.[4]

In interpreting these results and those of similar experiments to be done using other substituents it was desirable to determine if the first step was also reversible in the cyclisation of the unsubstituted system (1, R=H). This was achieved by generating the diazo-compound (10) selectively deuteriated at one of the cyclisation sites in the aryl ring. As usual in these reactions the diazo intermediate was generated <u>in situ</u> by the thermal decomposition of a tosylhydrazone salt under aprotic conditions. The tosylhydrazone was made from the ketone (9) which was synthesised by the reaction of the Grignard reagent of 2-deuteriobromobenzene (90% monodeuteriated) with the protected ketoester (8). The resulting ketone was thus a mixture containing <u>ca</u> 80% (9a), 18% (9b) and 2% non-deuteriated product.



(8) (9a) (9b)

In the cyclisation, Scheme 2, the fraction (α) of the product resulting from ^2H transfer was determined from the ^2H n.m.r. spectrum of the total product by measuring the ratio of the integrals of the aliphatic (δ2.8) and aromatic (δ7.2) absorption bands.



Scheme 2

If the ratio (aromatic ^2H)/(aliphatic ^2H) = R then $\alpha = {}^{2}/_{1+R}$ and moreover the same relationship applies to the cyclisation of the diazo-compound derived from the monodeuteriated ketone (9b)[3] so the result is independent of the proportions of (9a) and (9b) used in preparing the reactant. Two cyclisations gave R=9.9 and 9.8 so α = 0.84 and the product ratio $^{(12)}/_{(11)}$ is therefore 4.4 (the precision possible in the measurement of integral ratios is not high and the resulting uncertainty in the product ratio is <u>ca</u> $\pm$0.5). This result therefore shows that for (10), as for the methyl substituted analogues (6) and (7) ring-closure at the non-deuteriated site is favoured and by approximately the same factor. The magnitude of this effect is too large to be attributable to a secondary isotope effect

in the first step and it is therefore again adduced as evidence in favour of a mechanism involving a pre-equilibrium between the diazo-compound (10) and the intermediates followed by a second step whose rate constant is at least comparable with but probably much less than k_{-1}.

This work has thus not yet produced an unambiguous solution to the problem of the origin of the substituent directive effect in the diazo-compound cyclisation, Scheme 1, but it has shown that the course of the reaction is very sensitive to changes in the rate constant of the second, hydrogen migration, step. It seems likely therefore that substituents which favour (2) exert a substantial part of their effect in this step via a steric or electronic acceleration of the (4) → (2) conversion.

We thank the S.R.C. for a studentship (T.K.M.).

References and Notes

1. T.K. Miller, J.T. Sharp, H.R. Sood, and E. Stefaniuk, Tetrahedron Letters, 1980, 1379.
2. All ratios given are for reactions carried out in boiling cyclohexane, similar changes were observed for reactions done in 1,2-dimethoxyethane.
3. This assumes a statistical distribution of deuterium in the monodeuteriated substrate which follows from its preparation method.
4. If the steady state approximation is applied to the intermediates then even if $k_{-1} >> k_2$ the product ratio still depends on the ratio of the equilibrium constants for the first step i.e.

$$\frac{[2]}{[3]} = \frac{k_2(o)}{k_2(p)} \times \frac{K_1(o)}{K_1(p)} \qquad \text{where } K_1 = {}^{k_1}/_{k_{-1}}$$

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