Gas-phase Pyrolysis of 2,3-Dihydro-1,4-diazepines: Involvement of the Saturated Portion of the Ring in Chemical Reactions and Novel *cis–trans* Isomerisation of a Fused Ring System

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Flash vacuum pyrolysis of 2,3-dihydro-1,4-diazepines in the range 450–550 °C involves interaction of the saturated portion of the molecule with the vinamidine system and causes 1,5-hydrogen shifts which have been established by deuterium labelling experiments; at higher temperatures, ring contraction occurs to give pyrazines as major products.

Previous studies of the chemical properties of the 2,3-dihydro-1,4-diazepine system **1** have shown that their reactions are dominated by the conjugated portion of the molecules: either electrophilic attack at positions 1, 4 or 6, or nucleophilic attack at positions 5 or 7.[1] The saturated region of these compounds (positions 2 and 3) has not been seen to participate directly in chemical reactions, and has served only to maintain the unsaturated portion in a rigid near planar geometry. We now report the results of a study of the gas phase thermal reactions of 2,3-dihydro-1,4-diazepines which we have unexpectedly found to involve also the saturated portion and to be controlled by hydrogen shift reactions from the 3-position. Some earlier thermal studies of these compounds have been carried out in solution but here their high base strength is a complicating factor.[2]

We first demonstrated the existence of a hydrogen shift mechanism by flash vacuum pyrolysis (FVP) of the *cis*-cyclohexano derivative **2**,† which was made by a standard method.[3] At temperatures above 450 °C, characteristic aliphatic peaks of the known *trans*-isomer **3** (δ_C 23.94, 34.51 and 62.77; lit.,[3] 23.99, 34.66 and 62.84) appeared in the ^{13}C NMR spectrum of the crude pyrolysate, and at 550 °C this formed the major component. The most likely explanation for this novel *cis–trans* isomerisation of a fused ring system involves sequential 1,5-hydrogen shifts between the 3- and 7-positions (Scheme 1), and we sought to prove this mechanism by a deuterium labelling experiment.

Two important features were taken into account in the design of this experiment. First, because of rapid prototropic shifts involving the 1-H moiety, which render the 1- and 4-, 5- and 7-, and 2- and 3-positions equivalent, it was essential to employ an *N*-substituted diazepine. Second, because of the poor availability of *C*-deuteriated ethylenediamine derivatives, we chose to synthesise instead the [5,7-$^2H_2$]diazepine **4** from *N*-methylethylenediamine and the vinamidinium salt **5** which was itself obtained from [$^2H_7$]dimethylformamide in 72% yield (based on the isotopically labelled precursor) (Scheme 2). No loss of the label could be detected during the synthesis, which provides further testimony to the vanishingly low reactivity of vinami-

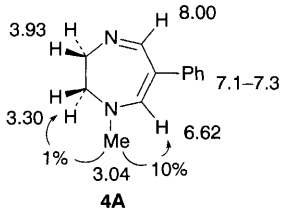
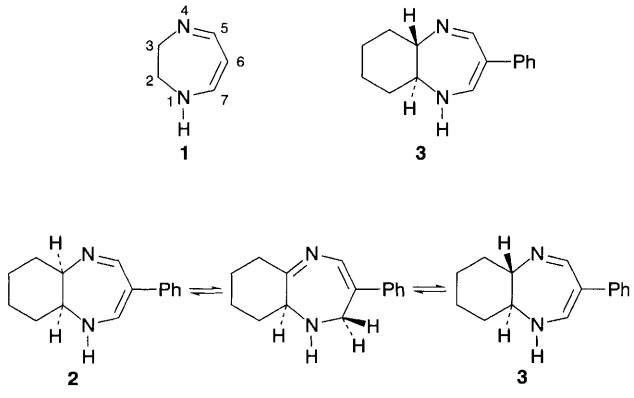
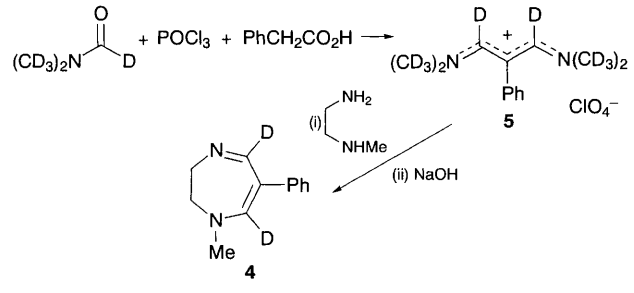


Fig. 1 Proton NMR chemical shifts and NOE data for **4A**



Scheme 1



Scheme 2

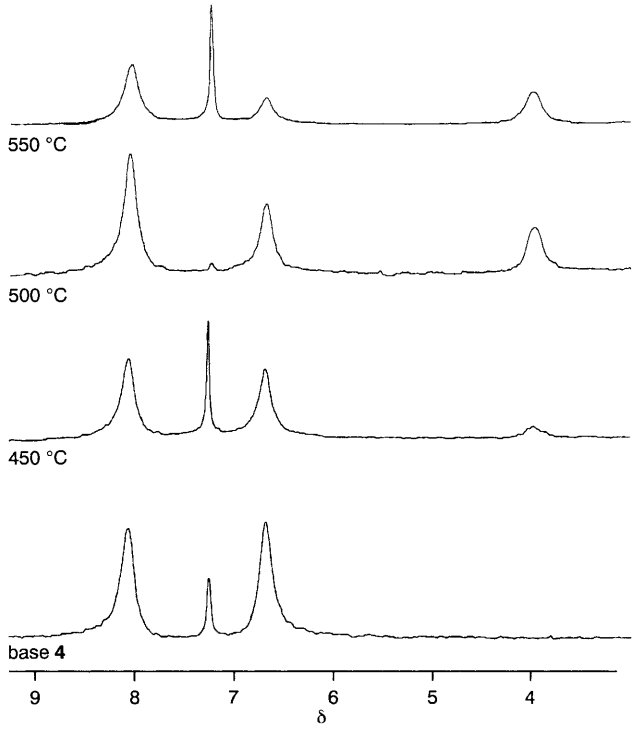
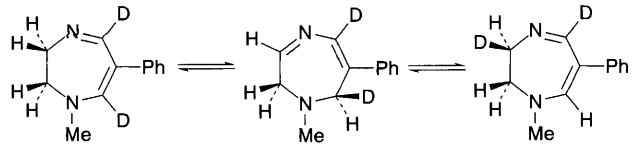
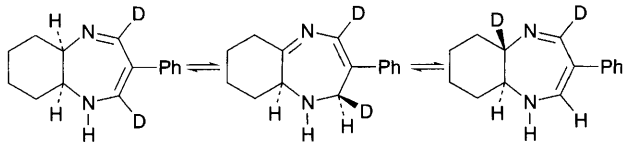


Fig. 2 ^2H NMR spectra of the labelled base **4** and its 450–550 °C pyrolysates. (The peak at δ 7.25 is due to [^2H]chloroform in each case).



Scheme 3



Scheme 4

Table 1 Deuterium incorporation and degree of isomerisation data (see Scheme 4)

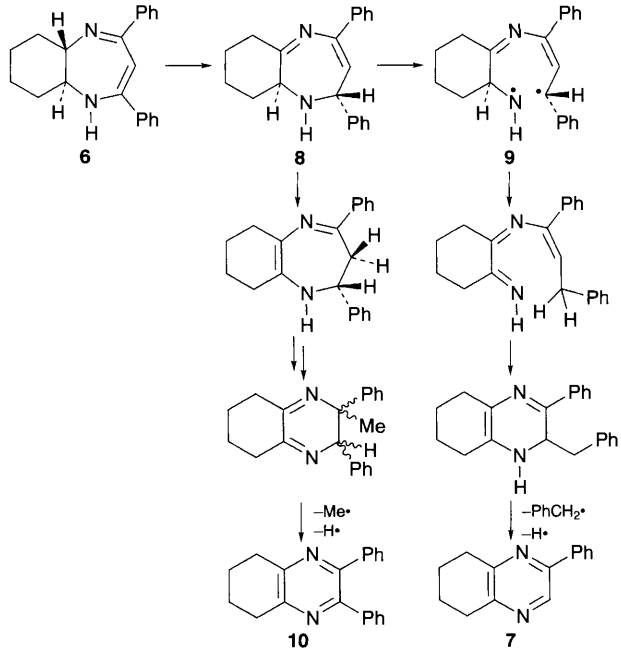
T/°C	Deuterium incorporation at the 3-position (^{2}H NMR)	Degree of isomerisation (*cis*:*trans* ratio) (^{13}C NMR)
450	5.0:1	5.3:1
500	1.15:1	1.17:1

dinium α-positions towards proton sources. The assignments of the ^{1}H (and hence ^{2}H) NMR spectrum on which the analysis was based were confirmed using NOE measurements on the protiated compound **4A** as shown in Fig. 1.

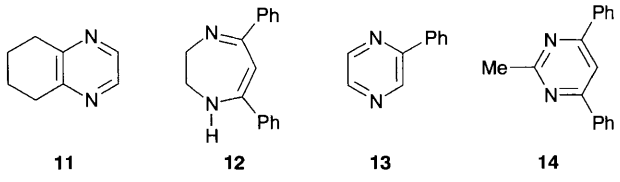
^{2}H NMR spectra obtained after FVP of the labelled precursor **4** are shown in Fig. 2. It is clear that there is label incorporation at position 3 (and not at position 2) concomitant with loss of label at position 7 (and not position 5), in agreement with the specific occurrence of 1,5-hydrogen shifts (Scheme 3) as the lowest energy thermal pathway available to this ring system.

The suprafacial nature of the sigmatropic shift was established by a further labelling experiment, shown in Scheme 4. Thus, if protium transfer across the top of the π-surface is followed by deuterium transfer across the bottom of the surface, the amount of deuterium incorporation at the 3-position should match exactly with the degree of isomerisation (as measured by the *cis*:*trans* ratio). The data shown in Table 1 confirm this relationship.

At higher temperatures, the reactions are dominated by radical processes which lead to ring contraction further controlled by cleavage of benzyl radicals. For example, pyrolysis of **6**[4] at 750 °C leads to 2-phenyl-5,6,7,8-tetrahydroquinoxaline **7** in 46% yield, and this can be rationalised by the mechanism shown in Scheme 5. Cleavage of the 2,7-dihydrodiazepine intermediate **8** gives the diradical **9** whose pentadienyl component is further stabilised by the terminal phenyl group. Consolidation, electrocyclisation and benzyl radical cleavage gives the product. A further 1,5-shift from the intermediate **8** followed by a similar pathway (though lacking a phenyl-stabilised pentadienyl) probably accounts for the formation of the diphenyl derivative **10** as a minor by-product (4%). This latter route provides the major product-forming pathway for the 6-phenyl compound **2** to give 5,6,7,8-tetrahydroquinoxaline **11** (50%); with this substitution pattern, a phenyl-stabilised pentadienyl is again a key intermediate.



Scheme 5



2,3-Unsubstituted analogues give similar products at high temperatures, but increased degrees of freedom in the 2- and 3-positions of the intermediates lead to more complex mixtures of products which will be considered in detail in a full paper. For example, 5,7-diphenyl-2,3-dihydro-1,4-diazepine **12**[5] gives 2-phenylpyrazine **13** (21%) together with 2-methyl-4,5-diphenylpyrimidine **14** (19%).

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Footnote

† New compounds were characterised by their spectra and by elemental analysis; diazepine bases were characterised as their perchlorate salts.

References

1 D. Lloyd and H. McNab, *Adv. Heterocycl. Chem.*, 1993, **56**, 1.
2 H. Quast, H.-M. Seidenpinner and J. Stawitz, *Liebigs Ann. Chem.*, 1983, 1230.
3 D. Lloyd, K. S. Tucker and D. R. Marshall, *J. Chem. Soc., Perkin Trans. 1*, 1981, 726.
4 D. Lloyd, H. McNab and D. R. Marshall, *Aust. J. Chem.*, 1977, **30**, 365.
5 A. M. Gorringe, D. Lloyd and D. R. Marshall, *J. Chem. Soc. (C)*, 1967, 2340.