Methyl Transfer by Endocyclic Nucleophilic Displacement

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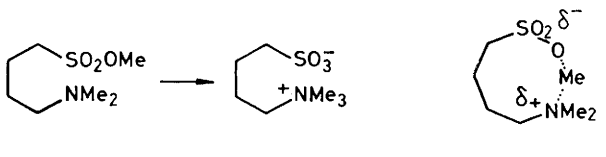
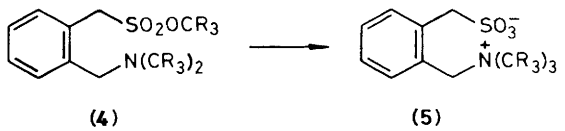
Conversion of the amino-ester (**6**) into the betaine (**7**) proceeds at low concentrations partly by way of an intramolecular methyl transfer, whereas the corresponding reaction of the lower homologue (**4**) is entirely intermolecular; the intramolecular reaction is the first proved example of methyl transfer by an endocyclic nucleophilic substitution.

We have recently shown[1] that conversion of (**1**) into (**2**) occurs *via* an intermolecular pathway and not by way of the endocyclic[2] reaction involving the eight-membered cyclic transition state (**3**). The lack of any sign of the endocyclic process even at low concentrations, may partly reflect the usual difficulty of forming medium rings with saturated carbon atoms.[3] With certain benzo-fused ring systems, however, the medium ring effect is virtually absent,[4] and so, in order to increase the likelihood of seeing the endocyclic process, we have looked at the reaction of the benzo-fused compounds (**4**) and (**6**). We now report our observations which show that the reaction of (**6**) provides the first clearly demonstrated example of endocyclic methyl transfer by nucleophilic displacement.

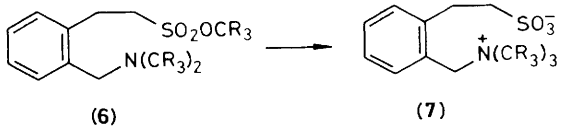
The amino-esters (**4**) and (**6**) were prepared from the



(1) (2) (3)



(4) (5)



(6) (7)

a; R = H

b; R = D

corresponding sultams *via* the cyclic sulphonylammonium salts, as described earlier[1] for (**1**). At relatively high concentrations (**4**) and (**6**) were converted quantitatively into the respective betaines (**5**) and (**7**); when followed by n.m.r. spectroscopy the reactions showed second-order behaviour to >80% reaction, with specific rates of 2.2×10^{-3} and 1.9×10^{-3} $dm^3 mol^{-1} s^{-1}$, respectively (in C_6D_6 at 110 °C). Cross-labelling experiments with an equimolar mixture of (**4a**) and (**4b**), even with initial concentrations as low as 5×10^{-4} M, showed a completely intermolecular pathway to (**5**). An equimolar mixture of (**6a**) and (**6b**), however, gave betaine (**7**) with a labelling pattern in accord with 16% of endocyclic reaction and 84% of the intermolecular process.† As expected the proportion of the intramolecular reaction decreased regularly with increase in the initial concentration; a consistent value for the effective concentration,‡ c_{eff}, of *ca.* 2×10^{-3} M was estimated from these results by computer simulation.

From the absence of any indication of intramolecular reaction from the lower homologue (**4**) we estimate that c_{eff} for the endocyclic reaction of (**4**) must be $<10^{-5}$ M, and since the bimolecular reactions of (**4**) and (**6**) have similar rates, endocyclic methyl transfer with (**4**) must therefore be >200 times slower than with (**6**). These c_{eff} values of 2×10^{-3} M and $<10^{-5}$ M for the endocyclic reactions of (**4**) and (**6**) are below the range of 0.3 to 0.05 M reported for exocyclic[2] processes leading to benzo-fused eight- to ten-membered rings,[5] suggesting that the endocyclic reactions of (**6**) and (**4**) are subject to greater steric strain than the exocyclic processes. We ascribe at least some of this extra strain to deviation from the ideal 180° orientation of nucleophile, methyl carbon, and nucleofuge in the nine- and (especially) eight-membered cyclic transition states.

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† In benzene at 110 °C for 7 h, c_0 5×10^{-3} M, 17% conversion of (**6**). More extensive reaction leads to complications arising from a subsequent reaction of (**7**).

‡ The effective concentration is defined as $c_{eff} = k_{intra}/k_{inter}$, where the rate constants refer to the intra- and inter-molecular reactions of the amino-ester.