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# HOFMANN ELIMINATION IN CYCLIC COMPOUNDS

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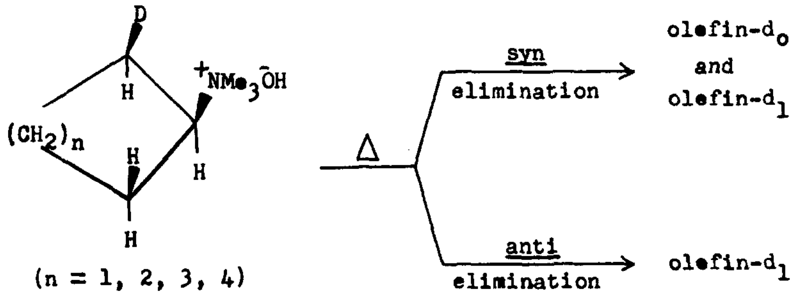
It has recently been suggested (1,2) that in Hofmann eliminations trans olefins are formed largely or possibly entirely by a syn mechanism and cis olefins are formed largely or possibly entirely by an anti mechanism. This conclusion was reached on the basis of comparative rate studies (1,2) and eliminations on two deuterium labeled substrates (3,4). An independent study on the cyclohexyl system (5) seems to substantiate this suggestion. We wish to report evidence which strongly indicates that the stereochemistry of Hofmann elimination in small and medium ring compounds (four through eight membered rings) is more complex than earlier workers have suggested.

The method used was to prepare the cis-2-$d_1$-cycloalkylamines by treatment of the corresponding cycloalkenes with diborane-$d_6$ followed by chloramine (6,7). The primary amines were converted to the corresponding trimethylammonium iodides by treatment with methyl iodide and base or by treatment with formaldehyde and formic acid followed by methyl iodide. Passage of the trimethylammonium iodides over Dowex 1-X8 basic resin and evaporation of the water (below 50°) gave the corresponding hydroxides which were subjected to Hofmann elimination. Eliminations were either carried out under normal conditions (called wet, 110°) with the olefins being purified by gas chromatography and analyzed by mass spectrometry or the hydroxides were decomposed directly into the mass spectrometer at $10^{-7}$ mm (called dry, 50°). The deuterium content of each olefin and its precursor was determined by mass spectrometry at 75 ev or at approximately 10 ev when M-1 fragmentation needed to be suppressed. All compounds had correct physical constants or were compared with authentic samples.



Since only one of the two *cis* positions in the cyclic amines was labeled with deuterium an isotope effect had to be known in order to interpret the results of deuterium analysis on the olefins. We have determined that the $\underline{syn}\ \frac{k_H}{k_D}$ for Hofmann elimination is 1.86 for the *exo*-norbornyl system (8), 1.71 for the 3,3-dimethylcyclopentyl system, (see adjacent communication) and 1.94 for the cyclooctyl system (see below). It was felt that the reasonable constancy of these *syn* isotope effects should allow the average value of 1.84 to be used as an approximation for all the ring systems in the present study. Because of the approximate nature of this isotope effect no attempt was made to include a temperature correction. Secondary isotope effects were assumed to be negligible.

Results of the eliminations and the calculated per cent *syn* mechanism for the parent non-deuterated amines (amine-$d_0$) are given in Table I. The results calculated for the amine-$d_0$ were obtained with the aid of the equation ($k_{\underline{syn}}$ and $k_{\underline{anti}}$ represent relative rate constants):

$$\frac{k_{\underline{syn}}}{\underline{syn}\ \frac{k_H}{k_D}} + k_{\underline{syn}} + 2k_{\underline{anti}} = 100$$

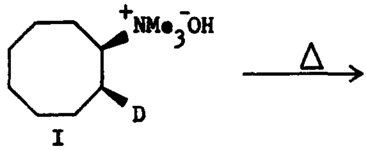
letting $$\frac{k_{\underline{syn}}}{\underline{syn}\ \frac{k_H}{k_D}} = \%\ \text{olefin-}d_0$$

TABLE I

| Ring Size | Conditions | %Olefin-$d_1$[a] | %Olefin-$d_0$[a] | Calc. % syn mechanism in amine-$d_0$[b] |
|---|---|---|---|---|
| four | dry, 50° | 69 | 31 | 90 |
| five | wet, 110° | 86 | 14 | 46 |
| six | wet, 110° | 99 | 1 | 4 |
| seven | dry, 50° | 89 | 11 | 37 |
| | wet, 110° | 91 | 9 | 31 |

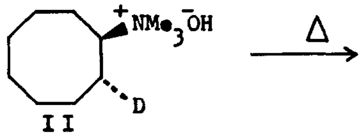
(a) These values are corrected for the isotopic purity of 97% for the original $d_1$-primary amines. (b) These values are calculated using a syn isotope effect of 1.84.

We have also examined the parent cyclooctyl system since this is the smallest size ring that gives rise to both cis and trans olefin on Hofmann elimination. Starting materials for this study were cis and trans-cyclooctene and these were converted to cis-2-$d_1$-cyclooctylamine and trans-2-$d_1$-cyclooctylamine respectively with diborane-$d_6$ and chloramine (6,7). There have been reports of diborane addition to medium size rings being a reversible reaction under normal hydroboration conditions. In these cases either an excess of diborane was used (9) or a very hindered olefin was used (10) and both of these conditions have been shown (11) to contribute to the reversibility of the addition step. In the present work a slight excess of olefin was used and the reaction temperature was kept low (0° with a short time at 25°). In view of earlier work (9,10) these conditions should be sufficient to inhibit any reversal of the addition step. In support of this our final results are incompatible with reversal being serious under the conditions used. The deuterium labeled cyclooctylamines were converted to the corresponding quaternary hydroxides as outlined earlier and pyrolysis of these at 95° and 20 mm gave mixtures of cis and trans-cyclooctene which were separated by gas chromatography. The purified olefins were analyzed by mass spectrometry at 75 ev for deuterium and the results are shown below (deuterium analyses are corrected for 97% isotopic purity of the starting amines).



I

34% <u>cis</u>-cyclooctene (85% $d_1$ ; 15% $d_o$)
and
66% <u>trans</u>-cyclooctene (100% $d_1$ ; 0% $d_o$)



II

38% <u>cis</u>-cyclooctene (89% $d_1$ ; 11% $d_o$)
and
62% <u>trans</u>-cyclooctene (66% $d_1$ ; 34% $d_o$)

From the results on compound I it can be seen that the <u>trans</u>-cyclooctene (total retention of deuterium) must be formed by an exclusively <u>syn</u> elimination, in agreement with earlier predictions (4). However, the <u>cis</u>-cyclooctene from I shows considerable loss of deuterium and this indicates it is formed by a substantial amount of <u>syn</u> elimination. This is contrary to earlier predictions (4). In order to use the data on the <u>cis</u>-cyclooctene from I to calculate how much <u>syn</u> mechanism would operate in production of <u>cis</u>-cyclooctene from the parent non-deuterated cyclooctyl derivative one must know an isotope effect for a <u>syn</u> Hofmann elimination giving <u>cis</u>-cyclooctene from I. If one makes the reasonable assumption that this can be approximated by the isotope effect for <u>syn</u> Hofmann elimination to give <u>trans</u>-cyclooctene then this data can be calculated from the results shown for compound II. The <u>trans</u>-cyclooctene formed from II must be formed exclusively by a <u>syn</u> mechanism in which there is a direct competition between loss of hydrogen on one side and loss of deuterium on the other. The <u>syn</u> $\frac{k_H}{k_D}$ can be calculated directly from the deuterium content of the <u>trans</u>-cyclooctene from II and the result is <u>syn</u> $\frac{k_H}{k_D} = 1.94$. Using this isotope effect as an approximation for the <u>syn</u> elimination of deuterium from I to form <u>cis</u>-cyclooctene one can calculate that the parent non-deuterated N,N,N-trimethylcyclooctylammonium hydroxide would form <u>cis</u>-cyclooctene by 51% <u>syn</u> elimination and 49% <u>anti</u> elimination.

From the above deductions and the deuterium content of <u>cis</u>-cyclooctene from compound II one can also calculate that for formation of <u>cis</u>-cyclooctene by Hofmann elimination there is an <u>anti</u> $\frac{k_H}{k_D} = 2.64$. In all this work we assume a negligible secondary isotope effect when hydrogen is lost from a carbon atom carrying deuterium.

In the simple cyclic compounds in this and related studies we have observed no evidence of exchange on the carbon undergoing proton loss during elimination. Also no evidence has appeared that isomerization of the nitrogen-bearing carbon is of any importance. We therefore conclude that these cyclic compounds undergo elimination by a true E2 mechanism with varying amounts of syn and anti elimination, depending on ring size.

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