Elimination Reactions. III. Hofmann Elimination in Cyclic Compounds[1a]

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Abstract: The amount of *syn* and *anti* mechanism in Hofmann elimination of unsubstituted monocyclic trimethylammonium hydroxides has been determined. The systems studied and the per cent *syn* elimination found were the four- (90% *syn*), five- (46% *syn*), six- (4% *syn*), and seven- (31–37% *syn*) membered rings. Hofmann elimination on N,N,N-trimethyl-3,3-dimethylcyclopentylammonium hydroxide has been found to give both 4,4-dimethylcyclopentene and 3,3-dimethylcyclopentene. The 4,4-dimethylcyclopentene is formed by a 76% *syn* and 24% *anti* elimination and a *syn* $k_H/k_D = 1.71$ has been found for this *syn* elimination. The reasons for these results are discussed.

It has long been assumed that Hofmann elimination of quaternary ammonium hydroxides shows a preferred *anti*-elimination[2] mechanism.[3] This generalization appears to have been deduced from a few well-investigated models. For example it has been observed that the *erythro* and *threo* isomers of 1,2-diphenylpropylamines when subjected to quaternization and Hofmann elimination with ethoxide give olefins that are compatible only with an *anti*-elimination mechanism.[4] The menthyl- and neomenthylamines have been used as substrates for studies supporting an *anti* mechanism.[5] A recent report[6] gives evidence on some aspects of the elimination mechanism on the menthyl compound but still rigorous proof of whether the mechanism is *syn* or *anti* is lacking. In the case of 2-methylcyclohexylammonium salts[7] it has been found that the *cis* isomer gives an *anti* elimination to yield very predominately 1-methylcyclohexene. It was found that the *trans* isomer under strongly basic conditions gave very predominately 3-methylcyclohexene by an unspecified mechanism. Both isomers of 2-phenylcyclohexylammonium salts undergo elimination to give 1-phenylcyclohexene.[8] The *trans* isomer must react by a *syn* mechanism while the *cis* isomer must react by an *anti* mechanism. It is interesting to note that the *anti* elimination is 133 times as fast as the *syn* elimination.[8c]

It is apparent that one of the major difficulties encountered in attempting to fit the above examples into a comprehensive theory is lack of knowledge concerning the parent unsubstituted systems. The complications introduced by using even as simple a substituent as a methyl group to determine the stereochemistry of elimination can be illustrated by citing the fact that *anti* elimination to the *trans* *t*-hydrogen in N,N,N-trimethyl-2-*cis*-methylcyclohexylammonium hydroxide is at least 19 times as fast as elimination to any other position.[7] Only one report has appeared on the stereochemistry of Hofmann elimination of an unsubstituted monocyclic ammonium hydroxide. This is the report by Finley and Saunders[9] that N,N,N-trimethyl-*cis*-cyclohexylammonium-2-d_1 hydroxide undergoes Hofmann elimination with retention of deuterium indicating an *anti* mechanism. As will be pointed out in the present work the cyclohexyl system is not a good model for any other ring system in a Hofmann elimination.

In view of an increasing number of reports of authentic *syn* Hofmann elimination mechanisms,[8,10] it seemed imperative to examine the stereochemistry of this reaction in unsubstituted monocyclic ammonium hydroxides. The mechanism followed by these parent compounds could then serve as a foundation to understanding more complex systems. A study involving the four-, five-, six- and seven-membered rings (Chart I, $n = 1, 2, 3, 4$) has been completed and the results shed considerable light on earlier work.

The general procedure followed was to react the cyclic olefins with diborane-d_6 and then with chloramine to give the 2-*cis*-d_1 cyclic primary amines.[10a,11] The

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[2] In discussing the mechanism of eliminations we will henceforth use the terminology [C. Ingold, *Proc. Chem. Soc.*, 265 (1962)] which defines the *syn* mechanism as that which depicts both departing groups in a conformationally *syn* arrangement and the *anti* mechanism as that which depicts both departing groups in a conformationally *anti* arrangement [W. Klyne and V. Prelog, *Experientia*, 16, 521 (1960)].

[3] (a) D. V. Banthrope, "Studies on Chemical Structure and Reactivity," J. H. Ridd, Ed., Methuen and Co., London, 1966, p 33; (b) W. H. Saunders, Jr., "The Chemistry of Alkenes," S. Patai, Ed., Interscience Publishers, Inc., New York, N. Y., 1964, p 149; (c) J. F. Bunnett, *Angew. Chem. Intern. Ed. Engl.*, 1, 225 (1962); (d) A. C. Cope and E. R. Trumbull, *Org. Reactions*, 11, 317 (1959); (e) D. J. Cram, "Steric Effects in Organic Chemistry," M. S. Newman, Ed., John Wiley and Sons, Inc., New York, N. Y., 1956, p 304.

[4] D. J. Cram, F. D. Greene, and C. H. DePuy, *J. Amer. Chem Soc.*, 78, 790 (1956).

[5] A. C. Cope and E. M. Acton, *ibid.*, 80, 355 (1958); N. L. McNiven and J. Read, *J. Chem. Soc.*, 153 (1952).

[6] M. A. Baldwin, D. V. Banthrope, A. G. Loudon, and F. D. Waller, *ibid.*, *B*, 509 (1967).

[7] T. H. Brownlee and W. H. Saunders, Jr., *Proc. Chem. Soc.*, 314 (1961).

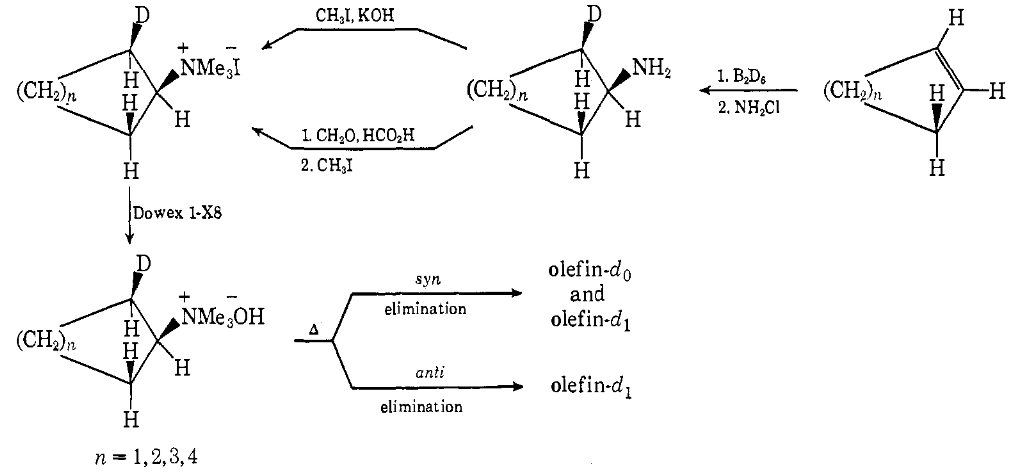
[8] (a) G. Ayrey, E. Buncel, and A. N. Bourns, *ibid.*, 458 (1961); (b) A. C. Cope, G. A. Berchtold, and D. L. Ross, *J. Amer. Chem. Soc.*, 83, 3859 (1961); (c) S. J. Cristol and F. R. Stermitz, *ibid.*, 82, 4692 (1960); (d) J. Weinstock and F. G. Bordwell, *ibid.*, 77, 6706 (1955); (e) R. T. Arnold and P. N. Richardson, *ibid.*, 76, 3649 (1954).

[9] K. T. Finley and W. H. Saunders, Jr., *ibid.*, 89, 898 (1967).

[10] (a) J. L. Coke and M. P. Cooke, Jr., *ibid.*, 89, 2779 (1967); (b) J. L. Coke and M. P. Cooke, Jr., *ibid.*, 89, 6701 (1967); (c) M. Pankova, J. Sicher, and J. Zavada, *Chem. Commun.*, 394 (1967); (d) J. Zavada, M. Svoboda, and J. Sicher, *Tetrahedron Lett.*, 1627 (1966); (e) C. W. Bird, R. C. Cookson, J. Hudec, and R. O. Williams, *J. Chem. Soc.*, 410 (1963); (f) A. C. Cope and A. S. Mehta, *J. Amer. Chem. Soc.*, 85, 1949 (1963).

[11] (a) H. C. Brown, W. R. Heydkamp, E. Breuer, and W. S. Murphy, *ibid.*, 86, 3565 (1964); (b) H. C. Brown, "Hydroboration," W. A. Benjamin, Inc., New York, N. Y., 1962, p 130; (c) see also L. Verbit and P. J. Heffron, *J. Org. Chem.*, 32, 3199 (1967), and M. W. Rathke, N. Inoue, K. R. Varma, and H. C. Brown, *J. Amer. Chem. Soc.*, 88, 2870 (1966).

Chart I



primary amines were then converted directly to the trimethylammonium iodides using an excess of methyl iodide and base[12] or were converted first to the dimethyl derivatives under Eschweiler–Clark conditions[13] and these were then allowed to react with methyl iodide. The quaternary ammonium iodides were passed over a column of Dowex 1-X8 resin in basic form and the water was removed under vacuum taking care to keep the temperature below 50°. The quaternary ammonium hydroxides were either decomposed in the normal fashion[3d] under slight vacuum at temperatures above 100° (wet conditions) and the olefins purified by vpc prior to mass spectral analysis or else the quaternary hydroxides were dried at 10^{-7} mm and decomposed directly into the mass spectrometer at about 50° (dry conditions). Mass spectral analyses of the olefins for deuterium were carried out at low voltage to suppress $M - 1$ fragmentation. The results are shown in Table I.

Table I. Hofmann Eliminations on 2-*cis*-d_1 Cyclic Amines

Ring size	Conditions	Olefin-d_1,[a] %	Olefin-d_0,[a] %	Calcd % *syn* mechanism in amine-d_0[b]
Four	Dry, 50°	69	31	90 ± 2
Five	Wet, 110°	86	14	46 ± 2
Six	Wet, 110°	99	1	4 ± 1
Seven	Dry, 50°	89	11	37 ± 1
	Wet, 110°	91	9	31 ± 1

[a] These values are corrected for the isotopic purity of 97% for the original d_1, primary amines. [b] These are calculated using *syn* $k_H/k_D = 1.84 \pm 0.08$. The ± per cent mechanism shown in the table is calculated assuming the average deviation in isotope effect is the only error (see Experimental Section). Because of the error in isotopic analysis of the olefins a ±5% error in the per cent *syn* mechanism is probably more reasonable.

In order to interpret the data from the mass spectral analyses of the olefins from elimination in terms of a *syn* or *anti* mechanistic scheme, an isotope effect must be taken into account. It is not feasible to determine an isotope effect directly for compounds of the type shown in Chart I since only one *cis* position is substituted with deuterium. A model isotope effect was used which was an average of the isotope effect found for the *syn* Hofmann elimination in three model systems. One of these is the 2-*exo*-bicyclo[2.2.1]heptyl system which has been shown[10b] to have a *syn* $k_H/k_D = 1.86$. Another is the 3,3-dimethylcyclopentyl system which has (see below) a *syn* $k_H/k_D = 1.71$. The third is the reaction of the cyclooctyl system to give *trans*-cyclooctene and this reaction shows[14] a *syn* $k_H/k_D = 1.94$. The average of these three isotope effects is a *syn* $k_H/k_D = 1.84 \pm 0.08$ (where 0.08 is the average deviation) and this was used to calculate the per cent *syn* and *anti* mechanism that would occur in the parent nondeuterated cyclic amines (amine-d_0). Representing the amount of total elimination that takes place at each of the four β bonds, in the d_1 compounds of the type shown, by the equation $k_{syn}/syn\ (k_H/k_D) + k_{syn} + 2k_{anti} = 100$ and letting $k_{syn}/syn\ (k_H/k_D) = \%$ olefin-d_0 that results on Hofmann elimination (k_{syn} and k_{anti} represent relative rate constants), the per cent *syn* mechanism expected for the amine-d_0 was calculated and the values are shown in Table I. Also shown are the errors caused by the average deviation in the model isotope effect. Since the results shown in Table I for the mechanism in the amine-d_0 cases are based on an approximate isotope effect, no attempt was made to apply a temperature correction or a correction for different experimental conditions. The error is probably not serious, however. It is also assumed that secondary isotope effects for removal of hydrogen from a carbon bearing a deuterium are negligible. The method of deuterium analysis is described in the Experimental Section.

In an effort to obtain another *syn* k_H/k_D Hofmann isotope effect and also to test rigorously the conclusions reached in the preceding unsubstituted monocyclic trimethylammonium compounds, it was desired to study a ring system in which elimination to opposite sides of the trimethylammonium group would produce olefins which are position isomers. The systems chosen for study were N,N,N-trimethyl-3,3-dimethylcyclopentylammonium hydroxide (I) and the corresponding *cis*-5-d_1 isomer (IV) (see Chart II). These were chosen for several reasons. Both olefins (II and III) needed for comparison with products of elimination are easily synthesized.[15] Olefin II was especially useful for the

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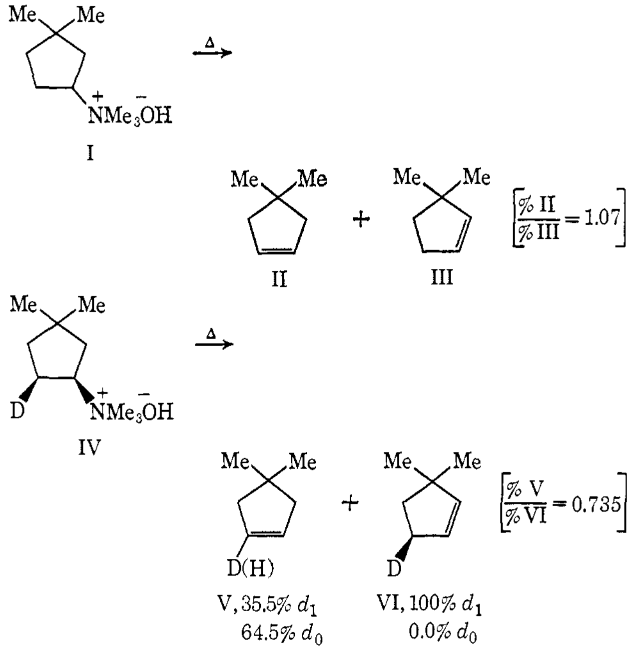
(12) R. Willstatter, *Ann.*, **317**, 204 (1901).

(13) R. N. Icke and B. B. Wisegarver, "Organic Syntheses," Coll. Vol. III, E. C. Horning, Ed., John Wiley and Sons, Inc., New York, N. Y., 1955, p 723.

(14) J. L. Coke and M. C. Mourning, *J. Amer. Chem. Soc.*, **90**, 5561 (1968).

(15) H. Kwart and J. A. Ford, Jr., *J. Org. Chem.*, **24**, 2060 (1959).

Chart II



$$syn\ \frac{k_H}{k_D} = \left[\frac{\left(\frac{\% II}{\% III}\right) + \left(\frac{\% V\text{-}d_1}{\% V\text{-}d_0}\right)\left(\frac{\% II}{\% III}\right)}{\left(\frac{\% V}{\% VI}\right)}\right] - \left(\frac{\% V\text{-}d_1}{\% V\text{-}d_0}\right) = 1.71$$

synthesis of compounds I and IV since it gives only one isomer on reaction with diborane or diborane-d_6. Reaction of olefin II with diborane and chloramine or diborane-d_6 and chloramine gave the primary amines corresponding to compounds I and IV, respectively.[10a,11] Complete methylation of these primary amines with methyl iodide and base[12] gave the corresponding quaternary iodides which were converted to hydroxides I and IV by passage over Dowex 1-X8 basic resin and removal of water below 50°.

Compound I was subjected to normal Hofmann elimination and the ratio of olefin II to olefin III was found to be 1.07 by gas chromatography. When compound IV was subjected to normal Hofmann elimination the ratio of olefin V to olefin VI was found to be 0.735. In addition, V and VI were separated by gas chromatography and analyzed by mass spectrometry. Olefin VI was found to be 100% olefin-d_1 after correction for isotopic purity of the starting material. This indicates that an E1cb mechanism with rapid reversion to starting material is not operating. Olefin V was found to be 64.5% olefin-d_0 and 35.5% olefin-d_1 after proper correction for isotopic purity of the starting material. This means that olefin V is actually formed by 64.5% *syn* elimination by loss of deuterium.

In order to extrapolate these results back to formation of olefin II from I, a *syn* k_H/k_D must be known and this can be calculated using the equation shown in Chart II. This equation can be derived with the aid of all the information outlined in Chart II. The *syn* k_H/k_D was calculated to be 1.71. Using this value one can calculate that hydroxide I gives olefin II by a 76% *syn* elimination and only 24% *anti* elimination. It is felt that the isotope effect found in this case should be a valid approximation for a *syn* elimination in an unsubstituted cyclopentylammonium hydroxide. This is because the transition state for *syn* elimination in the five-membered ring should not be disturbed much by the *gem*-dimethyl substituents. This conclusion is supported by the similarity between the isotope effect found in the present case for *syn* elimination and that found for *syn* elimination in two other cases.[10b,14] Secondary isotope effect in removal of hydrogen from a carbon bearing a deuterium are assumed to be negligible.

The mechanism of formation of olefin II from hydroxide I illustrates very dramatically a mistake commonly made by some earlier workers. It has apparently often been assumed that substitution of alkyl substituents about the reaction site in Hofmann eliminations does not materially affect the reaction mechanism. This is not a valid assumption. Hydroxide I gives olefin II by a 76% *syn* mechanism while the parent unsubstituted cyclopentylammonium hydroxide forms cyclopentene by a 46% *syn* mechanism. If it were to be assumed that the rate of *syn* elimination in compound I were the same as for the unsubstituted cyclopentyl system then the net effect of the *gem*-dimethyl substituents would be to decrease the rate of *anti* elimination by a factor of 3.7. This is presumed to be a steric factor and is readily understood in terms of conformational principles. In order to achieve a reasonably coplanar *anti*-elimination transition state in compound I to get olefin II, one must introduce very severe van der Waals interaction between the trimethylammonium group and one of the methyl groups on the five-membered ring. Thus the *anti* elimination in compound I is materially retarded relative to the parent unsubstituted five-membered ring. This work illustrates the need for understanding the mechanism of Hofmann elimination in simple parent systems before attempting to study and explain the mechanism in more highly substituted compounds. It also provides a good example of a steric effect in Hofmann eliminations.[16]

In all of the present cases we assume the elimination proceeds by a normal E2 mechanism. This is based in part on the fact that an ylide mechanism is not a common mode of reaction even in completely *syn* eliminations.[10a,b] An E1 mechanism is unlikely under the conditions used in this work. An E1cb mechanism with rapid reversion to starting material would be difficult to reconcile with the results from the cyclohexyl case and impossible to reconcile with the 3,3-dimethylcyclopentyl case. An E1cb mechanism without reversion to starting material is rejected on the basis that this mechanism is kinetically equivalent to an E2 mechanism and appears to be simply an unnecessary complication for which no experimental support has been found in simple compounds of the type used in this study. In support of this an E1cb mechanism with no reversion to starting material is incompatible with the observed all *anti* elimination for the cyclohexyl system and the all *syn* elimination in the bicyclo[2.2.2]-octyl system found earlier.[10b] The most likely mode of elimination for the compounds in the present study is therefore a normal E2 mechanism with concerted but not synchronous breakage of bonds.

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(16) H. C. Brown and I. Moritani, *J. Amer. Chem. Soc.*, 78, 2203 (1956).

The stereochemistry of elimination *vs.* ring size is rather interesting. The cyclohexyl system gives essentially all *anti* elimination, within experimental error, while the cyclobutyl system gives nearly all *syn* elimination. Molecular models indicate that severe torsional strain would be required to go from the ground state to the transition state for *anti* elimination in the cyclobutyl ring system. Severe eclipsing strain would be required to go from the ground state to the transition state for *syn* elimination in the cyclohexyl ring system. Models indicate that for the cyclopentyl and cycloheptyl rings there is little difference in conformational energy required to achieve the transition state for either *syn* or *anti* elimination and this is borne out by the nearly equal amounts of each mechanism in these two rings.

The present results indicate that one cannot make a complete generalization or prediction about the mechanism of *cis*-olefin formation in small ring compounds and that each case must be investigated separately. It should be noted that the conditions used in the present work are similar to those used in preparative Hofmann eliminations and that extrapolation of these results to other conditions especially reactions in solution, should be done with caution.

The present results also give a clue as to why so many of the previously investigated examples of Hofmann elimination indicate such preference for an *anti* mechanism. One good example is the *erythro* and *threo* isomers of 1,2-diphenylpropylamines.[4] In compounds like this where large groups have been placed about the elimination sites such that the stereochemistry of the olefin will identify the stereochemistry of elimination one has caused the *syn*-elimination transition state to be of very high energy due to eclipsing strain while affecting the *anti*-elimination transition state to a lesser extent. It is apparently this difference in the difficulty of achieving the two transition states which is fairly delicately balanced and slight steric effects can determine whether the mechanism will be *syn* or *anti.* This balance between the two types of mechanisms may well be caused by the very high degree of carbanion character of the transition states as indicated by the low k_H/k_D isotope effects observed for Hofmann eliminations in this work (assuming greater than half-way transfer of the proton to the base in the transition state)[17] and as a consequence of this it would be hazardous to extrapolate the present results and conclusions to elimination reactions of other types where the carbanion character of the transition state may be less. It is also clear from the present results and especially those from compounds I and IV that steric effects must be taken into account in any over-all theory concerning the mechanism of Hofmann eliminations. This work shows that eclipsing effects and van der Waals interaction with the bulky trimethylammonium group can have an effect on the mechanism.[16] The exact effect and magnitude remain to be elucidated.

Experimental Section[18]

All mass spectral analyses were performed on a Hitachi Perkin-Elmer RMU-6E mass spectrometer at the voltages stated. The deuterium analyses were performed according to the procedure of Biemann.[19] In all cases the M − 1 peak intensity was relatively small, in some cases being entirely negligible but in others amounting to a significant intensity. In all cases the % d_0 and % d_1 olefins were calculated by correcting the apparent intensity of the parent peak of the d_1 olefin for any M + 1 contribution by d_0 olefin and then correcting the parent peak of the d_0 olefin for any M − 1 contribution by the d_1 olefin. The intensity of M − 1 and M + 1 peaks were found from d_0 olefin standards run under the same conditions as the final analysis and it was assumed that these relative intensities would be the same for d_0 and d_1 olefin. The results on several samples, notably the cyclohexene and 3,3-dimethylcyclopentene, support the validity of this assumption and indicate that no serious error is introduced by preferential loss of deuterium or hydrogen from the olefins analyzed. The corrected intensities of the parent ion peaks for d_0 and d_1 olefins were then used to calculate the per cent of each olefin in each product. Precursors of all Hofmann elimination products were analyzed for isotopic purity by mass spectrometry and were all found to be 97% d_1 and 3% d_0. An appropriate correction for this 3% d_0 isotopic impurity was made in the olefins from Hofmann elimination. The % d_1 and % d_0 olefins are probably not accurate to greater than ±1%. A ±1% error makes approximately a ±3% error in calculated % *syn* mechanism. We therefore feel that a reasonable error in calculated % *syn* mechanism is in the order of ±5%. Gas chromatographic comparisons of olefins and collection of olefin samples[19] were carried out on an F & M Model 500 gas chromatograph on a 2-ft silicone rubber column unless otherwise stated. All olefin products and precursors were compared with authentic samples.

2-*cis*-Cyclobutylamine-d_1. To a solution of 1.5 g (0.028 mol) of cyclobutene (prepared by the method of Roberts and Sauer[20]) in 30 ml of dry tetrahydrofuran at 0° was added a solution of diborane-d_6 in dry tetrahydrofuran prepared by the direct method of Brown[21] from 0.95 g (0.023 mol) of sodium borodeuteride and the solution was stirred for 1 hr at 25°. There was added successively 52 ml of 3 *N* sodium hydroxide and 134 ml of chloramine solution.[22] The mixture was stirred for 1 hr and was then worked up in the usual way[11a] to give a solution of 2-*cis*-cyclobutylamine-d_1 in ether which was concentrated on a steam bath. Because of the small quantity of product no attempt was made to further purify the product; however, a small amount was converted to the benzenesulfonamide derivative, mp 83.5–85° (lit.[23] mp 85–86°). A mixture melting point with an authentic sample was undepressed. Mass spectral analysis of the 2-*cis*-cyclobutylbenzenesulfonamide-d_1 at 75 eV indicated 97% d_1 species.

N,N,N-Trimethyl-2-*cis*-cyclobutylammonium-d_1 Iodide. The crude amine from the preceding experiment was converted directly to the methiodide by the method of Willstatter.[12] The product was extracted from the crude salts in a Soxhlet extractor with chloroform for 12 hr. The chloroform was evaporated and the residue was crystallized from a mixture of ethanol and ether to yield pure N,N,N-trimethyl-2-*cis*-cyclobutylammonium-d_1 iodide, mp 271–274° dec (lit.[24] mp 256–257°); however, an authentic sample prepared in our laboratories showed mp 273–275° dec.

2-*cis*-Cyclopentylamine-d_1. A solution of 20.4 g (0.30 mol) of cyclopentene in dry tetrahydrofuran was treated with diborane-d_6 generated from 2.2 g (0.0525 mol) of sodium borodeuteride by the external generation method of Brown and Tierney.[25] The reaction mixture was stirred for 1 hr at 25° and was then treated successively with 120 ml of 3 *N* sodium hydroxide and 310 ml of chloramine solution[22] and was then worked up in the usual way[11a] to yield 6.8 g (38%) of 2-*cis*-cyclopentylamine-d_1: bp 107–108°; $n^{20}\text{D}$ 1.4459 (lit.[26] bp 108°). Mass spectral analysis on the primary amine at 75 eV indicated 97% d_1 species.

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[17] F. H. Westheimer, *Chem. Rev.*, 61, 265 (1961).

[18] No distinction will be made in physical constants for deuterated and nondeuterated compounds.

[19] K. Biemann, "Mass Spectrometry, Organic Chemical Applications," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, Chapter 5.

[20] J. D. Roberts and C. W. Sauer, *J. Amer. Chem. Soc.*, **71**, 3925 (1949).

[21] See ref 11b, p 98.

[22] F. Raschig, *Ber.*, 40, 4580 (1907). The solution was prepared at 0° by mixing 210 ml of 5.25% sodium hypochlorite (commercial Clorox) and 20 ml of 29% ammonium hydroxide diluted to 100 ml with water.

[23] D. C. Iffland, G. X. Criner, M. Koral, F. J. Lotspeich, Z. B. Papanastassiou, and S. M. White, Jr., *J. Amer. Chem. Soc.*, **75**, 4044 (1953).

[24] R. Willstatter and W. von Schmaedel, *Ber.*, **38**, 1992 (1905).

[25] H. C. Brown and P. A. Tierney, *J. Amer. Chem. Soc.*, **80**, 1552 (1958).

[26] J. D. Roberts and V. C. Chambers, *ibid.*, **73**, 5030 (1951).

N,N-Dimethyl-2-*cis*-cyclopentylamine-d_1. The general procedure of Icke, *et al.*,[13] was used to convert 6.4 g (0.075 mol) of the primary amine from the preceding experiment to 4.1 g (48%) of N,N-dimethyl-2-*cis*-cyclopentylamine-d_1: bp 135–137°; n^{20}D 1.4400 (lit.[26] bp 65° (84 mm); n^{25}D 1.4379).

N,N,N-Trimethyl-2-*cis*-cyclopentylammonium-d_1 Iodide. A solution of 3.45 g (0.03 mol) of *t*-amine from the preceding experiment and 14.2 g (0.10 mol) of methyl iodide in 50 ml of ether was allowed to stand overnight. The resulting solid was collected by filtration and recrystallized from ethanol to yield 7.4 g (96%) of N,N,N-trimethyl-2-*cis*-cyclopentylammonium-d_1 iodide, mp 269–271° dec (lit.[27] mp 260°).

2-*cis*-Cyclohexylamine-d_1. In a manner identical with that used in the cyclopentyl case above, 16.4 g (0.20 mol) of cyclohexene and 1.47 g (0.035 mol) of sodium borodeuteride were converted to 3.5 g (16%) of 2-*cis*-cyclohexylamine-d_1, bp 136–138° (lit.[26] bp 133.7°).

N,N-Dimethyl-2-*cis*-cyclohexylamine-d_1. Using the procedure of Icke, *et al.*,[13] 3.3 g (0.033 mol) of the primary amine from the preceding experiment was converted to 2.5 g (58%) of N,N-dimethyl-2-*cis*-cyclohexylamine-d_1: bp 76–77° (45 mm); n^{23}D 1.4518 (lit.[26] bp 75° (47 mm); n^{25}D 1.4517). Mass spectral analysis of the pure product at 75 eV indicated 97% d_1 species.

N,N,N-Trimethyl-2-*cis*-cyclohexylammonium-d_1 Iodide. A solution of 2.4 g (0.018 mol) of *t*-amine from the preceding experiment and 9 g (0.064 mol) of methyl iodide in 30 ml of ether was allowed to stand overnight. The resulting solid was collected by filtration and recrystallized from ethanol to yield 4.75 g (97%) of N,N,N-trimethyl-2-*cis*-cyclohexylammonium-d_1 iodide, mp 277–279° dec (lit.[28] mp 274–278°).

2-*cis*-Cycloheptylamine-d_1. A solution of 5.4 g of boron trifluoride ethereate in dry tetrahydrofuran was added to a stirred mixture of 9.6 g (0.10 mol) of cycloheptene and 1.18 g (0.028 mol) of sodium borodeuteride in tetrahydrofuran by the direct generation method of Brown.[21] The reaction mixture was stirred for 2 hr and was then treated successively with 65 ml of 3 *N* sodium hydroxide and 166 ml of chloramine solution.[22] The mixture was stirred for 1 hr and worked up in the usual manner[11a] to yield 4.3 g (38%) of 2-*cis*-cycloheptylamine-d_1, bp 93–97° (72 mm) (lit.[29] bp 60°, 18 mm). Mass spectral analysis of the pure primary amine at 75 eV indicated 97% d_1 species.

N,N,N-Trimethyl-2-*cis*-cycloheptylammonium-d_1 Iodide. The method of Willstatter[12] was used to convert 4.1 g (0.036 mol) of primary amine from the preceding experiment to the crude product which was extracted with chloroform in a Soxhlet extractor for 12 hr. The chloroform was evaporated and the product was crystallized from a mixture of ethanol and ether to yield 9.4 g (92%) of N,N,N-trimethyl-2-*cis*-cycloheptylammonium-d_1 iodide, mp 259° dec (lit.[12] mp 259°).

Preparation of 2-*cis*-d_1 Cyclic Quaternary Hydroxides. The quaternary hydroxides were prepared by passage of an aqueous solution of the corresponding quaternary iodide from the above preparations over a fourfold excess of Dowex 1-X8 ion-exchange resin in the basic form followed by evaporation of the water under vacuum at 45–50°. The resulting hydroxides were used directly.

Hofmann Elimination of Compounds Shown in Chart I and Olefin Analysis. Method A. In this procedure a quaternary hydroxide from the above preparations was placed in a flask attached directly to the mass spectrometer and dried at 10^{-7} mm for 0.5 hr and was then heated at 50° directly in the suboven of the mass spectrometer to carry out the Hofmann elimination. The olefin was analyzed for deuterium directly. The cyclobutene was analyzed at 10 eV and the cycloheptene was analyzed at 17 eV. These conditions are called dry, 50° and the results are shown in Table I.

Method B. In this procedure a quaternary hydroxide from the above preparations was pyrolyzed at oil bath temperatures of 120–140° and approximately 60 mm pressure with the volatile products being collected in a Dry Ice trap. The olefins were washed with dilute hydrochloric acid followed by water and were then purified by gas chromatography. Retention times of olefins were shown at be identical with those of authentic samples. The pure olefins were analyzed for deuterium by mass spectrometry at 8 eV for cyclopentene, 10 eV for cyclohexene, and 17 eV for cycloheptene. These conditions are called wet, 110° and the results are shown in Table I. The temperature reported is the estimated temperature inside the reaction flask.

Cyclobutene produced by Hofmann elimination has been reported to sometimes be contaminated with 1,3-butadiene.[24] In the preparation of cyclobutene for synthesis in the present work using Dowex 1-X8 resin and preparative pyrolysis conditions the cyclobutane was shown to be free of 1,3-butadiene by infrared spectroscopy.[20] These conditions are fairly similar to those used for Hofmann elimination on the deuterated cyclobutyl derivative.

The trimethylamine from pyrolysis of N,N,N-trimethyl-2-*cis*-cyclopentylammonium-d_1 hydroxide was analyzed by mass spectrometry and was found to contain no detectable amount of deuterium during the initial stages of reaction. The trimethylamine from total reaction was found to contain approximately 96% trimethylamine-d_0 and 4% trimethylamine-d_1. This is the expected result.[10a,b]

4,4-Dimethylcyclopentene (II). The 4,4-dimethylcyclopentene (II) used in this work was prepared by a slight modification of the procedure of Kwart and Ford[15] and had the following physical constants: bp 77–78°; n^{22}D 1.4169 (lit.[15] bp 74–75°; n^{22}D 1.4160).

3,3-Dimethylcyclopentene (III). The 3,3-dimethylcyclopentene (III) used in this work was prepared by the procedure of Kwart and Ford[15] and had the following physical constants: bp 79–81°; n^{25}D 1.4178 (lit.[15] bp 78–80°; n^{25}D 1.4151).

N,N,N-Trimethyl-3,3-dimethylcyclopentylammonium Iodide. A solution of 3.2 g (0.033 mol) of 4,4-dimethylcyclopentene in tetrahydrofuran was treated with 12.7 ml (0.0127 mol of BH_3) of commercial diborane solution (1.0 *M* in BH_3, Ventron Corp.) and stirred for 1 hr. The resulting solution was treated successively with 22 ml of 3 *N* sodium hydroxide and 56 ml of chloramine solution.[11a,22] The mixture was stirred for 1 hr at 25° and was then acidified with concentrated hydrochloric acid and extracted with ether, the ether extracts being discarded. The aqueous phase was made strongly basic and extracted with ether. The ether solutions were combined, dried and evaporated to yield crude 3,3-dimethylcyclopentylamine which was not further purified due to the small amount and to the fact that it reacted rapidly with carbon dioxide in the air. The primary amine was converted directly to the methiodide by the method of Willstatter[12] in methanol using methyl iodide and potassium hydroxide. The crude product was extracted with chloroform in a Soxhlet extractor for 12 hr and the chloroform was evaporated. Recrystallization of the product from a mixture of ethanol and ether yielded 3.9 g (42% from the olefin) of N,N,N-trimethyl-3,3-dimethylcyclopentylammonium iodide, mp 289–291° dec.

Anal. Calcd for $C_{10}H_{22}NI$: C, 42.41; H, 7.83; N, 4.95. Found: C, 42.20; H, 7.81; N, 5.22.

N,N,N-Trimethyl-*cis*-3,3-dimethylcyclopentylammonium-5-d_1 Iodide. Using the direct generation of Brown[21] a solution of 1.55 ml of freshly distilled boron trifluoride etherate in tetrahydrofuran was added slowly to a stirred mixture of 3.2 g (0.033 mol) of 4,4-dimethylcyclopentene and 0.40 g (0.0095 mol) of sodium borodeuteride in tetrahydrofuran under nitrogen. The resulting mixture was stirred for 2 hr at 25° and was then filtered and treated successively with 22 ml of 3 *N* sodium hydroxide and 56 ml of chloramine solution[22] and was worked up in a manner identical with that in the preceding experiment. Mass spectral analysis of the crude *cis*-3,3-dimethylcyclopentylamine-5-d_1 at 75 eV indicated 97% d_1 species. The crude primary amine was converted directly as in the preceding experiment to 3.9 g (41% from the olefin) of N,N,N-trimethyl-*cis*-3,3-dimethylcyclopentylammonium-5-d_1 iodide, mp 289–290° dec. A mixture melting point with the nondeuterated sample was undepressed.

Quaternary Hydroxides I and IV and Hofmann Elimination. The quaternary hydroxides I and IV were prepared by passage of an aqueous solution of 2 g of the corresponding quaternary iodide over a fourfold excess of Dowex 1-X8 ion-exchange resin in the basic form followed by evaporation of the water under vacuum at 45–50°. The resulting hydroxides I and IV were pyrolyzed at 115° and 45 mm pressure and the products were collected in a Dry Ice trap. The products were washed with a small amount of dilute hydrochloric acid followed by water and were then analyzed or separated by gas chromatography on a 6-ft stainless steel column packed with 40% ethylene glycol saturated with silver nitrate and 60% Chromosorb W (60–80 mesh) at 50° with a helium flow rate of 75 cc/min. Olefins II and V had a retention time of 1.77 min while olefins III and VI had a retention time of 5.64 min. Hofmann eliminations on I and IV were each run in duplicate and the results were extremely reproducible. Hydroxide I gave a mixture of olefins which was 51.7% olefin II and 48.3% olefin III. Hydroxide IV gave a mixture of olefins which was 42.3% olefin V and 57.7% olefin VI. Olefins V and VI were separated by gas chromatography

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and analyzed by mass spectrometry at 75 eV and V was found to be 35.5% olefin d_1 and 64.5% olefin d_0 (after appropriate correction for the 97% isotopic purity of the precursor) while VI was found to be 100% olefin d_1 (after appropriate correction for the 97% isotopic purity of the precursor). An isotope effect of *syn* k_H/k_D = 1.71 can be calculated using the equation shown in Chart II.

Elimination Reactions. IV. Hofmann Elimination of N,N,N-Trimethylcyclooctylammonium Hydroxide[1]

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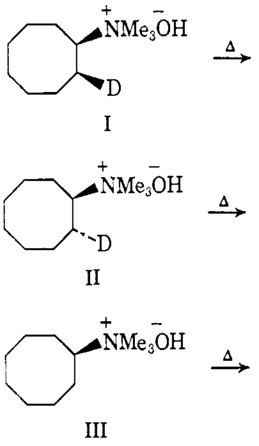
Abstract: Hofmann elimination of N,N,N-trimethylcyclooctylammonium hydroxide has been found to give a mixture of *cis*- and *trans*-cyclooctene. The *trans*-cyclooctene is formed by a 100% *syn* mechanism with a *syn* k_H/k_D = 1.94. The *cis*-cyclooctene is formed by a 51% *syn* mechanism and 49% *anti* mechanism. An *anti* k_H/k_D = 2.64 for the *anti* elimination to form *cis*-cyclooctene is calculated. The importance of these results is discussed.

It has recently been proposed on the basis of comparative rate studies[2,3] that in Hofmann eliminations *cis* olefins are formed by an *anti* mechanism and *trans* olefins are formed by a *syn* mechanism. This general prediction was tested in one deuterium-labeled aliphatic compound[4] and one deuterium-labeled tetramethyl-substituted cyclodecyl compound.[5] The conclusions reached by these earlier workers bear considerable scrutiny because of the rather wide implications of their predictions. The comparative rate studies used in the earlier work[2,3] may be a reflection only of the major reaction path and cannot be construed as a rigorous test of whether the elimination mechanism is completely stereospecific. For example it could be argued that the energetics for both mechanisms, *syn* and *anti*, leading to *cis* olefin might be similar with respect to van der Waals interactions in a given compound and thus a comparative rate study would not distinguish between the two mechanisms. The data given on the two examples using deuterium-labeled compounds for Hofmann elimination[4,5] also cannot be used as rigorous proof of the lower limits of each type of mechanism leading to each olefin because the olefins produced in the reaction were not separated and analyzed individually by mass spectrometry for deuterium but were simply analyzed as a mixture. This leads to a sizable error in determining the exact amount of mechanistic path leading to each olefin. It has also been shown that conclusions reached on the mechanism of Hofmann elimination operating in an alkyl-substituted cyclic system are not necessarily valid for the nonsubstituted parent systems.[6]

In view of the above uncertainties and the known dual mechanistic path leading to *cis* olefins in several ring systems[6,7] it seemed important to investigate at least one case of Hofmann elimination on a parent ring system which leads to both a *cis* and *trans* olefin. The system chosen was the cyclooctane ring and the results are shown in Chart I. The results indicate that the stereochemistry of Hofmann elimination in medium size rings is more complex than earlier workers[2,3] have suggested.

Chart I



I: 34% *cis*-cyclooctene (85% d_1; 15% d_0) and 66% *trans*-cyclooctene (100% d_1; 0% d_0)

II: 38% *cis*-cyclooctene (89% d_1; 11% d_0) and 62% *trans*-cyclooctene (66% d_1; 34% d_0)

III: 36% *cis*-cyclooctene and 64% *trans*-cyclooctene

Starting materials for the present work were *cis*- and *trans*-cyclooctene and these were treated individually with diborane-d_6 and then with chloramine to give *cis*- and *trans*-cyclooctylamine-2-d_1, respectively.[8,9] This reaction sequence requires comment since there have been two reports[10,11] of diborane addition to medium ring olefins being reversible under normal conditions. In these two cases either an excess of diborane[11] or a fairly hindered olefin was used[10] and both these conditions have been shown to be

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