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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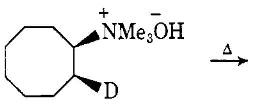
Abstract: Hofmann elimination of N,N,N-trimethylcyclooctylammonium hydroxide has been found to give a mixture of *cis*- and *trans*-cyclooctene. The *trans*-cyclooctene is formed by a 100% *syn* mechanism with a *syn* k_H/k_D = 1.94. The *cis*-cyclooctene is formed by a 51% *syn* mechanism and 49% *anti* 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]

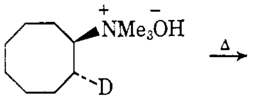
In view of the above uncertainties and the known dual mechanistic path leading to *cis* olefins in several ring systems[6,7] it seemed important to investigate at least one case of Hofmann elimination on a parent ring system which leads to both a *cis* and *trans* olefin. The system chosen was the cyclooctane 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



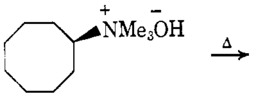
I

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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[1] This investigation was supported in part by a Public Health Service Research Grant HE 07050 from the National Heart Institute, U. S. Public Health Service.

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conducive to rearrangement by elimination–addition.[12] In the present work there was no excess diborane and low temperatures were used. These conditions appear to inhibit rearrangement[10,11] and our final results are incompatible with extensive rearrangement in the initial addition. The two deuterium-labeled cyclooctylamines were converted to hydroxides I and II by successive treatment with formaldehyde and formic acid, methyl iodide and passage over Dowex 1-X8 basic resin followed by removal of the water below 50°. Pyrolysis of I and II under normal Hofmann conditions gave mixtures of *cis*- and *trans*-cyclooctene which were separated by gas chromatography and each pure olefin from I and II was analyzed by mass spectrometry for deuterium. The deuterium analyses after proper correction for the 97% isotopic purity of the starting compounds are shown in Chart I. For comparison the results of elimination on the nondeuterated parent cyclooctyl system III are shown also.

The deuterium content of the olefins from compound I is rather revealing. The *trans*-cyclooctene has lost none of its deuterium indicating it is formed by a completely *syn* mechanism, in agreement with earlier predictions.[2–5] However, the *cis*-cyclooctene has lost 15% of its deuterium indicating that both a *syn* and *anti* mechanism must be operating in the formation of *cis*-cyclooctene. This is not in agreement with earlier predictions.[2–5] In the formation of *cis*-cyclooctene from I deuterium can only be lost by a *syn* mechanism. In order to calculate how much *syn* elimination actually would occur in the formation of *cis*-cyclooctene from the nondeuterated parent cyclooctyl compound III it is necessary to know a *syn* k_H/k_D for Hofmann elimination in the cyclooctyl ring. This can readily be determined from compound II.

If it can be assumed that the *syn* k_H/k_D for formation of *cis*-cyclooctene by *syn* elimination from I can be approximated by the *syn* k_H/k_D for formation of *trans*-cyclooctene by a *syn* elimination from II then the necessary isotope effect can be determined directly from the deuterium content of *trans*-cyclooctene from II. This is because *trans*-cyclooctene from II is produced exclusively by a *syn* elimination in which there is direct competition between loss of hydrogen on one side or deuterium on the other. In formation of *trans*-cyclooctene from II loss of hydrogen results in *trans*-cyclooctene-d_1 (66%) and loss of deuterium results in *trans*-cyclooctene-d_0 (34%) and a *syn* $k_H/k_D = 1.94$ can be calculated from these data. This isotope effect for a *syn* mechanism seems reasonable in view of similar ones found in two other cases.[6,13] Using this isotope effect as an approximation for the *syn* elimination to form *cis*-cyclooctene, one can calculate from the results on compound I that N,N,N-trimethylcyclooctylammonium hydroxide (III) forms *cis*-cyclooctene by a 51% *syn* elimination and 49% *anti* elimination.

There is another rather interesting piece of information that can be obtained from the results in Chart I. Inspection of the data reveals that in the formation of *cis*-cyclooctene from II deuterium can only be lost by an *anti* mechanism. From the above calculated relative rates of *syn* and *anti* elimination of hydrogen in formation of *cis*-cyclooctene and the amount of *cis*-cyclooctene-d_0 (11%) formed from II one can calculate that from II the *cis*-cyclooctene is formed by a 29% *anti* loss of hydrogen, 11% *anti* loss of deuterium, and a 60% *syn* loss of hydrogen. From the relative amount of *anti* loss of hydrogen (29%) to *anti* loss of deuterium (11%) an *anti* $k_H/k_D = 2.64$ can be calculated. In all the above interpretations we are ignoring any contribution of secondary isotope effects to rate of loss of hydrogen from a carbon bearing a deuterium. It is felt that the error introduced by this assumption is not serious in terms of the mechanistic conclusions reached.

One question which might be raised is whether or not there is any equilibration of the *cis*- and *trans*-cyclooctene under the conditions of Hofmann elimination which thereby might invalidate the deuterium analyses of the olefins. It has been estimated that the equilibrium would lie heavily in favor of the *cis*-cyclooctene.[14] The fact that the *trans*-cyclooctene from I shows no loss of deuterium indicates that none of it was formed by isomerization of the *cis*-cyclooctene. If *trans*-cyclooctene (100% d_1) from I is partially isomerized to the *cis*-cyclooctene then our estimation of the amount of *syn* elimination from I to form *cis*-cyclooctene is too low. The fact that the relative quantities of *cis*- and *trans*-cyclooctene were extremely reproducible on duplicate reactions even though the time of reaction varied somewhat is strong evidence that no isomerization occurred under the reaction conditions used. It is interesting to note that the relative amounts of olefins found in the present work differ slightly from that reported by Cope and coworkers.[15] Since ion-exchange resin was used in the present work to form the hydroxides and silver hydroxide had been used in the earlier work,[15] we repeated the Hofmann elimination on III using silver hydroxide to form the quaternary hydroxide from the iodide and obtained 60% *trans*-cyclooctene and 40% *cis*-cyclooctene by gas chromatographic analysis. These results are identical with those obtained by the earlier workers[15] but the amount of *trans*-cyclooctene is lower than by the ion-exchange method. It is possible that traces of silver salts either partially extract out and retain the *trans*-cyclooctene or catalyze partial isomerization of the *trans*- to *cis*-cyclooctene at the elevated temperature of reaction although Cope and coworkers[15] did not observe this kind of isomerization at room temperature. It is not likely that much thermal isomerization of the olefins could have taken place under the reaction conditions.[16]

The fact that the *trans*-cyclooctene from I retained all of its deuterium is very strong evidence that there is no E1cb mechanism, with rapid reversion to starting material, operating in the formation of either olefin from the cyclooctylammonium hydroxides. Thus the mechanisms for formation of both olefins are assumed to be E2 eliminations with concerted but not synchronous breakage of bonds. It is interesting to note that the *syn* and *anti* isotope effects found in the pres-

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ent work indicate different degrees of carbon–hydrogen bond breakage in the transition states for *syn* and *anti* elimination. Assuming proton transfer to base is greater than half-way in both mechanisms then the isotope effects indicate proton transfer in the transition state is greater in the *syn* elimination than it is in *anti* elimination.

Experimental Section

All mass spectral analyses were performed on a Hitachi Perkin-Elmer RMU-6E mass spectrometer. The cyclooctenes were analyzed at 75 eV and the N,N-dimethylcyclooctylamines were analyzed at 11 eV. For the method of treating the mass spectral data see the preceding paper. Gas chromatographic analyses and separations were carried out with an F & M Model 500 gas chromatograph using a 2-m column of 25% TCEP on Chromosorb P at 85° and a flow rate of 60 cc/min of helium. The *cis*-cyclooctene has a retention time of 5.5 min and *trans*-cyclooctene has a retention time of 8 min. The *cis*-cyclooctene was purchased from Aldrich Chemical Co. and was distilled prior to use while the *trans*-cyclooctene was prepared according to the procedure of Cope and co-workers[15] and was greater than 98% pure.

Cyclooctylamine. Into a stirred solution of 26.5 g (0.24 mol) of *cis*-cyclooctene in 250 ml of dry tetrahydrofuran at 0° was passed a stream of diborane prepared by the external generation method of Brown and Tierney[17] from slow addition of 2.5 g (0.066 mol) of sodium borohydride to an excess of boron trifluoride–etherate. The reaction mixture was stirred 1 hr at 25° and then there was added consecutively ice, 134 ml of 3 *N* sodium hydroxide, and 670 ml of freshly prepared chloramine solution[18] at 0°.[8] The mixture was stirred for 1 hr at 25° and was acidified with concentrated hydrochloric acid and extracted with ether, the ether extracts being discarded. The aqueous phase was made strongly basic with sodium hydroxide and extracted with ether. The ether extracts were combined, dried, and evaporated and the residue was distilled to yield 8.9 g (36%) of cyclooctylamine: bp 80–82° (20 mm); n^{25}D 1.4790 (lit.[19] bp 80° (10 mm)).

***cis*-Cyclooctylamine-2-d_1.** A repeat of the preceding experiment using 26.5 g (0.24 mol) of *cis*-cyclooctene and 2.5 g (0.06 mol) of sodium borodeuteride gave *cis*-cyclooctylamine-2-d_1: bp 80–81° (20 mm); n^{25}D 1.4782.

***trans*-Cyclooctylamine-2-d_1.** A repeat of the preceding experiment using 13.8 g (0.125 mol) of *trans*-cyclooctene and 1.26 g (0.03 mol) of sodium borodeuteride gave *trans*-cyclooctylamine-2-d_1, bp 80° (20 mm).

N,N-Dimethylcyclooctylamine. The general procedure of Icke, *et al.*,[20] was used to convert 17 g (0.134 mol) of cyclooctylamine to 12.4 g (59%) of N,N-dimethylcyclooctylamine: bp 84° (11 mm); n^{25}D 1.4707 (lit.[15,21] bp 86° (11 mm); n^{25}D 1.4710).

N,N-Dimethyl-*cis*-cyclooctylamine-2-d_1. A repeat of the preceding experiment using 15 g (0.117 mol) of *cis*-cyclooctylamine-2-d_1 gave N,N-dimethyl-*cis*-2-cyclooctylamine-2-d_1: bp 85–86° (11 mm); n^{25}D 1.4701. Mass spectral analysis at 11 eV indicated 97% d_1 species and 3% d_0 species.

N,N-Dimethyl-*trans*-cyclooctylamine-2-d_1. A repeat of the preceding experiment using 1 g (0.0079 mol) of *trans*-cyclooctylamine-2-d_1 gave N,N-dimethyl-*trans*-cyclooctylamine-2-d_1, bp 85° (11 mm). Mass spectral analysis at 11 eV indicated 97% d_1 species and 3% d_0 species.

N,N,N-Trimethylcyclooctylammonium Iodide. A solution of 41 g (0.264 mol) of N,N-dimethylcyclooctylamine and 98 g (0.69 mol) of methyl iodide in 500 ml of ether was allowed to stand overnight at 25°. The solid which developed was collected by filtration and dried under vacuum to yield 74.5 g (95%) of N,N,N-trimethylcyclooctylammonium iodide, mp 284–285° dec (lit.[21] mp 270–271°).

N,N,N-Trimethyl-*cis*-cyclooctylammonium-2-d_1 Iodide. A repeat of the preceding experiment using 7.8 g (0.05 mol) of N,N-dimethyl-*cis*-cyclooctylamine-2-d_1 and 26 g (0.184 mol) of methyl iodide gave N,N,N-trimethyl-*cis*-cyclooctylammonium-2-d_1 iodide, mp 282° dec.

N,N,N-Trimethyl-*trans*-cyclooctylammonium-2-d_1 Iodide. A repeat of the preceding experiment using 0.73 g (0.0047 mol) of N,N-dimethyl-*trans*-cyclooctylamine-2-d_1 and 1.35 g (0.0095 mol) of methyl iodide gave N,N,N-trimethyl-*trans*-cyclooctylammonium-2-d_1 iodide, mp 279–280° dec.

Hofmann Eliminations. The quaternary iodides were converted to the corresponding hydroxides I, II, and III by passage of an aqueous solution of the iodides over a fourfold excess of Dowex 1-X8 ion-exchange resin in the hydroxide form followed by evaporation of the water under vacuum at 45–50°. The resulting oil was pyrolyzed at 95° and 20 mm pressure with the volatile products being collected in a Dry Ice trap. The volatile products were mixed with cold dilute sulfuric acid and frozen and the olefinic products were collected. The olefins were analyzed and separated by gas chromatography. Each olefin isomer from the two deuterated hydroxides I and II was analyzed for deuterium separately by mass spectrometry at 75 eV. The results are shown in Chart I.

In a separate experiment in which hydroxide III was prepared using silver hydroxide the olefinic product consisted of 60% *trans*- and 40% *cis*-cyclooctene.

Acknowledgment. We wish to thank Dr. Manning P. Cooke, Jr., for performing the mass spectral analyses.

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