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Proximity Effects. XXII. Evidence for the Mechanism of the Reaction of Medium-sized Ring Epoxides with Lithium Diethylamide

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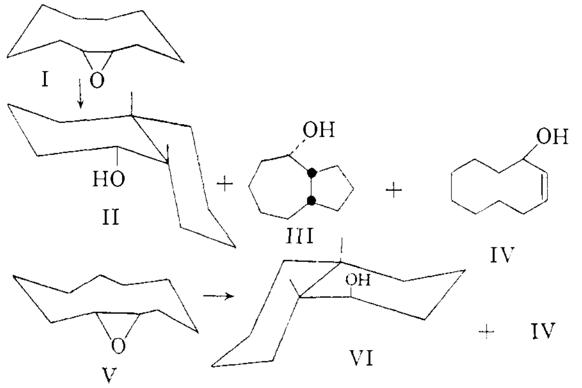
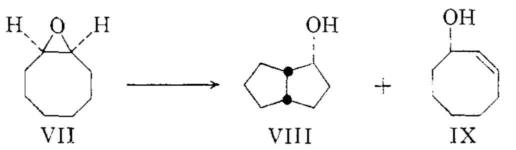
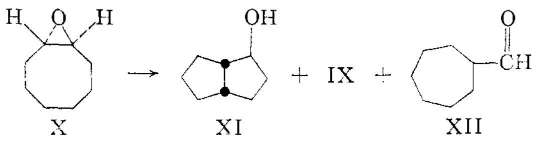
The reactions of *cis*-cyclodecene-1,2-d_2 oxide and *cis*-cycloöctene-5,6-d_2 oxide with lithium diethylamide have been studied. The bicyclic alcohol products are formed by the loss of a hydrogen or deuterium atom from a carbon atom of the epoxide ring. The mechanistic implications of these results are discussed.

Previous work[2] has established that *cis*-cyclodecene oxide (I) reacts with lithium diethylamide to produce, after hydrolysis, *cis-cis*-1-decalol (II), *endo-cis*-bicyclo[5.3.0]decan-2-ol (III) and 2-cyclodecen-1-ol (IV) in yields of 83%, 9% and 8%, respectively. Similarly, *trans*-cyclodecene oxide (V) yielded *cis-trans*-1-decalol (VI) in addition to IV,[2] thereby establishing the stereochemical selectivity of the reaction. Similar reactions were observed for the eight-membered ring epoxides. *cis*-Cycloöctene oxide (VII) produced *endo-cis*-bicyclo[3.3.0]octan-2-ol (VIII) as the major product and a small amount of 2-cycloöcten-1-ol (IX) while *trans*-cycloöctene oxide (X) produced *exo-cis*-bicyclo[3.3.0]octan-2-ol (XI) and IX in addition to cyclohetplanecarboxaldehyde (XII).[3]







Two reaction paths leading to the bicyclic alcohols appeared to be possible. In the case of *cis*-cyclodecene oxide, for example, the base could remove a proton from a carbon atom located across the ring from the epoxide ring (C_6 or C_7) with concerted opening of the epoxide by the carbanion so formed (path 1 in Fig. 1). Attack by the carbanion on the other carbon of the epoxide ring would produce III. In the second possible reaction path (path 2 in Fig. 1), the base removes a proton from one of the carbon atoms of the epoxide ring, followed by a breaking of the bond between the oxygen atom and the carbon atom which has lost a proton to form a concerted carbene intermediate, which could then form a bond to a carbon atom across the ring with simultaneous transfer of hydride ion from the same carbon atom to the electron-deficient carbon atom. Similar attack on C_7 would produce III. The processes are represented as concerted reactions since the products are single stereoisomers. Similar transition states may be drawn for the other above-mentioned examples of this reaction.

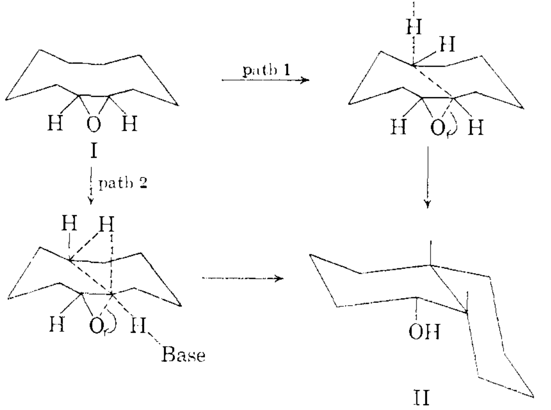
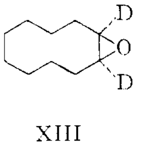
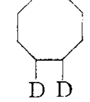


Fig. 1.—Possible transition states for the reaction of *cis*-cyclodecene oxide with lithium diethylamide.

Paths 1 and 2 can be distinguished by deuterium tracer studies with an epoxide which is labeled either on the carbon atoms of the epoxide ring or on the carbon atoms across the ring. Consequently, XIII and XIV were synthesized in order to study their reaction with lithium diethylamide.[4]



XIII



XIV

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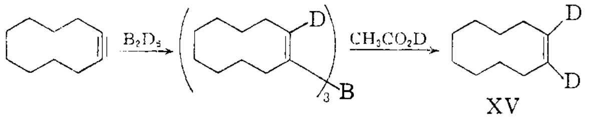
[1] (a) Postdoctoral Fellow, 1959–1960; (b) National Institutes of Health Postdoctoral Fellow, 1956–1958; (c) Postdoctoral Fellow, 1958–1959.

[2] A. C. Cope, M. Brown and H. H. Lee, This Journal, **80**, 2855 (1958).

[3] A. C. Cope, H. H. Lee and H. E. Petree, *ibid.*, **80**, 2849 (1958).

[4] For the synthesis and deuterium distribution of XIV, see A. C. Cope, G. A. Berchtold, P. E. Peterson and S. H. Sharman, *ibid.*, **82**, 6366 (1960).

cis-Cyclodecene-1,2-d_2 (XV) was synthesized by the deuteroboration of cyclodecyne with diborane-d_6 generated from lithium aluminum deuteride and boron trifluoride etherate and subsequent deuterolysis of the intermediate trialkenylborane with deuterium acetate, a modification of the hydroboration of acetylenes by Brown and Zweifel for the production of pure *cis*-olefins.[5] Mass spectrograph analysis indicated XV to consist of 1% undeuterated, 18% monodeuterated, 81% dideuterated and 0% trideuterated (or higher) species. Since the lithium aluminum deuteride used to generate the diborane-d_6 had an isotopic purity of greater than 99% and since any active hydrogen present in the reaction mixture would destroy the diborane-d_6 rather than exchange with it, the incomplete deuteration is assumed to arise from a small amount of acetic acid present in the deuterium acetate. A few per cent. of acetic acid might give rise to the hydrogen content observed by virtue of an isotope rate effect, since the deuterolysis is carried out in a large excess of acid. Gas chromatography on 4-methyl-4-nitropimelonitrile[6] indicated XV to be free of the *trans* isomer. Epoxidation with monoperphthalic acid converted XV to XIII.



If the reaction of XIII with lithium diethylamide proceeds according to path 1 (Fig. 1), the bicyclic products (XVI and XVII of Fig. 2) should retain all the deuterium that was present in XIII. Conversely, if path 2 is occurring, 0.8 to 1.0 atom of deuterium per molecule[7] would be lost and the bicyclic alcohols would have the deuterium distribution indicated by structures XVIII and XIX of Fig. 2.

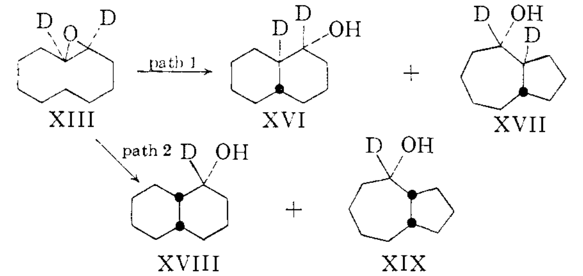
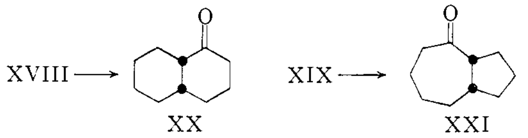


Fig. 2.—Possible distribution of deuterium in products from the reaction of XIII with lithium diethylamide.

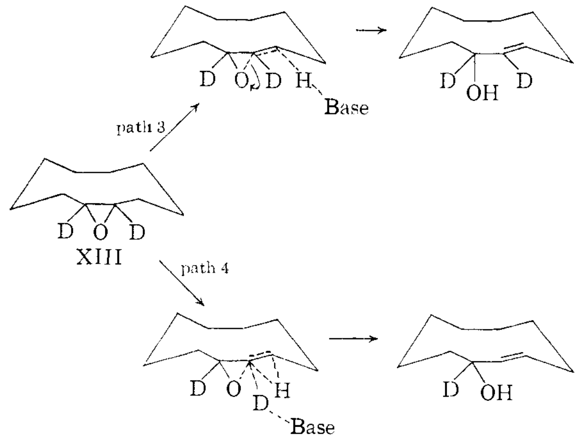
The reaction of XIII with lithium diethylamide was carried out as previously described for the undeuterated compound.[2] The *cis-cis*-1-decalol and bicyclo[5.3.0]decan-2-ol contained 0.96 and 0.93 atom of deuterium per molecule, respectively. This corresponds to a loss of 0.82 and 0.85 atom of deuterium per molecule. Thus, path 2 appears to be the route by which these bicyclic alcohols are formed. The correct structures are then XVIII and XIX.

In order to establish the position of the deuterium in XVIII and XIX, these alcohols were oxidized to the corresponding bicyclic ketones (XX and XXI) by chromic anhydride in pyridine.[8] The *cis*-1-decalone so obtained still possessed 0.03 atom of deuterium per molecule and the bicyclo[5.3.0]-decan-2-one analyzed for 0.02 atom of deuterium per molecule. This existence of a small amount of deuterium in the ketones is apparently due to exchange during the reaction rather than the bicyclic alcohols being formed to the extent of 2–3% by path 1 since exchangeable hydrogens are present in the reaction mixture.[9]



That exchange does occur was demonstrated by treating *cis*-cyclodecene oxide with lithium diethylamide in the presence of diethylamine-N-*d*. The *cis-cis*-1-decalol contained 0.04 atom of deuterium per molecule and the recovered oxide contained 0.10 atom of deuterium per molecule. Oxidation of this *cis-cis*-1-decalol with chromic anhydride in pyridine gave *cis*-1-decalone containing 0.03 atom of deuterium per molecule, the same quantity which is found in XX. Thus it appears that the bicyclic alcohols are formed exclusively by path 2.

The 2-cyclodecen-1-ol (XXII) obtained from the reaction of XIII with lithium diethylamide contained 1.52 atoms of deuterium per molecule. This indicates that both path 3 and path 4 are involved in the formation of the allylic alcohol. The exact extent of path 3 and path 4 cannot be determined



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[5] H. C. Brown and G. Zweifel, This Journal, **81**, 1512 (1959).

[6] Reference 4, footnote 14.

[7] Since XIII is incompletely deuterated, *i.e.*, contains 1.78 rather than 2.00 atoms of deuterium per molecule, the exact amount of deuterium lost by path 2 will depend on the isotope rate effect. If no isotope effect is involved, 0.89 atom of deuterium should be lost; if the C–H bond breaks faster than the C–D bond, the amount of deuterium lost would be correspondingly less than this value and, conversely, if the C–D bond breaks faster, the reverse would be true.

[8] This method was previously shown not to equilibrate deuterium atoms on the α-positions of ketones (ref. 4, footnote 7). Furthermore, if equilibration of the hydrogen or deuterium atom at the point of ring fusion did occur during the oxidation of *cis-cis*-1-decalol, the more stable *trans*-decalin ring system should be formed. The product of this oxidation is pure *cis*-1-decalone.

[9] Diethylamine is used in 10% excess in the formation of lithium diethylamide from diethylamine and *n*-butyllithium and diethylamine-N-*d* is formed during the reaction.

because of the incomplete deuteration of XIII. It appears, however, that path 3 occurs to the extent of approximately 65% and path 4 to the extent of approximately 35%.[10]

Further support for a concerted carbene intermediate in the reaction of medium-sized ring epoxides with lithium diethylamide was obtained from the reaction of XIV with this reagent.[11] The *endo-cis*-bicyclo[3.3.0]octan-2-ol (XXIII) contained 1.97 atoms of deuterium per molecule, showing that no deuterium is removed from C_5 or C_6 of the epoxide. Oxidation of this alcohol with chromic anhydride in pyridine yielded *cis*-bicyclo[3.3.0]octan-2-one (XXIV) which contained 1.94 atoms of deuterium per molecule before equilibration of the α-positions and 1.46 atoms of deuterium per molecule after equilibration. This reaction, therefore, occurred by a mechanism analogous to path 2 with essentially equal amounts of hydride and deuteride shift.

Experimental[12]

***cis*-Cyclodecene-1,2-d_2.**—Diborane-d_6 was slowly generated over a period of 1.5 hours by the dropwise addition of a slurry of 2.31 g. of lithium aluminum deuteride[13] in 60 ml. of ether to a solution of 14.2 g. of boron trifluoride etherate in 50 ml. of ether at 0°. The diborane-d_6 was bubbled into a stirred solution of 27.2 g. of cyclodecyne[14] in 70 ml. of ether at 0°. An acetone trap was used to prevent any diborane-d_6 from escaping into the atmosphere. After the addition was completed, nitrogen was slowly bubbled through the system for 30 minutes, after which time the trialkenylborane precipitated. Deuterium acetate (30 ml.) was added and the mixture was stirred at room temperature for 30 hours. The mixture was poured into ether and extracted three times with water and once with 10% sodium carbonate. After drying, the ether was removed by distillation and the residue was fractionated through a 45 × 0.5-cm. spinning band column to obtain 11.9 g. (43%) of product, b.p. 90–92.5° (28 mm.); deuterium analysis: 1.78 atoms of deuterium per molecule; mass spectrograph analysis: 1% undeuterated, 18% monodeuterated and 81% dideuterated species.

***cis*-Cyclodecene-1,2-d_2 Oxide.**—The olefin (11.0 g.) was dissolved in 500 ml. of an ethereal solution of monoperphthalic acid containing 21.9 g. of peracid. The solution was kept in the dark and the reaction was followed by iodometric titration. When the reaction was complete, the mixture was filtered to remove the precipitated phthalic acid. The solution was washed with 5% aqueous sodium hydroxide, water and dried. The ether was removed by distillation through a Vigreux column and the residue was distilled through a 45 × 0.5-cm. spinning band column to obtain 10.4 g. (85%) of XIII, b.p. 121–122.5° (24 mm.).

Reaction of XIII with Lithium Diethylamide.—Compound XIII was treated with lithium diethylamide and the products were isolated as previously described for the undeuterated compound.[2] Final purification of XVIII was effected by recrystallization from hexane; m.p. 91.9–92.5°; deuterium analysis; 0.96 atom of deuterium per molecule. Compounds XIX and XXII were purified by gas chromatography on Silicone oil[6]; deuterium analysis of XIX: 0.93 atom of deuterium per molecule; deuterium analysis of XXII: 1.52 atoms of deuterium per molecule.

Oxidation of XVIII with Chromic Anhydride–Pyridine Complex.—Compound XVIII (200 mg.) was oxidized by the procedure previously described for the undeuterated compound.[2] The product XX (124 mg.) was purified by gas chromatography on 1,2,3-tris-(2-cyanoethoxy)-propane[15]; deuterium analysis: 0.03 atom of deuterium per molecule.

Oxidation of XIX with Chromic Anhydride–Pyridine Complex.—Compound XIX (75 mg.) was oxidized by the procedure previously described for the undeuterated compound.[2] The product XXI (30 mg.) was purified by gas chromatography on Silicone oil[6]; deuterium analysis: 0.02 atom of deuterium per molecule.

Reaction of XIV with Lithium Diethylamide.—Compound XIV (1.02 g.) was treated with lithium diethylamide and the *endo-cis*-bicyclo[3.3.0]octan-2-ol (667 mg.) was isolated by the method previously described for the undeuterated compound.[3] The product was further purified by gas chromatography on Silicone oil[6]; deuterium analysis: 1.97 atoms of deuterium per molecule.

Oxidation of XXIII with Chromic Anhydride–Pyridine Complex.—Compound XXIII (550 mg.) was oxidized by the same procedure described for XVIII. The product XXIV (310 mg.) was purified by gas chromatography on Silicone oil[6]; deuterium analysis: 1.94 atoms of deuterium per molecule.

Equilibration of XXIV.—Compound XXIV was equilibrated by the method previously described for the equilibration of 4-cycloöcten-1-one-8-d_1[4]; deuterium analysis after one equilibration: 1.48 atoms of deuterium per molecule; after two equilibrations: 1.46 atoms of deuterium per molecule.

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[10] A. C. Cope and J. K. Heeren (to be published) have observed through similar deuterium studies that *cis*- and *trans*-4-octene oxides react with lithium diethylamide to form the corresponding allylic alcohols by a mechanism analogous to path 3.

[11] Although XIV was shown by mass spectrograph analysis to consist of 13% monodeuterated, 74% dideuterated and 13% trideuterated species, all the deuterium was shown to be on C_5 and C_6 (see ref. 4). Since these two carbon atoms are equivalent in XIV, it is assumed that the unequal labeling will have no effect on the results of this study.

[12] Melting points are corrected and boiling points are uncorrected. All deuterium analyses indicating the number of atoms of deuterium per molecule were determined by the falling drop method; these analyses were performed by Mr. Josef Nemeth, Urbana, Ill. Mass spectrographic analyses were determined with a C. E. C. type 21-103C instrument with a heated inlet system. We are indebted to Drs. K. Biemann and J. Seibl for these analyses.

[13] Metal Hydrides, Inc., Beverly, Mass.: minimum isotopic purity: 99%.

[14] A. T. Blomquist, R. E. Burge, Jr., and A. C. Sucsy, THIS JOURNAL, **74**, 3636 (1952).

[15] This column was an 8-mm. Pyrex tube of 100-cm. length containing 30% by weight of liquid phase absorbant on a 60–80 mesh firebrick support. The column temperature was 130°.