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Intramolecular Substitution Reactions. X. The Hydrolysis of trans-4-Chlorocyclohexanol

BY HAROLD W. HEINE

It has been established that 1,4-epoxycyclohexane is the main reaction product in the alkaline hydrolysis of trans-4-chlorocyclohexanol.   The rate of ring closure was 1/1100 as fast as the formation of tetrahydrofuran from the alkaline hydrolysis of tetramethylene chlorohydrin.   The reaction of trans-4-chlorocyclohexanol with water also was studied.   The product of hydrolysis was predominantly 3-cyclohexenol.

Stereochemical and kinetic studies have been utilized in the past as evidence for 1,4-nucleophilic displacements in cyclohexyl systems. Thus, the retention of configuration observed in the acetolysis of trans-4-methoxycyclohexyl p-toluene-sulfonate and a rate fivefold that of the cis isomer has been explained by the formation of a five-membered ring oxonium ion (I) with two inversions accompanying the solvolysis.[1] Similarly the reaction of
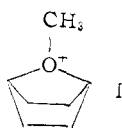
the bistosylate of cis-1,4-cyclohexanediol with sodium iodide in acetone to give principally trans-1,4-diiodocyclohexane has been interpreted as proceeding through a cyclic 1,4-iodonium intermediate.[2,3]

In the present kinetic study of the alkaline hydrolysis of trans-4-chlorocyclohexanol, the idea of 1,4-nucleophilic participation in cyclohexyl systems has been substantiated by the isolation of 1,4-epoxycyclohexane as the main reaction product.[4] The reaction was found to be first order with respect to hydroxide ion and first order with respect to chlorohydrin.

It was also observed that trans-4-chlorocyclohexanol undergoes a reaction with water which competes with the second-order process. The product of this hydrolytic process was mainly 3-cyclohexenol.

Experimental

Method of Rate Measurement.—The procedure for following the rate of release of chloride ion from the trans-4-chlorocyclohexanol was the same as described previously for the hydrolysis of tetramethylene chlorohydrin.[5] The measurement of the second-order process was complicated because of a concurrent first-order hydrolytic process. To evaluate the true second-order rate constant, it was necessary to integrate the equation for a simultaneous first- and second-order reaction, i.e.

$$d[Cl^-]/dt = k_1(b - x) + k_2(a - x)(b - x) \quad (1)$$

$$\frac{t[k_1 + k_2(a - b)]}{2.303} = \log \frac{b[k_1 + k_2(a - x)]}{(b - x)(k_1 + k_2a)} \quad (2)$$

(1) D. S. Noyce and B. R. Thomas, THIS JOURNAL, **79**, 755 (1957).

(2) L. N. Owen and P. A. Robins, J. Chem. Soc., 320 (1949).

(3) E. L. Bennett and C. Niemann, THIS JOURNAL, **74**, 5076 (1952).

(4) Owen and Robins[2] had previously reported that treatment of a mixture of cis- and trans-4-chlorocyclohexanol with potassium hydroxide in boiling ether failed to yield the desired 1,4-epoxide. They also reported that refluxing the mixed chlorohydrins with alcoholic alkali or solid potassium hydroxide at 160° gave complex mixtures from which no 1,4-epoxycyclohexane was isolated.

(5) H. W. Heine and W. Siegfried, THIS JOURNAL, **76**, 489 (1954).

determine experimentally the first-order hydrolytic constants and assume various values of k_2 until the two sides of equation 2 were equated.   This method previously was employed by Chadwick and Pacsu[6a] and Heine.[6b]

Typical rate data for the hydrolyses are given in Table I. The constants listed in Table I for the alkaline hydrolysis were calculated by means of the above equation.   In calculating the rate constants the first sample was taken as the starting point of the reaction.   Table II is a summary of all the kinetic studies.

TABLE I

RATE OF HYDROLYSIS OF trans-4-CHLOROCYCLOHEXANOL AT 80.6°

Time, min.	Vol. 0.05 N AgNO₃, ml.	$k_1 \times 10^5$, sec.$^{-1}$
44.44	0.48	2.60
165.6	1.71	2.78
229.8	2.22	2.71
331.1	3.02	2.78
479.4	3.88	2.76
657.7	4.33	2.78
Inf.	7.07	(Mean) 2.73

RATE OF ALKALINE HYDROLYSIS OF trans-4-CHLOROCYCLO-HEXANOL AT 80.6° IN 0.1681 N NaOH[a]

Time, min.	Moles Cl⁻/10 ml.	$k_2 \times 10^4$, 1. moles^{-1} sec.$^{-1}$
21.22	0.068	9.11
39.02	.112	9.03
63.80	.160	8.93
93.70	.206	9.11
128.8	.241	8.93
171.1	.273	9.08
Inf.	.335	(Mean) 9.03

[a] Calculated by means of equation 2.

TABLE II

RATE CONSTANTS FOR THE FIRST- AND SECOND-ORDER ALKALINE HYDROLYSIS OF trans-4-CHLOROCYCLOHEXANOL

Chloro-hydrin, N	NaOH, N	Temp., °C.	$k_2 \times 10^4$, 1. moles^{-1} sec.$^{-1}$	$k_1 \times 10^5$, sec.$^{-1}$
0.0354	0	80.5		2.73
.0357	0	80.5		2.76
.0333	0.1098	80.5	8.96	
.0335	.1681	80.5	9.03	
.0307	.2235	80.5	8.98	
.0200	0	70.5		0.840
.0400	0	70.5		0.845
.0396	0.0929	70.5	3.23	
.0394	0.1393	70.5	3.15	

1,4-Epoxycyclohexane.—This compound was prepared by the hydrogenation of hydroquinone in the presence of Raney nickel followed by dehydration of the resulting mixture of 1,4-cyclohexanediols with alumina.   The method was essentially that of Fehnel and co-workers[7] with the exception

(6) (a) A. F. Chadwick and E. Pacsu, ibid., **65**, 392 (1913); (b) H. W. Heine, ibid., **78**, 3708 (1956).

(7) E. Fehnel, S. Goodyear and J. Berkowitz, ibid., **73**, 4978 (1951).

that 2-propanol was used as the solvent for the hydrogenation instead of methanol. An over-all yield of 48% epoxide was obtained.

trans-4-**Chlorocyclohexanol.**—This compound was prepared by the method of Bennett and Niemann.[3] After several recrystallizations from cyclohexane it melted at 83–85°.

Products of the Alkaline Hydrolysis of *trans*-4-Chlorocyclohexanol. Method A.—The yield of 1,4-epoxycyclohexane was estimated by means of mass spectrometry. Aliquots were taken from a rate run after the theoretical quantity of halide had been displaced and compared with standards made from authentic samples of 1,4-epoxycyclohexane and 3-cyclohexenol. At a ratio of alkali to chlorohydrin of 4:1 the presence of 70% 1,4-epoxide and 30% 3-cyclohexenol were detected; at a ratio of 2:1 an aliquot was estimated to contain 55% 1,4-epoxide and 45% 3-cyclohexenol. This method has an accuracy of ±10%.[8]
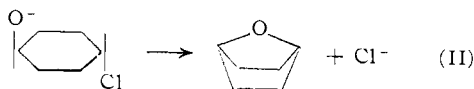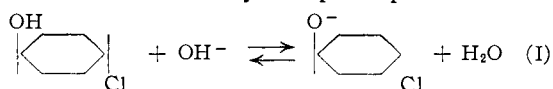
Method B.—To a solution containing 10.6 g. (0.265 mole) of sodium hydroxide in 3 l. of water at 80° was added 19.0 g. (0.141 mole) of *trans*-4-chlorocyclohexanol. The reaction mixture was shaken to assure complete solution of the chlorohydrin. After all the halogen was released, the solution was thoroughly extracted with ether. The ethereal extracts were dried over anhydrous magnesium sulfate, filtered and the ether removed by slow distillation. The residue was distilled to give 7.3 g. (53%) of crude 1,4-epoxide boiling from 121–133° which on redistillation boiled at 118–119°, n^{25}D 1.4475. The refractive index of an authentic sample of 1,4-epoxycyclohexane at 25° is 1.4475. A 3.55-g. (26%) fraction of crude 3-cyclohexenol boiling from 159–163° also was obtained. This fraction formed an α-naphthylurethan with ease which melted at 129°; reported value[2] 128.5°.

Products of the Reaction of *trans*-4-Chlorocyclohexanol with Water. Method A.—Using an analogous procedure as described for the alkaline hydrolysis described above, it was possible to estimate by means of mass spectrometry that the products of the reaction of water with the chlorohydrin were 16% of the 1,4-epoxide and 84% 3-cyclohexenol.

Method B.—In 3 l. of water at 80° was placed 18.8 g. (0.139 mole) of *trans*-4-chlorocyclohexanol. The reaction mixture was vigorously agitated and then maintained at 80° until all the chloride had been hydrolyzed. The reaction mixture was then neutralized with sodium hydroxide solution, saturated with sodium nitrate and extracted with nine 100-ml. portions of ether. The ethereal extracts were dried over anhydrous magnesium sulfate, filtered and the solvent removed by distillation. The residue was distilled to give 8.0 g. (66%) of crude 3-cyclohexenol boiling at 155–165° (5 g. of which distilled at 163–165°). This material discharged the color of dilute permanganate instantaneously and was shown to be 3-cyclohexenol by infrared analysis, mass spectrometry analysis and by formation of an α-naphthylurethan melting at 129–129.5°. A half-gram of low boiling material possessing the characteristic 1,4-epoxycyclohexane odor also was obtained.

Discussion

The formation of 1,4-epoxycyclohexane and the observed second-order kinetics for the alkaline hydrolysis of *trans*-4-chlorocyclohexanol is explicable on the basis of a concerted mechanism involving the attack of the hydroxide ion on the hydrogen of the hydroxyl group simultaneous with the displacement of the halogen by the nucleophilic oxygen. Alternatively the kinetics and products can be accounted for by a stepwise process in which

an alkoxide ion is formed in the first step, followed by a displacement of chloride ion by the negatively charged oxygen, as is shown by equations (I) and (II).

These mechanisms are similar to those previously proposed for the alkaline hydrolysis of tetramethylene chlorohydrin to form tetrahydrofuran.[5] The formation of 3-cyclohexenol is most likely due to the rapid concurrent first-order hydrolytic process and not to a second-order elimination reaction.

It is of interest to compare the relative reactivities of tetramethylene chlorohydrin and *trans*-4-chlorocyclohexanol with hydroxide ion. The thermodynamic parameters for these two systems are presented in Table III together with the estimated rates of reaction at a common temperature.

TABLE III
THERMODYNAMICS OF ACTIVATION, TOGETHER WITH ESTIMATED RATES OF REACTION AT 30.0° FOR *trans*-3-CHLOROCYCLOHEXANOL AND TETRAMETHYLENE CHLOROHYDRIN WITH HYDROXIDE ION

Chlorohydrin	$\Delta H^{\ddagger}$, kcal.	$T\Delta S^{\ddagger}$, kcal.	$\Delta F^{\ddagger}$, kcal.	k_2, l. moles^{-1} sec.$^{-1}$
Tetramethylene	19.8	−1.5	21.3	2.8×10^{-3}
trans-4-Chlorocyclohexanol	24.3	−1.7	26.0	2.4×10^{-6}

As shown in Table III the displacement of chloride ion in the cyclohexyl system is some 1/1100 as fast as the acyclic analog. The considerable difference in velocity constants is due almost entirely to the heats of activation and not to the entropies of activation which are essentially equal for the two processes. The lower reactivity of *trans*-4-chlorocyclohexanol is attributable primarily to the energy required to convert the chair to the boat conformation necessary for ring closure and also in part to the difficulty of cyclohexyl systems to form a pentacoördinate transition state.[9–11]

Mass spectrometric analyses of aliquots of the reaction of *trans*-4-chlorocyclohexanol with water after all the halide has been hydrolyzed revealed a 16% yield of 1,4-epoxycyclohexane and 84% 3-cyclohexenol. The formation of the 1,4-epoxide can be explained in terms of anchimeric assistance by the hydroxyl group as in the case of the hydrolysis of tetramethylene chlorohydrin[12,13] to form a five-membered transition state, *i.e.*
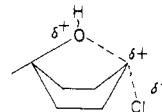
This mechanism is similar to that proposed to account for the 20% yield of *trans*-4-methoxycyclohexyl acetate in the acetolysis of *trans*-4-methoxycyclohexyl-*p*-toluene sulfonate.[1] On the other hand it is not unreasonable to attribute the formation of the 1,4-epoxide and the 3-cyclohexenol to a rate determining ionization of the *trans*-4-chloro-

(9) J. B. Conant and R. E. Hussey, THIS JOURNAL, **47**, 476 (1925).

(10) H. S. Brown, R. S. Fletcher and R. B. Johannesen, *ibid.*, **73**, 212 (1951).

(11) J. D. Roberts and V. C. Chambers, *ibid.*, **73**, 5034 (1951).

(12) H. W. Heine, A. D. Miller, W. H. Barton and R. W. Greiner, *ibid.*, **75**, 4778 (1953).

(13) A. Streitwieser, *Chem. Revs.*, **56**, 684 (1956).

cyclohexanol to the carbonium ion intermediate (II) which subsequently undergoes either ring closure by attack of the hydroxyl group or elimination by expulsion of a proton, i.e.
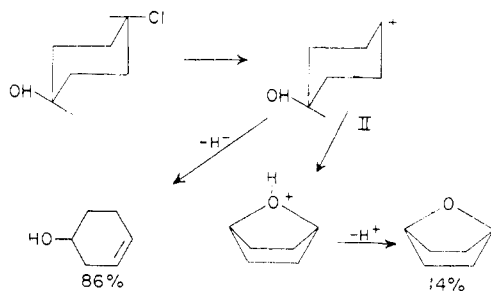
In considering these alternative interpretations, it was of interest to observe in this Laboratory that a 0.003 M solution of cyclohexyl chloride at 80° hydrolyzed as rapidly as the trans-4-chlorocyclohexanol. It is also to be noted that the acetolysis of cyclohexyl p-toluenesulfonate[14] proceeds at a comparable rate to the trans-4-methoxycyclohexyl tosylate,[1] viz., 4.27 × 10⁻⁵ sec.⁻¹ at 74.9° and 3.20 × 10⁻⁵ sec.⁻¹ at 75.09°, respectively.

Acknowledgments.—The author wishes to acknowledge the helpful assistance of Gordon F. MacKenzie and Howard Crawford.

(14) S. Winstein, E. Grunwald, R. E. Buckles and C. Hanson, THIS JOURNAL, 70, 816 (1948).

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Addition of Hydrogen Bromide to 1-Halocyclohexene and the Rearrangement of Dihalocyclohexanes in the Presence of Ferric Chloride[1,2]

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The ionic addition of hydrogen bromide to 1-chlorocyclohexene and 1-bromocyclohexene in excess liquid hydrogen bromide in the presence of a small amount of ferric chloride gives 1-bromo-1-chlorocyclohexane and 1,1-dibromocyclohexane, respectively. In the presence of larger amounts of ferric chloride the initially formed gem-dihalide undergoes halogen exchange and rearrangement. Thus both 1-chlorocyclohexene and 1-bromocyclohexene can be converted to trans-1,4-dibromocyclohexane in good yields. Examination of products from a series of experiments in which the amount of ferric chloride was varied indicates the following sequence for the conversion of 1-chlorocyclohexene to trans-1,4-dibromocyclohexane: 1-chlorocyclohexene → 1-bromo-1-chlorocyclohexane → 1,1-dibromocyclohexane → cis-1,2-dibromocyclohexane → 1,3-dibromocyclohexane → trans-1,4-dibromocyclohexane. Apparently, trans-1,2-dibromocyclohexane is not involved as an intermediate in this process. Under appropriate conditions 1-chlorocyclohexene can be converted to 1-bromo-1-chlorocyclohexane, 1,1-dibromocyclohexane or trans-1,4-dibromocyclohexane in good yields.

Introduction

The ionic addition of hydrogen bromide to 1-halocyclohexene in the presence of small amounts of anhydrous $FeCl_3$ in excess liquid hydrogen bromide proceeds rapidly at low temperature and gives the normal addition product. Thus 1-chlorocyclohexene (I) and 1-bromocyclohexene are converted to 1-bromo-1-chlorocyclohexane (II) and 1,1-dibromocyclohexane (III), respectively, in good yields.[3] However, in the presence of larger amounts of $FeCl_3$ the initially formed gem-dihalide undergoes halogen exchange and rearrangement. Indeed, our first attempts to prepare 1-bromo-1-chlorocyclohexane from I by the addition of hydrogen bromide in the presence of $FeCl_3$ resulted instead in the formation of trans-1,4-dibromocyclohexane (VI), isolated in pure form in yields of about 80%. Similarly, 1-bromocyclohexene was converted to VI. This paper describes an investigation of the halogen exchange and rearrangement involved in the conversion of I and 1-bromocyclohexene to VI.

Results

To obtain information concerning intermediates involved in the conversion of 1-chlorocyclohexene (I) to trans-1,4-dibromocyclohexane (VI), a number of experiments was carried out in which the amount of $FeCl_3$ was varied. The results of these experiments are summarized in Table I. In these

TABLE I

REACTION OF 1-CHLOROCYCLOHEXENE WITH HYDROGEN BROMIDE IN THE PRESENCE OF $FeCl_3$[a]

			Product			
Expt.	FeCl₃, g.	Weight, g.	B.p. °C.	Mm.	$n^{25}D$	Composition
1	0.1	15.3	86–89	26	1.5109	II
2	.4	11.7	60–65	7	1.5082	II
3	.6	15.6	66–74	6	1.5276	II and III
4	.75	16.2	73–78	7	1.5391	III
5	1.0	16.2	91–98	8	1.5499	III, IV, V and VI
6	2.0	17.0				VI
7	2.5[b]	15.5	60–67	7	1.5100	II and III

[a] Ten grams of I and 50 g. of hydrogen bromide were used in all of these experiments; reaction time, 24 hr. [b] Reaction time, 1.5 hr.

experiments 50 g. of solid hydrogen bromide, 10 g. of I and a weighed amount of $FeCl_3$ were collected in a Pyrex reaction vessel cooled in liquid air. The frozen anhydrous reaction mixture was placed in a bomb and allowed to stand at room temperature for 24 hr. Presumably under these conditions the