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
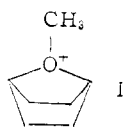
the bistosylate of *cis*-1,4-cyclohexanediol with sodium iodide in acetone to give principally *trans*-1,4-diiodocyclohexane has been interpreted as proceeding through a cyclic 1,4-iodonium intermediate.[2,3]

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.*

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

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

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.	$k_2 \times 10^4$, l. 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.	$k_2 \times 10^4$, l. 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

(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).

(6) (a) A. F. Chadwick and E. Pacsu, *ibid.*, **65**, 392 (1943); (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 hydrogena-
tion instead of methanol. An over-all yield of 48% epoxide
was obtained.

trans-4-**Chlorocyclohexanol.**—This compound was pre-
pared 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-Chlorocy-
clohexanol. 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
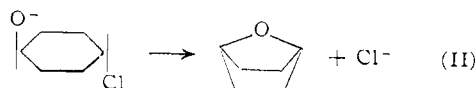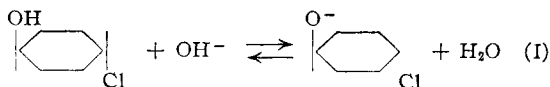method has an accuracy of ±10%.[8]

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 reac-
tion mixture was shaken to assure complete solution of the
chlorohydrin. After all the halogen was released, the solu-
tion was thoroughly extracted with ether. The ethereal ex-
tracts were dried over anhydrous magnesium sulfate, fil-
tered and the ether removed by slow distillation. The
residue was distilled to give 7.3 g. (53%) of crude 1,4-epox-
ide 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-naph-
thylurethan 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 solu-
tion, 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-naphthyl-
urethan 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 ex-
plicable on the basis of a concerted mechanism in-
volving the attack of the hydroxide ion on the hy-
drogen 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 tetra-
methylene 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 reac-
tion.

It is of interest to compare the relative reac-
tivities of tetramethylene chlorohydrin and *trans*-4-
chlorocyclohexanol with hydroxide ion. The ther-
modynamic 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 ESTI-
MATED RATES OF REACTION AT 30.0° FOR *trans*-3-CHLORO-
CYCLOHEXANOL AND TETRAMETHYLENE CHLOROHYDRIN WITH
HYDROXIDE ION

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

As shown in Table III the displacement of chlo-
ride ion in the cyclohexyl system is some 1/1100
as fast as the acyclic analog. The consid-
erable difference in velocity constants is due al-
most 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 pri-
marily 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 sys-
tems 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 hydrol-
ysis of tetramethylene chlorohydrin[12,13] to form a
five-membered transition state, *i.e.*
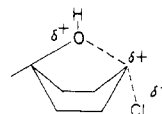
This mechanism is similar to that proposed to ac-
count for the 20% yield of *trans*-4-methoxycyclo-
hexyl acetate in the acetolysis of *trans*-4-methoxy-
cyclohexyl-*p*-toluene sulfonate.[1] On the other
hand it is not unreasonable to attribute the forma-
tion of the 1,4-epoxide and the 3-cyclohexenol 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.
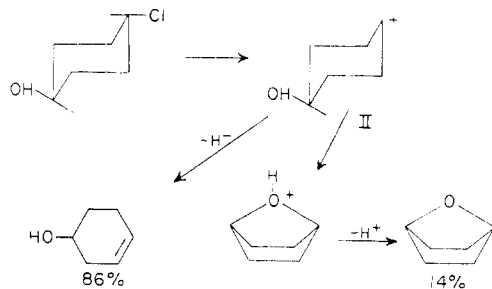
In considering these alternative interpretations, it was of interest to observe in this Laboratory that a 0.003 M solution of cyclohexyl chloride at 80° hydrolyzed as rapidly as the trans-4-chlorocyclohexanol. It is also to be noted that the acetolysis of cyclohexyl p-toluenesulfonate[14] proceeds at 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.

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]

Expt.	$FeCl_3$, 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