229. Stereochemistry of the Conversion of 1,3-Chloroalcohols in Alkaline Medium

The Chemistry of 1,3-Bifunctional Systems. XXII

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Summary

The transformations of isomeric 1,3-chloroalcohols **1–4**, with cyclohexane skeleton, were studied in aqueous solution containing barium hydroxide. As regards the compounds with *cis*-configuration, **1** gives the oxetane **5** by intramolecular nucleophilic substitution, while **3** gives the unsaturated alcohols **7** and **8** by elimination. In the case of the *trans*-isomers **2** and **4**, fragmentation reactions occur in competition with elimination. The main reaction kinetic parameters of the transformations of the four compounds were determined.

We earlier reported results obtained during investigations of the reactions of aliphatic 1,3-chloroalcohols with alkali [1] [2]. Depending on the structure of the chloroalcohol, four reaction directions were observed, which could also occur in parallel with one another. These were: the formation of oxetanes by intramolecular nucleophilic substitution; the formation of unsaturated alcohols by elimination; the formation of diols by nucleophilic substitution; and fragmentation reactions accompanied by the formation of olefins and oxo compounds. The significance of research into this topic is demonstrated by a number of important results [3–7]. *Grob et al.* [8] [9] have dealt in detail with the conditions for the four possible reactions to proceed simultaneously, with the conditions for one or other reaction path to become predominant, and in particular with the theory of the fragmentation reactions. In our work we selected the four cyclohexane skeleton 1,3-chloroalcohol isomers **1–4** (see *Scheme 1*) as model compounds, in order to be able to obtain further data on the steric and stereoelectronic conditions relating to the individual reaction directions, and especially the fragmentation reactions.

Results. - On the basis of ^{1}H-NMR. examinations [10], the configurations and conformations of the isomers **1–4** may be given as follows:

In the case of the *trans*-isomers **2** and **4**, the functional groups are equatorial, and the ring is free from conformational motion. In the *cis*-isomers **1** and **3**, the hetereoatom is axial, and the chair conformation is distorted to a certain extent.

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Table 1. *Product composition after alkaline reaction* (mol %)

Compound	**5**	**6**	**7**	**8**	Cyclohexene	Diol	Polymer	Unidentified
1	85	8	0	0	0	5	0	2
2	0	17	0	0	0	8	62	13
3	0	0	83	7	0	0	0	10
4	0	0	0	40	54	0	0	6

Table 2. *Kinetic data for reactions of* **1**–**4**

Compound	Temp. [°C]	OH^- [g.-equiv/l][a])	Chloroalcohol [mol/l][a])	k [l/mol.min]	ΔH^+ [kcal/mol]	ΔS^+ [cal/mol. degree]
1	90	0.01480	0.01002	$5.37 \cdot 10^{-2}$		
	95	0.01806	0.01006	$8.14 \cdot 10^{-2}$	21.3	2.1
	100	0.01020	0.01020	$1.25 \cdot 10^{-1}$		
2	90	0.01623	0.01006	$1.65 \cdot 10^{-2}$		
	95	0.01806	0.01007	$2.60 \cdot 10^{-2}$	21.7	0.9
	100	0.01480	0.01007	$3.93 \cdot 10^{-2}$		
3	80	0.01612	0.01004	$5.57 \cdot 10^{-2}$		
	85	0.01612	0.01004	$8.12 \cdot 10^{-2}$		
	90	0.01612	0.01006	$1.22 \cdot 10^{-1}$	20.3	1.1
	95	0.01612	0.01006	$1.97 \cdot 10^{-1}$		
4	80	0.01612	0.01002	$1.53 \cdot 10^{-1}$		
	85	0.01612	0.01002	$2.37 \cdot 10^{-1}$	19.3	0.2
	90	0.01612	0.01008	$3.53 \cdot 10^{-1}$		
	95	0.01612	0.01014	$5.11 \cdot 10^{-1}$		

[a]) Initial concentrations

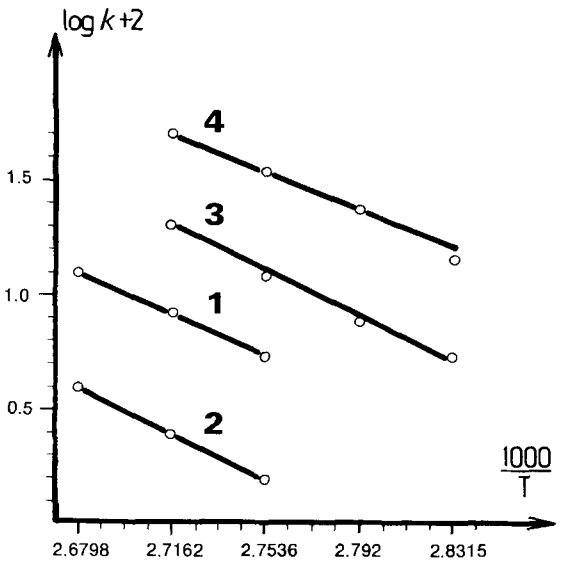
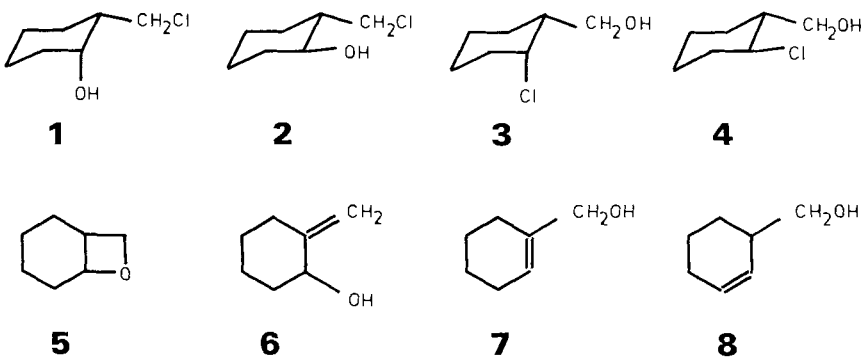


Figure. *Dependence of the rate of the alkaline reaction of* **1**–**4** *as a function of the temperature*

Although the reactions of some cyclic 1,3-haloalcohols in alkali have been dealt with in detail [6] [11–14], the transformations of the four isomers in question under the same experimental conditions, and the reaction kinetics of these transformations, have not been investigated, However, some observations on the behaviour of the individual isomers under alkaline conditions have been described [15–19]. Our experimental results are given in *Tables 1* and *2* and in the *Figure.* In spite of the fact that there were differences in the reactant concentrations, in the reaction kinetic measurements and in the preparative experiments performed to establish the product composition (see Experimental Part), the corresponding experimental data may be compared, since we have demonstrated that the reaction directions under the reaction kinetic conditions agreed with the results of the preparative experiments (the higher alkali concentration chosen in the preparative experiments can be explained by the simpler working up of the reaction product). We similarly proved that each of the products formed in the alkaline hydrolysis is a primary reaction product; secondary reactions did not occur.

Discussion. – On the basis of our experimental data, and relying on the relevant literature data and the known general regularities, we may write the reaction pathways outlined in *Schemes 1–4* for the transformations of compounds **1–4**.

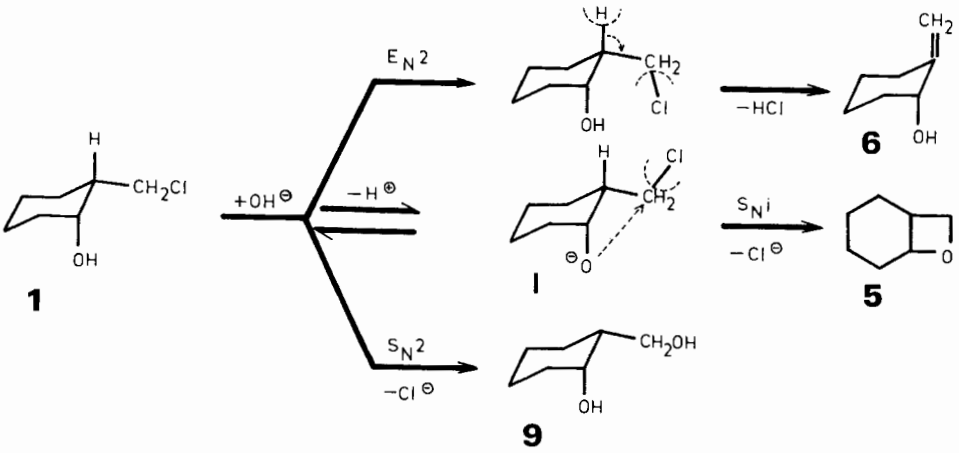
Scheme 1



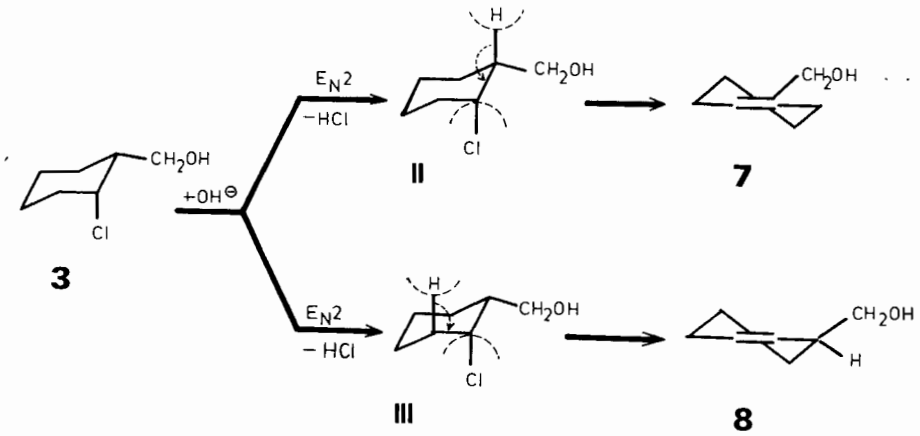
In the case of **1**, *cis*-2-chloromethylcyclohexanol *(Scheme 1)*, the reactions involving E_N2 and S_N2 mechanisms can be regarded as side-reactions; the main reaction direction is the ND_1-($^-$O-4) reaction taking place in the conjugated base transition state I [5], which leads to formation of the oxetane **5**[2]) *(Scheme 2)*. The occurrence of the reaction is promoted by the fact that, as a consequence of the slightly twisted conformation of the cyclohexane skeleton [10], the negatively-charged O-atom comes into close proximity to the C-atom of the chloromethyl group. The pre-

[2]) The study of the structure of **5** by means of various physical methods is under way. The preliminary results indicate that the cyclohexane skeleton is strongly distorted.

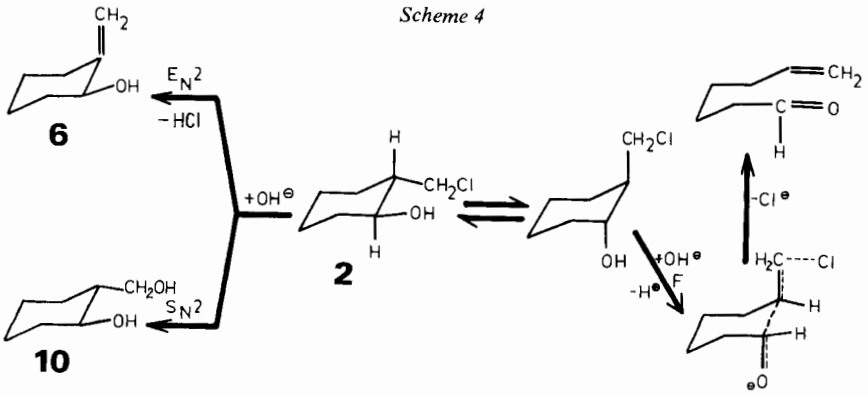
Scheme 2



Scheme 3



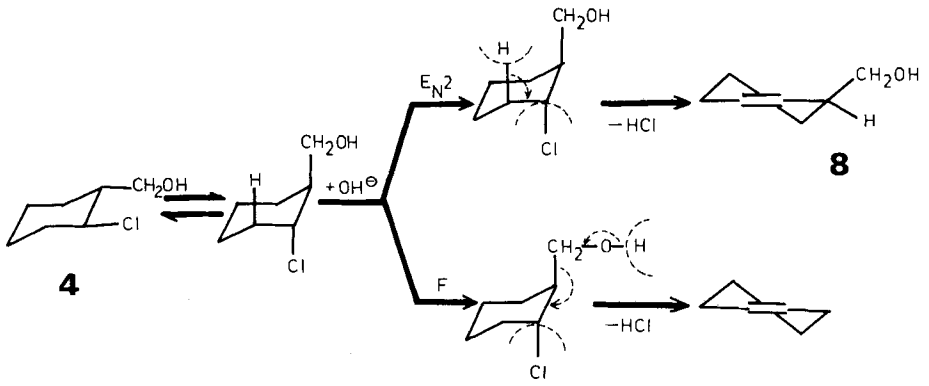
Scheme 4



dominance of the reaction with the S_Ni mechanism is also caused by the absence of the stereochemical conditions necessary for the faster fragmentation and elimination processes to take place: in **1** there is no 'antiperiplanar orientation of an oxygen lone pair and the C–Cl bond with respect to the C(1)–C(2) bond' [7], and therefore *F* can not occur (s. *Scheme 5*). The stereochemical conditions of the E_N2 reaction are likewise unfavourable, since in the case of the conformation containing axial eliminating groups (H^+ and Cl^-) the two bulky groups (OH and Cl) are in a 1,3-diaxial arrangement.

In accordance with the general regularity, **3** (= *cis*-(2-chlorocyclohexane)methanol) gives in alkaline medium the unsaturated alcohols **7** and **8** in an E_N2 reaction, since, compared to the chlorine atom, two *trans* axial H-atoms are to be found in the molecule II and III. Of the two possible eliminations, the formation of the unsaturated alcohol **7** predominates; this may be explained by its higher thermodynamic stability.

Scheme 5



In the case of **2** (= *trans*-2-chloromethylcyclohexanol), the main process is rapid fragmentation, for which the conditions are given [7]. From the presence of the vinyl band and the weak carbonyl band in the IR. spectrum of the crude reaction product, it was concluded that unsaturated aldehyde is formed as a product of fragmentation, and that this gives a polymerization product under alkaline conditions [17]. Besides the *F*-reaction, *E*2- and S_N2-reactions take place too, similarly as for **1**. The stereochemical conditions of the *E*2-reaction are more favourable for **3** (compared to **1**), for there is a H-atom in 1,3-diaxial interaction with the eliminating Cl-atom, and not a bulkier OH group as in the case of **1**.

With **4** (= *trans*-(2-chlorocyclohexane)methanol) two mutually competitive reactions occur: elimination and fragmentation. The stereochemical conditions of the two reactions have been described above. Their favourable natures are well illustrated in *Scheme 4*.

The foregoing conclusions are fully supported by the results of the reaction kinetic measurements.

Experimental Part

The chloroalcohol isomers **1**-**4** selected as model compounds were prepared as in [10]. Kinetic measurements were performed under conditions described previously [1]. Reaction products were identified by gas chromatography: *Carlo Erba* Fractovap P chromatograph, 2 m column, 15% *Carbowax* 1500 liquid phase on *Chromosorb* W support, 150 and 180°, 60 ml/min hydrogen, 5 µl injected material. Authentic unsaturated alcohols **6**, **7** and **8** necessary for identification, as well as diols **9** and **10**, were prepared by known methods [20] [21] [17].

The experimental conditions of the preparative-scale alkaline hydrolysis will be presented on the example of **1**.

Hydrolysis of **1**, cis-*2-chloromethylcyclohexanol (preparation of* **5** = cis-*7-oxabicyclo[4.2.0]octane).* A mixture of 4 g (0.026 mol) **1** and 210 ml of aqueous 4.5% $Ba(OH)_2$ solution was heated at 140° in a sealed bomb-tube for 6 h. After cooling and opening of the tube, the mixture was extracted with ether, the ether solution was dried and evaporated, and the crude product (3.5 g) was distilled after gas chromatographic examination. Yield of **5** 2.4 g (82%), b.p. 78-80°/60 Torr, $n_D^{22} = 1.4600$ ([17]: b.p. 35.5°/7 Torr, $n_D^{20} = 1.465$).

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