Studies on the Reaction between Chloral and Alcohols

III. Further Investigations on the Mutarotation of Hemiacetals of Chloral and Various Optically Active Secondary Alcohols

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The mutarotation of certain optically active chloral hemiacetals has been investigated. All the optically active alcohols used in the present investigation possess only one asymmetric centre and no polar or aromatic groups. Further, the asymmetric centre is placed in an open chain. It is shown that they all follow the rule that the sign of the rate of change in molecular rotation, $d[\varphi]/dt$, of the hemiacetal mixture is negative, if the steric arrangement of the large, medium and small groups together with the hydroxyl group is right-handed.

An attempt has been made to rationalize the present findings. It is proposed that the mutarotation mechanism is analogous to that of the well-known $\alpha - \beta$ isomerization of glucose. On this basis, it is possible to explain the anomalous behaviour of the hemiacetals from optically active α-methylbenzyl alcohol or ethyl lactate, previously reported.

In previous papers,[1,2] it was reported that acetic acid catalyzed the formation of chloral hemiacetals (1) in hydrocarbons or methylene chloride as solvents.
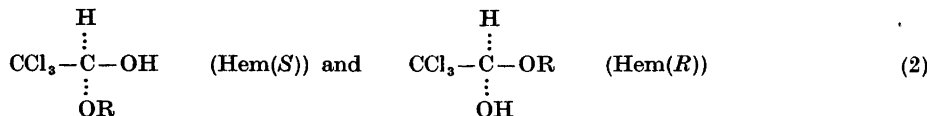
$$\text{Chl} + \text{ROH} \rightleftharpoons \text{Hem} \qquad (1)$$
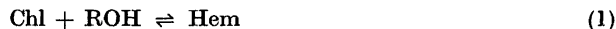
Chl = chloral
ROH = various primary, secondary, and tertiary alcohols
Hem = hemiacetal

Hem actually consists of a mixture of two hemiacetals (2),

$$
\begin{array}{cccc}
\quad\ \ \text{H} & & \quad\ \ \text{H} & \\
\quad\ \ | & & \quad\ \ | & \\
\text{CCl}_3-\text{C}-\text{OH} & (\text{Hem}(S))\ \text{and} & \text{CCl}_3-\text{C}-\text{OR} & (\text{Hem}(R)) \qquad (2)\\
\quad\ \ | & & \quad\ \ | & \\
\quad\ \ \text{OR} & & \quad\ \ \text{OH} &
\end{array}
$$

which, if derived from an optically active alcohol, are diastereomers.

The reaction of an optically active alcohol was in general accompanied by a continuous variation of the molecular rotation $[\varphi]$ of Hem (mutarotation).

Table 1. Stereoformulae and the corresponding signs of $d[\varphi]/dt$ of various chloral hemiacetals made from optically active secondary alcohols.

Name of alcohol	Relative bulk			Sequence	Sign of $d[\varphi]/dt$		Configuration, of the alcohol
	L	M	S		Predicted	Observed	
(R)-2-Butanol	CH_3CH_2	CH_3	H	L→M→S	negative	negative	F [b]
(S)-2-Butanol	CH_3CH_2	CH_3	H	L←M←S	positive	positive	F
(R)-2-Pentanol	$CH_3CH_2CH_2$	CH_3	H	L→M→S	negative	negative	F
(S)-2-Pentanol	$CH_3CH_2CH_2$	CH_3	H	L←M←S	positive	positive	F
(R)-2-Hexanol	$CH_3CH_2CH_2CH_2$	CH_3	H	L→M→S	negative	negative	F
(S)-2-Hexanol	$CH_3CH_2CH_2CH_2$	CH_3	H	L←M←S	positive	positive	F
(R)-2-Octanol [a]	$CH_3(CH_2)_4CH_2$	CH_3	H	L→M→S	negative	negative	F
(S)-2-Octanol [a]	$CH_3(CH_2)_4CH_2$	CH_3	H	L←M←S	positive	positive	F
(R)-3-Hexanol	$CH_3CH_2CH_2$	CH_3CH_2	H	L→M→S	negative	negative	F
(S)-3-Hexanol	$CH_3CH_2CH_2$	CH_3CH_2	H	L←M←S	positive	positive	F
(R)-3-Heptanol	$CH_3CH_2CH_2CH_2$	CH_3CH_2	H	L→M→S	negative	negative	F
(S)-3-Heptanol	$CH_3CH_2CH_2CH_2$	CH_3CH_2	H	L←M←S	positive	positive	F
(R)-3-Methyl-2-butanol	CH_3CH with CH_3	CH_3	H	L→M→S	negative	negative	F
(S)-3-Methyl-2-butanol	CH_3CH with CH_3	CH_3	H	L←M←S	positive	positive	F
(R)-4-Methyl-2-pentanol	CH_3CHCH_2 with CH_3	CH_3	H	L→M→S	negative	negative	F
(S)-4-Methyl-2-pentanol	CH_3CHCH_2 with CH_3	CH_3	H	L←M←S	positive	positive	F
(R)-2-Methyl-3-pentanol	CH_3CH with CH_3	CH_3CH_2	H	L→M→S	negative	negative	F
(S)-2-Methyl-3-pentanol	CH_3CH with CH_3	CH_3CH_2	H	L←M←S	positive	positive	F
(R)-3,3-Dimethyl-2-butanol	CH_3C with CH_3, CH_3	CH_3	H	L→M→S	negative	negative	F
(S)-3,3-Dimethyl-2-butanol	CH_3C with CH_3, CH_3	CH_3	H	L←M←S	positive	positive	F
(R)-1-Cyclohexyl-ethanol	cyclohexyl	CH_3	H	L→M→S	negative	negative	F
(S)-1-Cyclohexyl-ethanol	cyclohexyl	CH_3	H	L←M←S	positive	positive	F
(R)-1-Phenylethanol [a]	phenyl	CH_3	H	L→M→S	negative	positive	E [c]

Table 1. Continued.

(S)-1-Phenylethanol [a]		CH$_3$	H	L←M←S	positive	negative	E
(S)-Ethyl lactate [a]	COOC$_2$H$_5$	CH$_3$	H	L←M←S	positive	negative	E

[a] Investigations of these alcohols have been reported in a previous paper.[2]
[b] Freudenberg.[3]
[c] Eliel.[4]

In almost all cases studied, it was found that the sign of $d[\varphi]/dt$ was determined by the spatial arrangement of the groups L (large), M (medium), S (small) and OH surrounding the asymmetric carbon in the alcohol (3).

As already reported,[2] a right-handed spatial arrangement L→M→S (as viewed from the asymmetric carbon atom) makes $d[\varphi]/dt < 0$ and *vice versa*. Only few exceptions to this rule have been found.[2]

The aim of the present paper is to confirm this rule by considering the behaviour of 20 optically active secondary alcohols listed in Table 2 of the following type (3).

$$\begin{array}{c} L \\ \vdots \\ S-C-OH \\ \vdots \\ M \end{array} \qquad (3)$$

All these alcohols, characterized by containing only one asymmetric centre had no polar or aromatic groups; further, the asymmetric centre is not placed in an alicyclic ring. Table 1 shows that it is possible in nearly all cases to predict the sign of $d[\varphi]/dt$ on the basis of a purely steric estimate. The validity of the above-mentioned rule is thus strongly supported. Investigations of alicyclic alcohols containing more than one asymmetric centre placed in an alicyclic ring will be reported later.

The mutarotation can be explained as an interconversion of the two epimeric hemiacetals (4).

$$\text{Hem}(R) \rightleftharpoons \text{Hem}(S) \qquad (4)$$

Processes of this kind occur if two different products can be formed by parallel reversible reactions from a common precursor (5).

$$\text{Hem}(R) \rightleftharpoons \text{Chl} + \text{ROH} \rightleftharpoons \text{Hem}(S) \qquad (5)$$
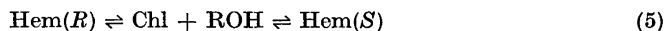
Initially, a non-equilibrium mixture of Hem(R) and Hem(S) is formed (kinetic control), which then tends towards equilibrium (thermodynamic control).

For discussion of the present epimerization, a model has been constructed (Fig. 1). The transition states proposed are hypothetical. It is postulated that the first step in hemiacetal formation is a reaction between chloral and acetic acid, by which a chloral-acetic acid complex, Chl···HA, is formed. This assumption is based on kinetic studies of the acid-catalysed formation
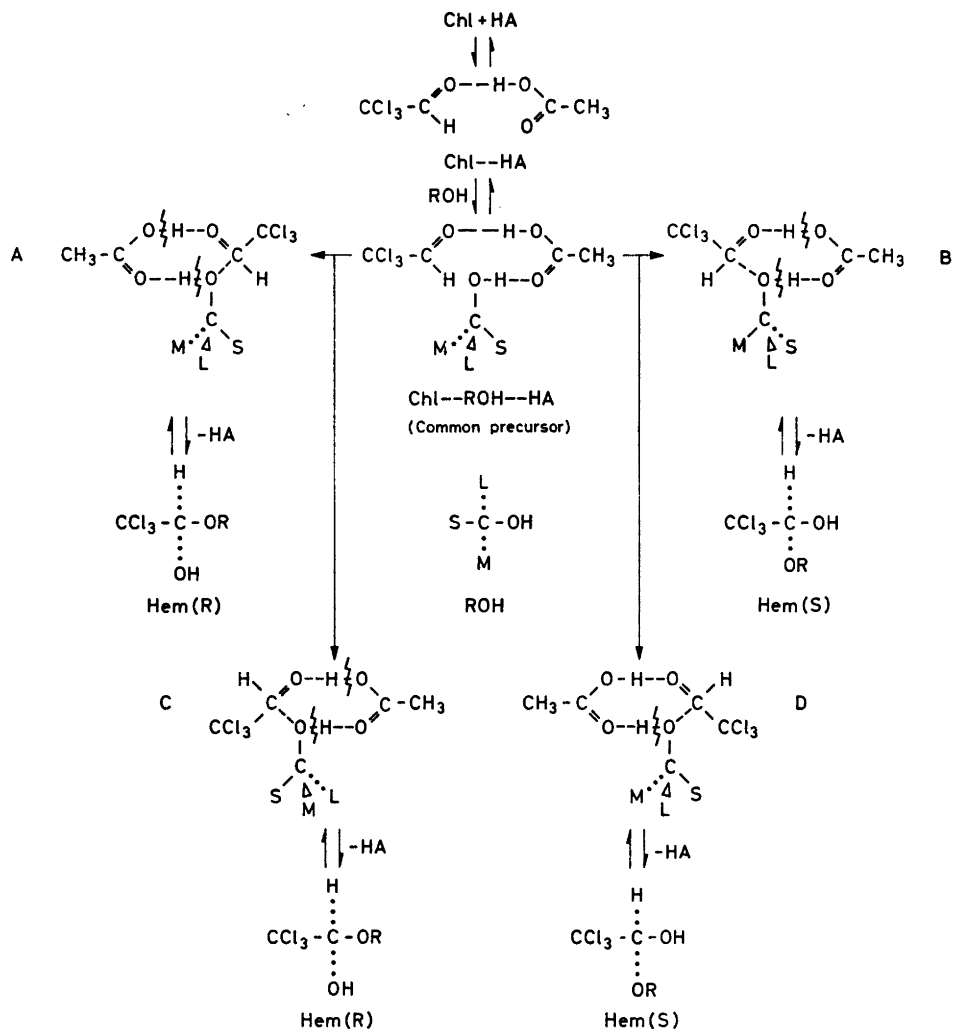
Fig. 1. Possible reaction paths in hemiacetal formation.

of hemiacetals from chloral and various alcohols (to be published in subsequent papers). These investigations indicate that the rate of disapperance of chloral is proportional only to the concentration of chloral and to the square-root of the concentration of acetic acid (because acetic acid is dimeric in inert solvents). The rate-determining step seems therefore to be a reaction between chloral and acetic acid.

The next step concerns the reaction between Chl···HA and the alcohol, ROH, by which a second complex (henceforth called the "common precursor"),

Table 2. The experimental conditions of the mutarotation of the chloral hemiacetals.

Name of the alcohol	Concentrations (mol/l) of			α_D of the alcohol [a]
	Chl	ROH	HA	
(R)-2-Butanol	0.02	0.02	0.02	−4.30
(S)-2-Butanol	0.02	0.02	0.02	8.67
(R)-2-Pentanol	0.02	0.02	0.02	−4.36
(S)-2-Pentanol	0.02	0.02	0.02	6.45
(R)-2-Hexanol	0.02	0.02	0.02	−6.90
(S)-2-Hexanol	0.02	0.02	0.02	7.50
(R)-3-Hexanol	0.2	0.2	0.2	−1.25
(S)-3-Hexanol	0.2	0.2	0.2	1.18
(R)-3-Heptanol	0.2	0.2	0.2	−2.32
(S)-3-Heptanol	0.2	0.2	0.2	1.71
(R)-3-Methyl-2-butanol	0.02	0.02	0.02	−1.34
(S)-3-Methyl-2-butanol	0.02	0.02	0.02	3.67
(R)-4-Methyl-2-pentanol	0.02	0.02	0.02	−11.13
(S)-4-Methyl-2-pentanol	0.02	0.02	0.02	12.88
(R)-2-Methyl-3-pentanol	0.2	0.2	0.2	−4.30
(S)-2-Methyl-3-pentanol	0.2	0.2	0.2	9.30
(R)-3,3-Dimethyl-2-butanol	0.02	0.02	0.02	−3.73
(S)-3,3-Dimethyl-2-butanol	0.02	0.02	0.02	3.35
(R)-1-Cyclohexylethanol	0.02	0.02	0.02	−3.51
(S)-1-Cyclohexylethanol	0.02	0.02	0.02	7.00

[a] α_D refers to the rotation of the pure liquid measured in a 1 dm tube.

Chl···HA···ROH, is formed. Ring closure of this compound will establish steric correspondence (asymmetric induction) between the centre that becomes asymmetric in the chloral part and the groups L, M and S in the alcohol part. Cyclic structures of similar character have been suggested by Bell in connection with his studies on the acid-catalysed hydration of various aldehydes.[5]

Formally, this ring closure may give rise to four different transition states, A, B, C and D. But strong steric interactions between the bulky trichloromethyl group and even the smallest group, S, make C and D very improbable transition states and their contribution to hemiacetal formation is therefore supposed to be negligible compared with the contributions from A and B. In B the most

bulky group, L, is placed nearer the ring atoms than in A, so that A is considered to be more stable. Therefore, the initial rate of hemiacetal formation through A is higher than through B.

The hemiacetals arising from the two optically active alcohols $C_6H_5-CHOH-CH_3$ and $CH_3-CHOH-COOC_2H_5$ show an anomalous behaviour as previously described.[2] In these two examples, the most bulky group is polar, and the anomaly may be explained by assuming an attraction between the polar group and the trichloromethyl group in the cyclic transition states considered. In this case, the formation of C and D will be favoured compared with the formation of A and B. If D owing to steric reasons (the steric effect is now a second-order effect) is more stable than C, the direction of the epimerization will be opposite to that predicted from steric reasons before. This idea is further supported by the fact that the mutarotation of the chloral hemiacetals of optically active 1-cyclohexylethanol (Table 1) proceeds in a normal way.

Since, by hypothesis, the kinetic control is determined by the relative activation energies of the reactions through A and B, it should be possible to establish a measure of the relative steric bulkiness of the substituents used. Attempts based on measurements of the initial slopes of the $[\varphi]$ versus time curve failed, however, primarily because of great uncertainty in $[\varphi]$ at the beginning of the reaction. We hope to be able to proceed along these lines by using NMR-techniques.*

From such experiments, we hope to be able to conclude that when L and M are large, the epimerization will no longer be sensitive to changes of their size or branching in a region distant from the ring in the transition states A and B.

EXPERIMENTAL

The conditions under which the various epimerizations were carried out are listed in Table 2. The same table also reports the optical purity of the resolved alcohols. Details about experimental conditions and treatment of the results are given in previous papers.[1,2] In the present study, the solvent used was heptane.

The enantiomers of the different alcohols were in all cases prepared by resolution of the brucine salts of their hydrogen phthalates.[6]

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* Preliminary NMR measurements on mixtures of *sec*-butyl alcohol, acetic acid and chloral indicate the occurrence of two signals from the former aldehydic proton in the hemiacetal.