Studies of the Reaction between Chloral and Alcohols

I. The Mutarotation of Chloral (R)-(-)-Mentholhemiacetal

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The acid catalyzed reaction between chloral and an optically active alcohol ROH, yields a mixture of two diastereomeric (epimeric) hemiacetals H(R) and H(S)

The symbols R and S are used in accordance with the rules formulated by Cahn, Ingold, and Prelog¹ for naming configurations of optically active substances. In the case of an asymmetric synthesis, $[\text{H(R)}]/[\text{H(S)}]$ will be different from 1 due to the presence of an optically active center in the alcohol.

Fig. 1A. The observed UV absorption, vs. reaction time, by 293 mμ, of a mixture of chloral (2×10^{-2} M), (R)-(-)-menthol (2×10^{-2} M), and acetic acid (2×10^{-4} M); in hexane.

B. The observed rotation for the same reaction mixture as in 1A.

An investigation has been made on the reaction between chloral and (R)-(-)-menthol in hexane solution with acetic acid as catalyst. The reaction was followed by ultraviolet spectroscopy and polarimetry. The process was shown to consist of at least two reactions.

As shown in Fig. 1A the transformation of chloral is almost complete in 200 min, by which time the concentration of chloral is one third of its initial value of $[\text{chloral}]_0$. The concentration of the hemiacetal at the time t , $[\text{H}]_t$, may now be calculated using the equation:

$$[\text{H}]_t = [\text{H(R)}]_t + [\text{H(S)}]_t = [\text{chloral}]_0 - [\text{chloral}]_t \quad (2)$$

The concentration of chloral, $[\text{chloral}]_t$, was determined by intensity measurements on the C=O absorption at 293 mμ.

When the optical rotation at 364 mμ, of the same reaction mixture, was plotted against the time, Fig. 1B, the change in rotation was observed to continue after the concentration of chloral was constant. Using the method of Hudson², $\log [(a - a_M)_t - (a - a_M)_\infty]$ was plotted against t (Fig. 2), where a is the measured rotation and a_M the calculated rotation for the untransformed menthol at the time t . The straight-line relationship obtained, indicates that reaction (1) is followed by

Fig. 2. $\log_{10}[(a - a_M)_t - (a - a_M)_\infty]$ vs. time.

a slow adjustment of the equilibrium (mutarotation):

The total optical rotation of the hemiacetals:

$$\alpha_H = \alpha_H(R) + \alpha_H(S) \quad (4)$$

was used for calculation of the molecular rotation $[\varphi_H] = \alpha_H \times 10 ([H(R)] + [H(S)])^{-1}$ of the hemiacetal mixture. A plot of $[\varphi_H]$ versus the time (Fig. 3) showed a slope different from zero indicating that an asymmetric synthesis had occurred.

The rule of optical superposition has been discussed by Eliel³ who concludes that: "Like functional groups in like surroundings make like contributions to the optical rotation". Applied on this case it may be inferred, that the molecular rotation of an optically active hemiacetal is made up by a contribution $[\varphi_{ROH}]$ from the active center(s) in the ROH component and of contribution $[\varphi_{CH}]$ from the created asymmetric center

$$[\varphi_H(R)] = [\varphi_{ROH}] + [\varphi_{CH}] \text{ and } [\varphi_H(S)] = [\varphi_{ROH}] - [\varphi_{CH}] \quad (5)$$

the sign of $[\varphi_{CH}]$ being unknown.

If the mole fractions of H(R) and H(S) in the hemiacetal mixture are designated x_R and x_S , respectively, the molecular rotation $[\varphi]$ for the mixture can be expressed as:

$$[\varphi] = x_R[\varphi_H(R)] + x_S[\varphi_H(S)] \quad (6)$$

By inserting (5) into (6), one obtains

$$[\varphi] = x_R[\varphi_{ROH}] + x_R[\varphi_{CH}] + x_S[\varphi_{ROH}] - x_S[\varphi_{CH}] \quad (7)$$

But $x_R + x_S = 1$, therefore

$$[\varphi] = [\varphi_{ROH}] + [\varphi_{CH}](2x_R - 1) \quad (8)$$

where $[\varphi_{ROH}]$ is independent of time. By differentiation (8) is transformed into

$$\frac{d[\varphi]}{dt} = 2[\varphi_{CH}] \frac{dx_R}{dt} \quad (9)$$

Fig. 3 shows that $d[\varphi]/dt$ is less than zero when the alcohol used is (R)-(-)-menthol.

Prelog's⁴ rule of asymmetric synthesis applied to the optically active hemiacetals indicates that the configuration of the asymmetric centers in the alcohol, and especially that of the carbon atom carrying the hydroxyl group, will be correlated with the configuration of the optically active center created. From this rule and the relationship given in eqn. (9) it follows that for an alcohol with a given configuration the sign of dx_R/dt will always be the

Fig. 3. The calculated rotation $[\varphi]$ vs. reaction time of the hemiacetal mixture.

same. Consequently, the R-configuration is to be attributed to alcohols when $d[\varphi]/dt < 0$.

It is accordingly proposed, that combined UV and polarimetric investigations might be useful for determining the absolute configuration of asymmetric alcohols.

Preliminary experiments seem to indicate a similar effect for optically active amines.

Further investigations, using alcohols and amines with known configurations, are in progress.

Experimental. The concentrations of chloral and menthol were both 2×10^{-2} M and that of acetic acid (analytical grade) was 2×10^{-4} M in all experiments. Hexane was used as solvent.

Polarimetric measurements were performed at 25.0°C on a Perkin-Elmer polarimeter model 141. The UV measurements were carried out at 25.0°C on a Perkin-Elmer Spectrophotometer, model 37UV.

The chloral was purified by treatment with concentrated H_2SO_4 , followed by distillation over freshly heated CaO.

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