Observation and quantification of a chiral medium induced difference in rate of enantiomerization

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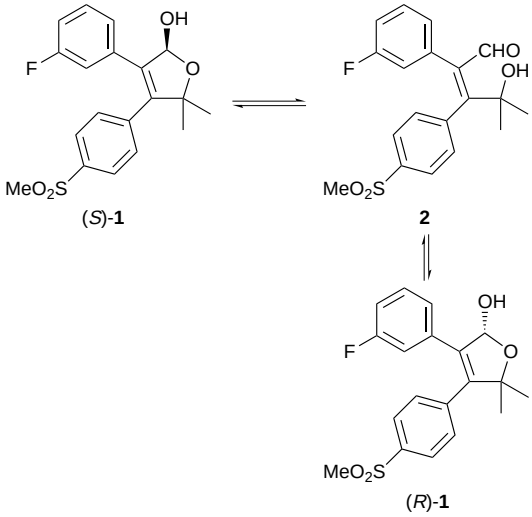
A chiral stationary phase HPLC column has been used both to separate the enantiomers of a γ-lactol and also to observe the rate of enantiomerization of the individual enantiomers; the rate of enantiomerization differed for both enantiomers in the presence of the chiral stationary phase.

A chiral medium interacting with a pair of enantiomers results in energetically differentiated, diastereomeric complexes and this differential stabilization of the enantiomers will contribute to the different reaction rates of the enantiomers in the chiral medium.[1] Chiral stationary phases (CSPs) have developed into very useful and reliable tools for the determination of the enantiomeric composition of mixtures. One of the most successful types of chiral stationary phases for HPLC and SFC (supercritical fluid chromatography) is prepared from crystalline carbamoylated or acylated cellulose or amylose deposited on SiO_2 (commercially available as Chiralcel and Chiralpak columns).[2]

The combination of these columns with the use of supercritical CO_2 as eluent is a particularly powerful tool for enantiomer separation.[3] The chromatographic separation of the enantiomers results from the formation of energetically different diastereomeric complexes between the enantiomers and the CSP and it would therefore appear reasonable to expect that enantiomers react at different rates in the presence of a chiral stationary phase.[4] We have examined this premise using the enantiomerization of γ-lactol **1** as a model reaction (Scheme 1) where (*R*)-**1** and (*S*)-**1** are chiral but the reaction intermediate hydroxy aldehyde **2** is not.†

Examination of **1** by ^{1}H NMR spectroscopy shows that it is exclusively present in the closed form, as would be expected from a *gem*-dimethyl substituted five-membered lactol. The enantiomers of **1** are separated on a Chiralpak AD column [25 cm length, supercritical CO_2 at 300 bar with 8% modifier (Pr^iOH–H_2O 95 : 5), flow 1 ml min^{-1}, 40 °C, retention time



Scheme 1

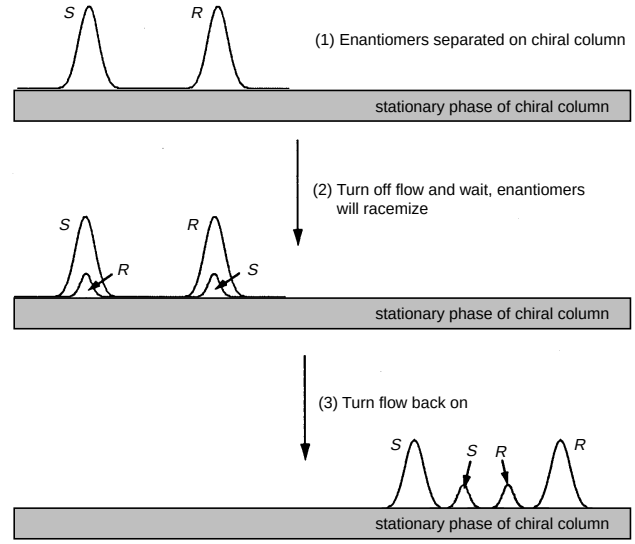


Fig. 1

t_R = 21.0 min, t_S = 29.8 min, dead volume time t_0 = 3.3 min, assignment of first peak as the *R*-isomer is arbitrary].‡ The procedure for measuring the rates of enantiomerization is described in Fig. 1. The flow of the mobile phase is turned off at a fraction of the regular run time when the enantiomers are already spatially separated on the column (*e.g.* at t_X = 0.33 t_R). The enantiomers are then allowed to partially enantiomerize in the presence of the chiral medium for a period of time *t* before the flow resumes.[5] A four-peak pattern is obtained, with the inside peaks resulting from the enantiomerization of the previously separated peaks.§

By varying the time *t* for which the flow is turned off, the rate of enantiomerization of each enantiomer in the presence of the chiral stationary phase can be determined. A plot of conversion R/R_0 and S/S_0 *vs. t* (Fig. 2) shows that the enantiomers react at

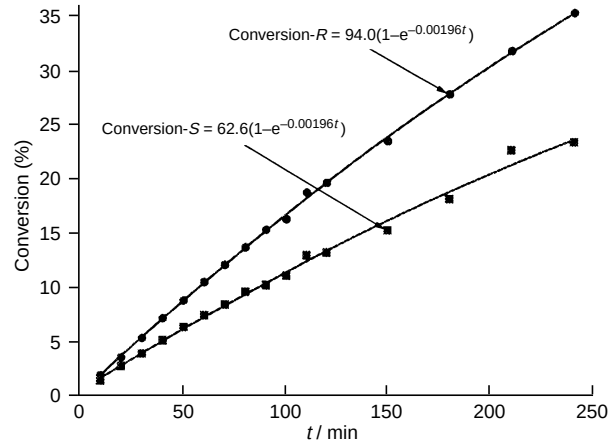


Fig. 2

different rates! Least square fit of the data to the kinetic equations of a reversible first-order system gives $k_R = 1.19 \times 10^{-3}$ min^{-1} and $k_S = 7.75 \times 10^{-4}$ min^{-1}.¶ This rate difference can be used to calculate the difference in Gibbs energy of activation for the enantiomerization of (*R*)- and (*S*)-**1** in the presence of the chiral medium at 40 °C: $\Delta G^{\ddagger} = \Delta G_R^{\ddagger} - \Delta G_S^{\ddagger} = -RT\ln k_R/k_S = -1.10$ kJ mol^{-1}. However, the differential binding energy of the two enantiomers on the CSP is responsible for the separation of the enantiomers on the column. It can be calculated from the observed chromatogaphic separation factor $\alpha = (t_S - t_0)/(t_R - t_0) = 1.50$ according to $\Delta G = -RT\ln \alpha$ and gives $\Delta G = -1.06$ kJ mol^{-1} (40 °C). As the intermediate hydroxy aldehyde **2** is achiral, the difference in Gibbs energy of activation $\Delta G^{\ddagger}$ obtained from the kinetic measurements will result from the differential binding strength of the two enantiomers of **1** on the chiral column as long the influence of the chiral medium on the energy of the transition states leading to the achiral intermediate **2** is negligible. Indeed, the value obtained from the kinetic measurement ($\Delta G^{\ddagger} = 1.10$ kJ mol^{-1}) is in good agreement with the number obtained from the chromatographic separation factor ($\Delta G = 1.06$ kJ mol^{-1}). Thus, the different rates of enantiomerization are caused by the differential binding of the enantiomers of the lactol **1** with the chiral medium and the transition states leading from **2** to the enantiomers of **1** are of nearly identical energy in the presence of the chiral medium.

In summary, we have demonstrated that the enantiomers of a chiral compound react at different rates in the presence of a CSP and that this rate difference is caused by the differential energetic stabilization of the individual enantiomers of the γ-lactol by the chiral medium. This example adds to the list of examples[6] where enantiodifferentiating reactivity is achieved by performing a reaction in the chiral environment provided by a chiral host.

Footnotes and References

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† An alternative mechanism would involve the oxonium ion, which is also achiral.

‡ All experiments were performed with the Hewlett Packard SFC (HP 1205) system with a HP 1050 diode array detector and instrument control and data analysis with the HP Chemstation Software. The Chiralpak AD column was obtained from Chiral Technologies, Exton, PA 19341. The lactol **1** was prepared by DIBAL-H reduction of the corresponding lactone.

§ The retention times of the middle peaks can be calculated as $t_R + (t_R - t_X)(t_S - t_R)/t_R$ and $t_R + t_X(t_S - t_R)/t_R$, where the retention times of the outer peaks are t_R and t_S, and the flow is stopped at time t_X. The timespan t during which the flow is stopped is obviously subtracted from the observed times and the issues involved with regaining equilibrium when the flow of the column is resumed are ignored. This is reasonable as the Hewlett Packard SFC instrument controls the pressure at the end of the column.

¶ The data were fitted to the equations of a reversible first-order reaction [eqns. (1) and (2)]

$$\text{conversion-}S = k_R/(k_R + k_S)\,[1 - e^{-(k_R + k_S)t}]$$

$$\text{conversion-}R = k_S/(k_R + k_S)\,[1 - e^{-(k_R + k_S)t}]$$

to give $k_R + k_S = 1.96 \times 10^{-3}$ min^{-1} and $k_R/k_S = 1.53$.

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