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Influence of Cholesteric Solvents on the Kinetics of Schiff Base Formation from Enantiomeric Amines

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In order to examine the influences of both the macroscopic and microscopic chirality of cholesteric media on a chemical process, the kinetics of the bimolecular reaction between *p*-ethoxybenzaldehyde (EBA) and enantiomeric S-(−)- or R-(+)-1-phenylethylamine (PEA) were studied in right-and left-handed cholesteric liquid crystals. The reaction was followed using two methods: (1) continuous monitoring of changes in pitch, and (2) monitoring changes in the intensity of IR absorption peaks, related to C=O and CH=N bonds. Differences between rates and activation parameters were observed when reactions were performed in steroidal cholesteric or chiral nematic solvents, and the effective helical twisting powers (HTP) of S-(−)- and R-(+)-PEA are not equivalent in the employed systems. That is, the reaction rate in the steroidal cholesteric solvent is lower for the enantiomer exhibiting the higher value of HTP. The value of HTP appears to be a guide to the strength of the solute-solvent interaction.

Keywords: Kinetics; enantiomers; Schiff base formation; cholesteric solvents

INTRODUCTION

A remarkable cooperative effect occurs in nematic liquid crystals when chiral solutes are added. The entire medium becomes "twisted"; that is, a macroscopic helicoidal array is established. Quantitatively, the magnitude of the induced helix pitch P depends inversely on the concentration of the chiral species c and its "helical twisting power" β according to the equation $P^{-1} = \beta c$. In this laboratory, the reverse effect is being explored; namely, what effect does a tightly twisted cholesteric solvent exert on solute

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molecules? Can one utilize cholesteric solvents in performing selective stereochemical processes? Although there have been numerous attempts at achieving chiral induction in chemical reactions performed in thermotropic cholesteric liquid crystals there has been little success in achieving asymmetric synthesis [1–6]. What has been learned regarding asymmetric induction in ordered media comes primarily from studies of either topochemically controlled reactions in the solid phase or reactions in chiral micelles [7–9]. It is clear from these studies that achieving chiral control requires strong *local* intermolecular interaction between solute and medium. Thus it appears useful to study the interactions between solute and cholesteric media in a manner which allows one to distinguish and understand both short and long range forces.

In this laboratory, the observation was recently made that there were pronounced non-symmetric effects of enantiomers on the chirality of right- and left-handed cholesteric phases [10]. All of these effects could be explained as being due to specific short-range solute-solvent interactions. In this work, the effect of these differences in short range diastereomeric interaction on the kinetics of the reaction of enantiomeric pairs is explored.

S-(−)- or R-(+)-1-phenylethylamine (PEA) can undergo a simple reaction with an appropriate aldehyde resulting in the formation of a chiral Schiff base. The reaction between S-(−)-PEA and *p*-ethoxybenzaldehyde (EBA) was previously investigated in a steroidal cholesteric solvent in an attempt to develop a simple cumulative thermal dosimeter (time temperature integrator) [11, 12]. In this work, the reaction between S-(−)- or R-(+)-PEA and EBA is studied in cholesteric solvents comprised of molecules of various helicities, where the non-symmetric response of the medium to these enantiomers suggested a difference in short-range coupling between enantiomeric solutes and chiral solvent.

EXPERIMENTAL

Materials

S-(−)- and R-(+)-PEA were purchased from Aldrich and used without purification. The specific optical rotations of the neat compounds were −38.0° and +38.0° respectively, which corresponds to ~96% ee [13]. Several cholesteric matrices with right- and left-handed helices were utilized in this study. Solvent **A** is a left-handed ternary mixture of cholesteryl oleyl carbonate, cholesteryl chloride, and cholesteryl nonanoate in weight ratios

of 2:1.1:0.9. Solvent **B** is a right-handed ternary mixture of *p*-pentylphenyl-*p*-methoxybenzoate, *p*-(2-methyl)butylphenyl-*p*-methoxybenzoate, and *p*-(2-methyl)butylphenyl-*p*-heptylphenylbenzoate in weight ratios of 55:28:17. Solvents **PBS** and **PBR** are left-and right-handed compositions, consisting of binary mixtures of *p*-pentylphenyl-*p*-methoxybenzoate and *p*-pentylphenyl-*p*-pentoxybenzoate in weight ratios of 56.5:37.6, doped with 5.9 wt.% of optically active dopants S 1011 or R 1011 (E.Merck & Co.) respectively. Clearing points and pitches of these compositions are given in a previous paper [10]. "Nematic Phase V" (**NP**)—a eutectic mixture of *p*-methoxy-azoxybenzenes which are *p'* substituted with ethyl and *n*-butyl groups (E.Merck & Co.), was employed for dilution of **A** in order to investigate the solvent effect of the reaction kinetics.

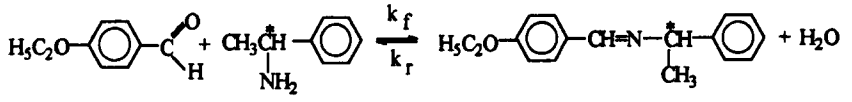
Instruments

Infrared spectra were recorded with a Mattson Instrument FTIR interfaced with a PC, operating with WinFirst software. A Perkin-Elmer 330 UV-VIS spectrophotometer, equipped with a thermostated sample holder was employed to monitor pitch (wavelength of maximum absorption) changes in cholesteric solvents.

RESULTS

IR Spectroscopy

There are two characteristic absorption bands that can be conveniently used to follow kinetics of the studied reaction (Scheme 1): one, at ~ 1702



cm^{-1}, associated with the carbonyl group in EBA and the other, at $\sim 1647.5\ cm^{-1}$, related to the CH=N group in the product S-(−)-or R-(+)-(*p*-ethoxybenzylidene)-α-phenylethylamine (EBPEA).

Figure 1 shows the spectra of the reacting mixture in the range of the characteristic absorption bands and Figure 2 illustrates the kinetic curves for EBA decrease and EBPEA formation as the reaction proceeds in solvent **A**. For this second order reaction, when the initial concentrations of the reagents are equal ($[PEA]_0 = [EBA]_0 = c_0$) and $k_f \gg k_r$, the following rate

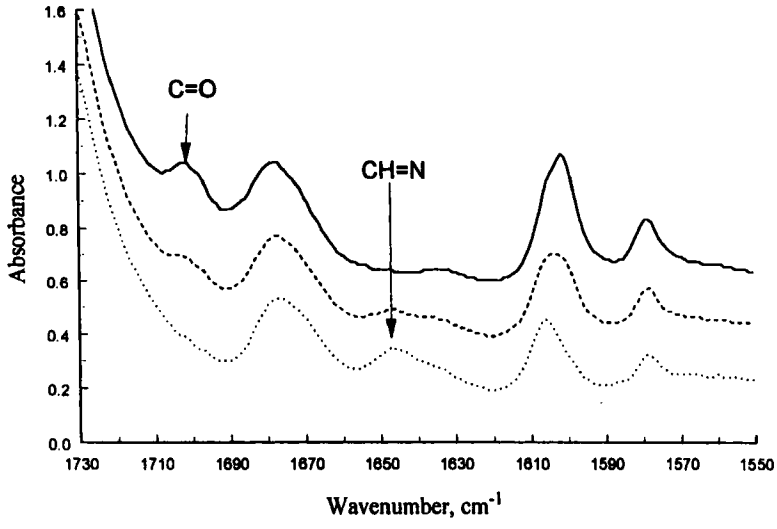


FIGURE 1 FT-IR spectra (plotted in symbols —;- - -;···) of the reaction mixture of S-(−)-PEA and EBA (0.3 mole l^{-1} each) in solvent A at 25°C. Solid line corresponds to a reaction time of 80 s, broken − 240 s, and dotted − 560 s. Solid and broken lines are shifted upwards 0.4 and 0.2 units respectively.

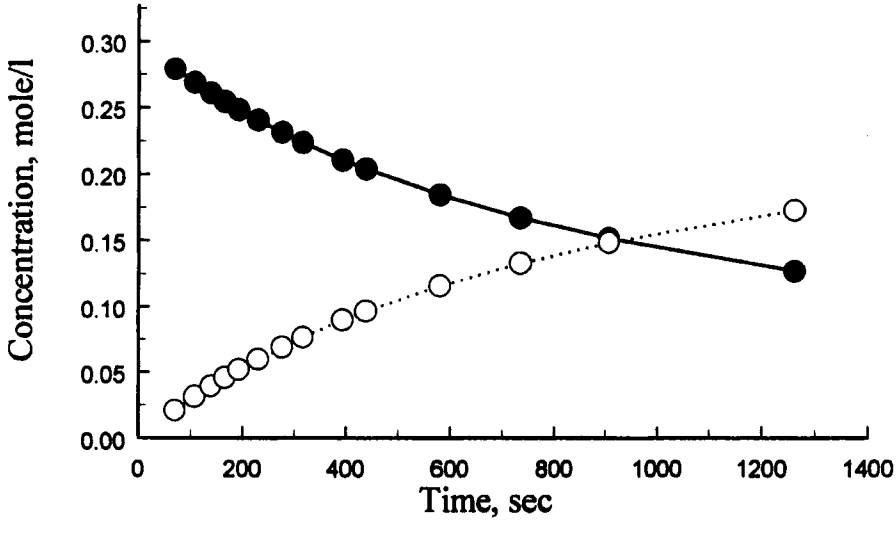


FIGURE 2 Kinetics of EBA disappearance (-●-) and S-(−)-EBPEA formation (..o..) in the reaction between S-(−)-PEA and EBA at 25°C in solvent A, followed by the intensity of IR absorption bands at ~1702 cm^{-1} and ~1647 cm^{-1} respectively.

equations, linearized with respect to time (1) or reciprocal time (2) can be obtained:

$$\frac{1}{[\mathrm{EBA}]_t} = \frac{1}{c_0} + k_f \times t; \tag{1}$$

$$\frac{c_0^2}{[\mathrm{EBPEA}]_t} = \frac{1}{k_f} \times \frac{1}{t} + c_0 \tag{2}$$

Typical kinetic data for the EBA decrease, plotted according to Eq. (1), are given in Figure 3. There is a factor which complicates the use of the FTIR method for monitoring the kinetics; namely, the strong absorption of some of the cholesteric solvents in the range of the characteristic bands (see Fig. 1). Therefore, another method based on monitoring the changes in the helix pitch was employed [11, 14].

Pitch Monitoring

If the pitch of the cholesteric liquid crystal is perturbed by the presence of a chiral (or nonchiral) solute, the induced change of the reciprocal pitch,

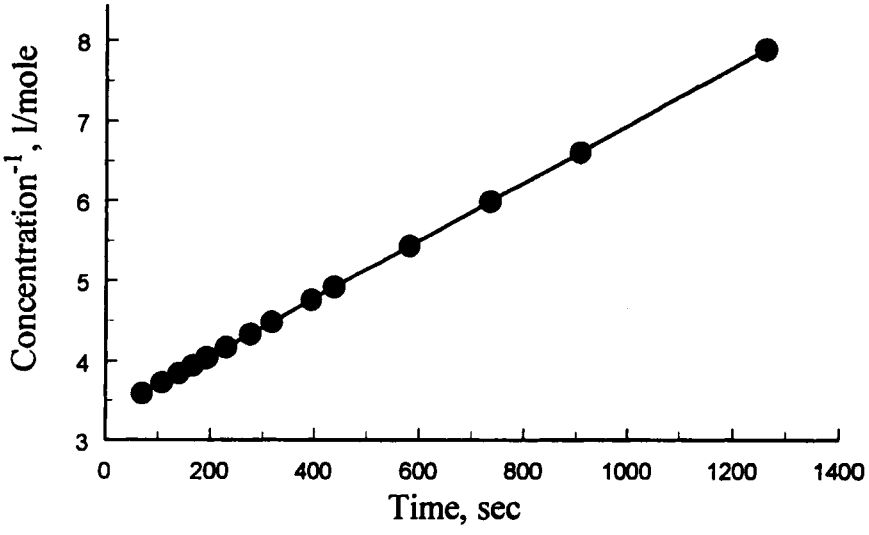


FIGURE 3 Kinetic data (from Fig. 2) on EBA disappearance in the reaction between S-(−)-PEA and EBA at 25°C in A, treated according to Eq. 1.

ΔP^{-1}, is proportional to changes in solute concentration Δc: $\Delta P^{-1} = \alpha \Delta c$. The proportionality constant α is referred to as the effective helical twisting power (EHTP) of the solute. When these changes are produced by the second order reaction, represented in Scheme 1, the overall pitch change at time t can be written as $\Delta P_t^{-1} = \alpha^0 \Delta c_{EBA}$, where α^0 is the EHTP of all reactants and products of the reaction: $\alpha^0 = \alpha_{EBA} + \alpha_{PEA} - \alpha_{EBPEA} - \alpha_{H_2O}$.

For normal incidence a cholesteric film reflects light with the wavelength $\lambda = n \times P$, where n is the mean refractive index of the liquid crystal. Since n is invariant to addition of small amounts of dopants, recording spectra of the cholesteric films light reflection affords a convenient method of following the changes in the pitch and, hence, the formation of the reaction product:

$$\Delta c_t = \Delta(1/\lambda)/(\alpha^0/n) = (1/\lambda_0 - 1/\lambda_t)/(\alpha^0/n) \tag{3}$$

Substituting Eq. (3) into Eq. (2) the following rate equation is obtained:

$$\frac{c_0^2}{(1/\lambda_0 - 1/\lambda_t)} = \frac{1}{k_f \cdot (\alpha^0/n)} \cdot \frac{1}{t} + \frac{c_0}{\alpha^0/n} \tag{4}$$

where λ_0 and λ_t represent the wavelengths of maximum light reflection of the reaction medium at the beginning of the reaction ($t=0$) and at time t, respectively. Figure 4 shows typical plots of the maximum wavelength change during the reaction between S-(−)-PEA or R-(+)-PEA and EBA in a left-handed steroidal solvent **A** and Figure 5 gives the same data, treated according to Eq. (4).

An important consideration in applying Eq. (4) to the treatment of the kinetic data is that the calculated slope and intercept (and hence the reaction rate constant and effective HTP) are very sensitive to the value of the initial wavelength λ_0 (at time $t=0$). λ_0 cannot be measured directly, because the pitch starts changing at the moment one starts mixing the reagents. Usually it takes about one minute to mix reagents properly and place the sample into a thermostated cell holder in the spectrophotometer. Another 3–4 minutes are needed to equilibrate the temperatures of the sample and sample holder before the first scan is done. During that time λ_0 changes between 2–10 nm, depending on the reaction rate.

There are two ways to determine λ_0: (1) extrapolation of the experimental $\lambda_t \sim t$ dependencies to zero time, and (2) calculation of λ_0 from the reflection wavelengths of the solutions of the each reagent, i.e. λ_0^{PEA} and λ_0^{EBA}. In the case when both solutions contain the same molar concentration of the

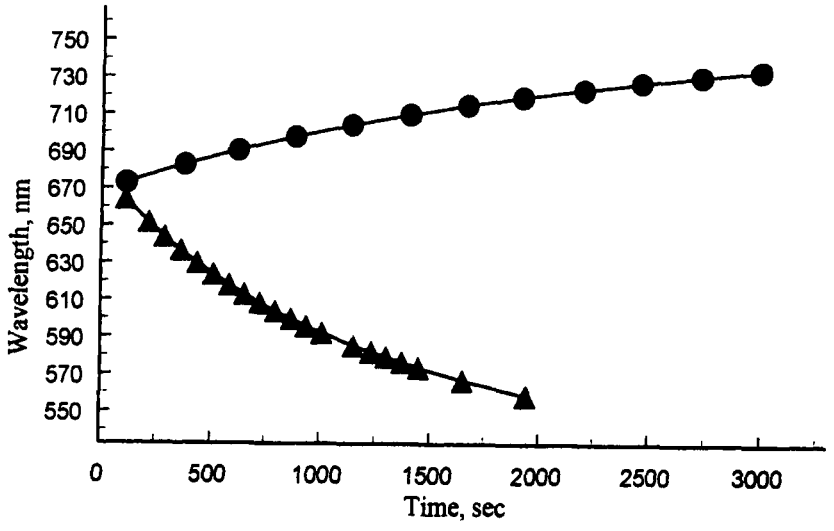


FIGURE 4 The shift in the wavelength of maximum reflection λ with time during the reaction between S-(−)-PEA (..▲..) or R-(+)-PEA (-●-) and EBA, performed in a cholesteric mixture A at 20°C. $[PEA]_0 = [EBA]_0 = 0.108$ mole·l^{-1}.

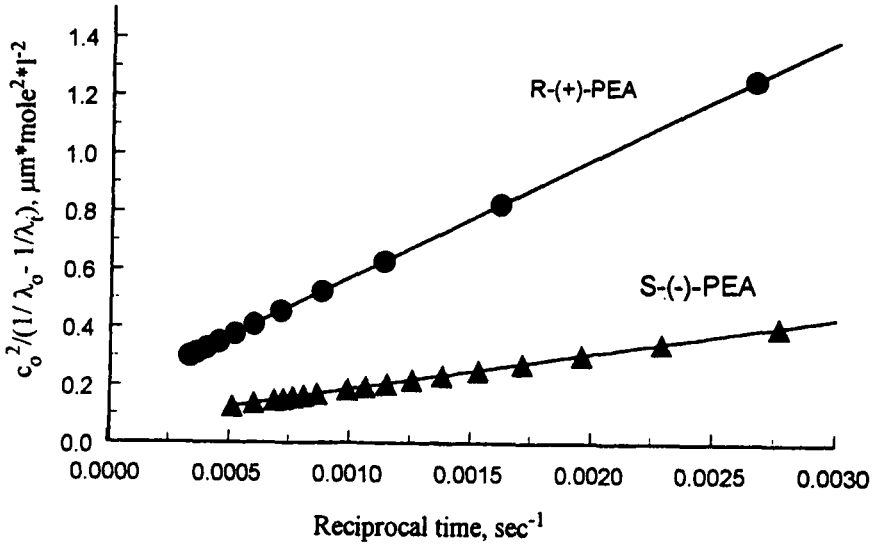


FIGURE 5 Kinetic data on chiral Schiff base formation in the reaction between S-(−)-PEA (..▲..) or R-(+)-PEA (-●-) and EBA in mixture A at 20°C, plotted with the coordinates of equation 4.

reagents and are mixed in 1:1 proportions, one can derive a simple equation for λ_0:

$$1/\lambda_0 = 0.5/\lambda_0^{PEA} + 0.5/\lambda_0^{EBA} \quad (5)$$

Since both methods, i.e. extrapolation and calculation, gave consistent values of λ_0, the calculation method was adopted throughout the study.

The rate constants and effective helical twisting powers are given in Table I. The precision of the $\alpha°/n$ and **k** determination was estimated as $\pm$ 8%.

DISCUSSION

Although both enantiomers S-(−)-PEA and R-(+)-PEA, when added to the solvent **A** (pitch 0.43μm), were found to produce a decrease in the helix pitch, the reaction between S-(−)-PEA or R-(+)-PEA and EBA results in opposite changes in pitch: the pitch decreases during the reaction between S-(−)-PEA and EBA and increases when R-(+)-PEA reacts with EBA. The changes are *not* symmetrical: S-(−)-PEA reacts faster than R-(+)-PEA, and there is also a noticeable difference in the activation parameters. The distinction in the reaction rate and activation parameters of PEA enantiomers is also observed when the reaction is performed in another cholesteric solvent **B** (pitch 0.45μm), though to a much lesser extent. In the solvents **PBS** and **PBR** (left- and right-handed media with pitches about 0.55μm) and in hexane, no differences are observed in the reaction of the enantiomers. Thus the solvent based on steroidal cholesterics induces the largest difference in reaction rates. Again, as in the previous study, we do not observe any correlation of the reaction rate and stereoselective kinetic effect with the macroscopic chirality of the solvent.

As can be seen in Table I, the reaction rate is higher for the PEA enantiomer which exhibits the lower value of HTP in a particular solvent. For example, in solvent **A** the reaction rate constants of S-(−)-PEA and R-(+)-PEA are 2.55×10^{-3} and 1.95×10^{-3} $l \cdot mole^{-1}s^{-1}$ respectively and their HTP's are -0.19 and -0.27 $l \cdot mole^{-1}\mu m^{-1}$ respectively. The values of HTP appear to be a guide to the strength of intermolecular coupling. Dilution of the solvent **A** by nematic **NP** results in decrease of both the HTP of the reactants and effective twisting power of the reaction products $\alpha°/n$, further indicating a specific guest-host interaction in the steroidal system.

TABLE I Kinetic parameters of the reaction between S-(−)- or R-(+)-PEA and EBA and helical twisting power (HTP) of PEA enantiomers in various cholesteric solvents

Solvent	*Reagent*	*HTP*[1], $\mu m^{-1} \cdot l \cdot mole^{-1}$	α°/n, $\mu m^{-1} \cdot l \cdot mole^{-1}$	$10^3 \cdot k$, $l \cdot mole^{-1} \cdot s^{-1}$	ΔH^* *kcal/mol*	ΔS^* *cal/mol·K*
A	S-(−)-PEA	−0.19	−3.20	2.55	13.2	−28.0
A	R-(+)-PEA	−0.27	+1.25	1.95	15.4	−19.0
A	S,R-(±)-PEA	−0.23	−1.30	2.10	–	–
A/NP(4:1)	S-(−)-PEA	−0.16	−2.6	2.40	10.5	−24.0
A/NP(2:3)	S-(−)-PEA	−0.12	−1.9[2]	2.3[2]	–	–
B	S-(−)-PEA	−0.08	−2.20	0.64	12.7	−36.9
B	R-(+)-PEA	−0.14	+1.80	0.53	8.6	−44.6
PBS	S-(−)-PEA	−0.07	−1.85	0.15	–	–
PBS	R-(+)-PEA	+0.05	+1.80	0.13	–	–
PBR	S-(−)-PEA	−0.05	−1.80	0.12	–	–
PBR	R-(+)-PEA	+0.08	+1.75	0.13	–	–
Hexane	S-(−)-PEA	–	–	0.37		
Hexane	R-(+)-PEA	–	–	0.37		

[1] Data from Ref. 10. [2] Data from Ref. 11.

If a racemic mixture of S-(−)- and R-(+)-PEA enantiomers is used in the reaction with EBA, one might expect that an excess of S-(−)-EBPEA over R-(+)-EBPEA will be formed due to the different reaction rates of the enantiomers. An estimate of the S-(−)-EBPEA excess occurring during the reaction can be made when pseudo-first-order conditions are used (that is by setting $[EBA]_0 \gg [PEA]_0$). Under these conditions, the kinetics of the reaction can be described by an exponential equation, and one can readily derive the following expressions for the maximum difference Δc_{max} in concentrations of enantiomers achievable and the time needed to reach this maximum:

$$\Delta c_{max} = 0.5 \times [S,R-PEA]_0 \times \left(1-\frac{k_r}{k_s}\right) \times \left(\frac{k_r}{k_s}\right)^{k_r/k_s-k_r} \tag{6}$$

$$t_{max} = (1/[EBA]_0) \times \ln(k_S/k_R)/(k_S-k_R) \tag{7}$$

Using the values of the rate constants from Table I ($k_S = 2.55 \times 10^{-3}$ $1 \cdot mol^{-1} \cdot s^{-1}$ and $k_R = 1.95 \times 10^{-3}$ $1 \cdot mol^{-1} \cdot s^{-1}$), and assuming $[EBA]_0 =$ 1.0 M and $[R,S\text{-}PEA]_0 = 0.2$ M (satisfying the requirement that $[EBA]_0 \gg [R,S\text{-}PEA]_0$), one finds that at time $t_{max} = 450$s, the difference in concentrations of S-(−)-EBPEA and R-(+)-EBPEA reaches $\Delta c_{max} \sim 0.01$ M and then gradually diminishes to zero. If the values of EHTPs in reactions between S-(−)-PEA or R-(+)-PEA and EBA were numerically equal (that is, if $\alpha^\circ/n_{S\text{-}(-)\text{-}PEA} = -\alpha^\circ/n_{R\text{-}(+)\text{-}PEA}$), one would expect to observe a decrease followed by an increase in the pitch of the solvent during the reaction. Since in solvent A $|\alpha^\circ/n_{S\text{-}(-)\text{-}PEA}|$ is approximately 2.5 times larger than $|\alpha^\circ/n_{R\text{-}(+)\text{-}PEA}|$, the reaction between racemic S,R-(+)-PEA and EBA causes a monotonic decrease in the helix pitch of this medium. The EHTPs of the reaction products, given in Table I, indicate that, although the reaction involves achiral species, the overall changes in the pitch are the same as if the compounds were optically left-handed. To account for this one can employ the assumption that there is a component in the effective HTP of the additives, which behaves in a left-handed manner irrespective of the optical sign of the enantiomer [10]. Then the effective twisting power of the reactants and products α°/n can be represented as the sum of two terms: β^+ or β^-, denoting twisting power originating from intrinsic molecular chirality, and β_G, denoting twisting power originating from a purely geometric factor:

$$\alpha^0/n_{S\text{-}(-)\text{-}PEA} = \beta^- + \beta_G; \quad \alpha^0/n_{R\text{-}(+)\text{-}PEA} = \beta^+ + \beta_G, \tag{8}$$

where subscripts S-(−)-PEA and R-(+)-PEA indicate which enantiomer is involved in the reaction. Using the values of α^0/n from Table I, the β^- terms can be calculated as:

$$\beta^+ = -\beta^- = 2.27 \mu m^{-1} \cdot l \cdot mole^{-1}; \quad \beta_G = -0.97 \mu m^{-1} \cdot l \cdot mole^{-1}.$$

Thus the expression for the effective twisting power of the products of the reaction between racemic S-(−)-, R-(+)-PEA and EBA in solvent **A** can be written as:

$$\alpha^0/n_{S,R\text{-}(\pm)\text{-PEA}} = 0.5(\beta^- + \beta_G) + 0.5(\beta^+ + \beta_G) = \beta_G, \tag{9}$$

if the reaction rates of the enantiomers are equal. In the event of a difference between reaction rates ($k_S \neq k_R$), Eq. (10) can be rewritten using weighted values of the twisting powers:

$$\alpha^0/n_{S,R\text{-}(\pm)\text{-PEA}} = \beta_G + (k_S \cdot \beta^- + k_R \cdot \beta^+)/(k_S + k_R) \tag{10}$$

Calculation of $\alpha^0/n_{S,R\text{-}(\pm)\text{-PEA}}$ according to Eq. (10) and (11) gives the values -0.97 $\mu m^{-1} \cdot l \cdot mol^{-1}$ and -2.24 $\mu m^{-1} \cdot l \cdot mole^{-1}$ respectively. The latter value is consistent with the experimentally observed value of -2.10 μ $m^{-1} \cdot l \cdot mole^{-1}$, indirectly proving that there is some stereoselective influence of the medium on the reaction rate of PEA enantiomers.

CONCLUSIONS

When enantiomers of PEA are allowed to react with EBA, the rate constants differ by a factor of ~ 1.3 in the steroidal cholesteric solvent A, and the activation parameters are markedly different. The HTPs of S-(−)- and R-(+)-PEA also differ by about the same factor, and their magnitudes are a guide to the strength of the solute-solvent interaction. In several other cholesteric media, there is also a (somewhat smaller) distinction in the reaction rate and activation parameters of the PEA enantiomers. There is no general correlation of the rate with the macroscopic chirality (pitch) of the solvent, indicating that short range solvent-solute interactions of a diastereomeric nature are largely responsible for the kinetic control.

Acknowledgement

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