Organic & Biomolecular Chemistry

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Journal:	*Organic & Biomolecular Chemistry*
Manuscript ID	OB-REV-07-2020-001497.R1
Article Type:	Review Article
Date Submitted by the Author:	16-Aug-2020
Complete List of Authors:	Polavarapu, Prasad; Vanderbilt University,

ARTICLE

Optical Purity, Enantiomeric Excess and The Horeau Effect

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Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

The optical purity of enantimeric mixture deduced from specific rotation measuremenrs was found by Horeau to be different from its enantiomeric excess, which came to be known as the Horeau effect. This observation had important implications in the practical use of specific rotations and has led to invetigations on homochiral and heterochiral aggregation processes. In this review, dedicated to The Horeau Principle, the theoretical basis for the observance of the Horeau effect, and a survey of the specific rotation studies investigating the Horeau effect, are provided and possible future investigations suggested.

Introduction

Historically, the enantiomeric composition of a synthesized chiral substance used to be estimated by taking the experimental ratio of its specific rotation (SR) to that of pure enantiomer at the same wavelength and concentration. Designating the SR of an enantiomeric mixture (em) with unknown enantiomeric composition as $[\alpha_{em}]$ and that of enantiopure (ep) substance as $[\alpha_{ep}]$, the optical purity (op) was defined as:

$$\text{op} = \frac{[\alpha_{em}]}{[\alpha_{ep}]} \qquad (1)$$

Enantiomeric excess (ee) is another measure of enantiomeric purity and is defined as,

$$\text{ee} = \frac{N_A - N_B}{N_A + N_B} \qquad (2)$$

where N_A and N_B are the number of molecules of mirror image enantiomers A and B. The most reliable determinations of ee are normally obtained through chiral chromatography separations. It was generally assumed, until the late sixties, that op determined from SRs is equivalent to ee.

In 1968, Krow and Hill reported [1] that the experimental SR of (*S*)-enantiomer of (α-methyl-α-ethyl) succinic acid, **1**, in chloroform, changes sign from being negative at higher concentrations to positive at lower concentrations.

For the case of enantiomeric mixtures, Horeau reported that for **1** [2], and also for (α-methyl-α-isopropyl) succinic acid, **2** [3], the measured op values do not change linearly with ee (see Figure 1). This observation came to be known as the Horeau effect.

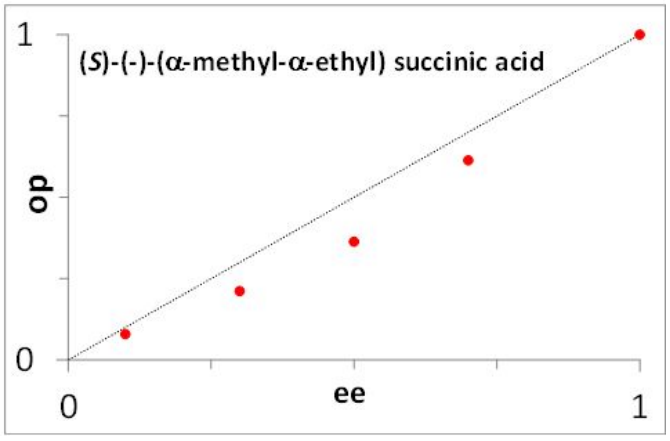

Figure 1. Optical purity (op) values determined from specific rotations were found by Horeau [2] to be less than enantiomeric excess (ee) values for (*S*)-(-)-(α-methyl-α-ethyl)succinic acid. Red circles are the observed data points while dotted line represents ideal situation for op = ee. Data taken from Ref [2] and replotted with permission from Elsevier. Copyright (1969).

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†For special issue of Organic and Biomolecular Chemistry (OBC) dedicated to The Horeau Principle.

These experimental observations laid the foundation for exploring possible homo chiral aggregation (formation of dimers and/or higher -mers among the molecules of enantiopure substance) and hetero chiral aggregation (formation of dimers and/or higher -mers among the molecules of opposite enantiomers) and the associated equilibria. Formation of dimers represents the simplest form of aggregation. The consideration of homo and hetero chiral monomer-dimer equilibria has provided insight into the conditions needed for the Horeau effect to be observable [4-7].

The theoretical basis for the observance of the Horeau effect, and the specific rotation studies investigating the Horeau effect, are reviewed in this article.

Theoretical Details

Optical Rotation, Specific Rotation and Intrinsic Rotation

The experimentally measured optical rotation (OR), α, for an enantiopure substance depends on its concentration, c, and the optical path length, ℓ, of the cell used to hold the sample for the measurements. These three quantities are reported in units of degrees, g cc^{-1}, and dm, respectively. The experimental ORs are converted to SRs for enantiopure substances using the relation [8, 9],

$$[\alpha] = \frac{\alpha}{c \times l} \qquad (3)$$

In more recent literature [6], $[\alpha]$ is also referred to as specific optical rotation (SOR). To be clear, SR and SOR are one and the same. $[\alpha]$ is considered to be a characteristic property of the associated chiral non-racemic substance and reported routinely, just as the melting point for example, for synthesized compounds. It was widely recognized that $[\alpha]$ depends on wavelength, temperature and solvent used for experimental measurements. However, since Equation (3) can be seen to imply normalization of α with concentration, a misconception of concentration independence for $[\alpha]$ of an enantiopure substance prevails at times.

There is a deeper meaning for $[\alpha]$, than is provided by Equation (3), which can be seen from the following equations, which are not available in the literature.

The observed OR depends on the concentration of enantiopure sample and should be zero when concentration of that sample is zero. To represent this concentration dependence, we use Taylor series expansion of α in c, as follows:

$$\alpha = \alpha_0 + \left(\frac{\partial \alpha}{\partial c}\right)_{c=0} c + \left(\frac{\partial^2 \alpha}{\partial c^2}\right)_{c=0} c^2 + \ldots\ldots \qquad (4)$$

In this equation, the derivatives of α with respect to c are taken at c = 0; α_0 represents the optical rotation of the enantiopure substance at zero concentration, which is zero. Thus,

$$\alpha = \left(\frac{\partial \alpha}{\partial c}\right)_{c=0} c + \left(\frac{\partial^2 \alpha}{\partial c^2}\right)_{c=0} c^2 + \ldots\ldots \qquad (5)$$

Dividing Equation (5) with concentration and path length, one obtains the equation for SR as:

$$[\alpha] = \frac{\alpha}{c \times l} = \frac{1}{l} \times \left(\frac{\partial \alpha}{\partial c}\right)_{c=0} + \frac{1}{l} \times \left(\frac{\partial^2 \alpha}{\partial c^2}\right)_{c=0} c + \ldots\ldots \qquad (6)$$

When concentration of the enantiopure substance is very small, the second and higher order terms on the right hand side of Eq (6) can become small. Then in the limit of c $\rightarrow$0, SR becomes a constant that is independent of the concentration.

$$[\alpha]_{c \rightarrow 0} = \{\alpha\} = \frac{1}{l} \times \left(\frac{\partial \alpha}{\partial c}\right)_{c=0} \qquad (7)$$

The SR determined in the limit of zero concentration is referred [8-10] to as intrinsic rotation, and designated as $\{\alpha\}$. In practice, $\{\alpha\}$ can be determined [11] by measuring α as a function of concentrations (both high and low), fitting $[\alpha]$ vs c data to appropriate (linear,

polynomial etc) function and extrapolating the [α] values to zero concentration.

Mathematically, {α} represents the path length-normalized first derivative of optical rotation with respect to concentration. In intuitive terms, {α} represents the SR value when solute-solute interactions are avoided. Furthermore, {α} values in different solvents transmit the influence of solvent medium on a solute molecule isolated in a solvent cage. However, {α} values are rarely reported [11, 12]. An alternate source for achieving intrinsic rotations is optical rotation measurements in gas phase, where concentrations are low enough to minimize solute-solute interactions [13, 14]. These gas-phase optical rotation measurements, although not yet routine, are becoming increasingly available [13-15]. The quantum chemical predictions of specific rotations [16, 17] for isolated molecules correspond to the experimental intrinsic rotations.

In solution phase, it is a common practice to report [α] at a finite chosen concentration. Such finite concentration values are expected to obey the following equation:

$$[\alpha] = \{\alpha\} + \frac{1}{l} \times \left(\frac{\partial^2 \alpha}{\partial c^2} \right)_{c=0} c + ... \qquad (8)$$

It should be remembered that, [α] ≠ 0 at c = 0 (even though α = 0). The reported SR values can vary among different laboratories when concentrations used are not the same, even when the same solvent is used.

Equation (8) can be written in a simpler form as follows:

$$[\alpha] = A + B c + ... \qquad (9)$$

where,

$$A = \{\alpha\}; \text{ and } B = \frac{1}{l} \times \left(\frac{\partial^2 \alpha}{\partial c^2} \right)_{c=0} \qquad (10)$$

As far as the meaning and behaviour of [α] is concerned, Equations (8) and (9) are much more revealing than Equation (3). This is because, Equations (8) and (9) indicate that, for an enantiopure substance: (1). [α] is truly a constant only when measured in the limit of c → 0; (2). in general, [α] can change at moderate to high concentrations. This change would be linear in concentration when higher order terms on the right hand side of Equations 4-6, 8 and 9 are negligible. (3). [α] can vary non-linearly with concentration when higher order terms on the right hand side of Equations 4-6, 8 and 9 are not negligible; (4). specific rotation [α], is actually determined by the first and higher derivatives of α with respect to concentration, a fact that has not been noted in the literature.

Homo chiral Monomer-Dimer equilibrium

For the concentration dependent experimental [α] values of an enantiopure substance, as in the experiment of Krow and Hill [1], insight can be gained from the consideration of homo chiral monomer-dimer equilibrium [18]. Designating the monomeric molecules of an enantiopure substance A as M_A and the dimeric molecules of same substance as D_{AA}, the monomer-dimer equilibrium is represented by the expression,

$$2M_A \rightleftharpoons D_{AA} \qquad (11)$$

The homochiral monomer-dimer equilibrium constant K_{hm} is given in terms of concentrations $[M_A]$ and $[D_{AA}]$ as,

$$K_{hm} = \frac{[D_{AA}]}{[M_A]^2} \qquad (12)$$

Designating the SR of monomer as $[\alpha]_{m,A}$, that of dimer as $[\alpha]_{d,AA}$, and the molar concentration of sample being studied as C_0, the SR of enantiopure sample, $[\alpha_{ep}]$, using the above equilibrium, becomes [7, 18]:

$$[\alpha_{ep}] = P_m [\alpha]_{m,A} + (1 - P_m)[\alpha]_{d,AA} \qquad (13)$$

In Equation (13), P_m represents the fractional monomer concentration which satisfies the following expressions:

$$P_m = \frac{2}{\left(1+\sqrt{1+8K_{hm}C_0}\right)} \quad (14)$$

$$[M_A] = P_m C_0 \quad (15)$$

$$[D_{AA}] = P_d C_0 \quad (16)$$

$$P_m + 2P_d = 1 \quad (17)$$

and

$$C_0 = [M_A] + 2\times[D_{AA}] \quad (18)$$

Equation (13) represents the fundamental equation that governs the SR of an enantiopure substance exhibiting monomer-dimer equilibrium. The salient features of Equation (13) are as follows:

(1). As C_o approaches zero, P_m approaches 1 (see Equation 14) indicating that the sample is dominated by monomeric molecules. In that situation, SR of enantiopure sample is equal to $[\alpha]_{m,A}$.

(2). As C_o approaches infinity, P_m approaches 0, which means all of the molecules are in the dimeric form. In that situation, SR of enantiopure sample is equal to $[\alpha]_{d,AA}$.

(3). When SRs of monomer and dimer are equal, monomer-dimer equilibrium should not influence the observed $[\alpha_{ep}]$. This point is clearly reflected in Equation (13).

(4). When enough experimental data points for $[\alpha_{ep}]$ vs C_0 are available it is possible to use non-linear least squares fitting [7] to determine three unknown parameters, $[\alpha]_{m,A}$, $[\alpha]_{d,AA}$ and K_{hm}.

Hetero chiral Monomer-Dimer equilibrium

For an enantiomeric mixture, as in the experiments of Horeau [2, 3], three monomer-dimer equilibria are to be considered as follows [4-7]:

$2M_A \rightleftharpoons D_{AA}$ (19)

$2M_B \rightleftharpoons D_{BB}$ (20)

$M_A + M_B \rightleftharpoons D_{AB}$ (21)

The subscripts in these equations represent the mirror image enantiomers A and B. While Equations (19) and (20) are same as that for homo chiral monomer-dimer equilibrium considered earlier (Equation 11), Equation (21) represents hetero chiral monomer-dimer equilibrium whose equilibrium constant, K_{ht}, is given as:

$$K_{ht} = \frac{[D_{AB}]}{[M_A][M_B]} \quad (22)$$

The concentrations of dissolved enantiomers, [A] and [B] respectively, are governed by the relations,

$[A] = [M_A] + 2 \times [D_{AA}] + [D_{AB}]$ (23)

$[B] = [M_B] + 2 \times [D_{BB}] + [D_{AB}]$ (24)

Combining Equations (23) and (24) with Equation (22), and equations analogous to Equation (12), two inter-dependent equations are obtained [4]:

$[A] = [M_A] + 2\, K_{hm} [M_A]^2 + K_{ht} [M_A] [M_B]$ (25)

$[B] = [M_B] + 2\, K_{hm} [M_B]^2 + K_{ht} [M_A] [M_B]$ (26)

For determining the monomer concentrations, Equations (25) and (26) require iterative solutions.

However, under a special condition,

$$K_{ht} = 2\times K_{hm} \quad (27)$$

closed expressions can be obtained [4] for the concentrations of monomers. Assuming that the hetero chiral dimer AB does not contribute to optical rotation (due to centrosymmetry), a convenient expression can be obtained for $[\alpha_{em}]$, the SR of enantiomeric mixture, as follows [6, 7].

$$[\alpha_{em}] = ee\times\{P_m[\alpha]_{m,A} + (1-P_m)[\alpha]_{d,AA}\} \quad (28)$$

P_m in Equation (28) is same as that given by Equation (14), except that C_0 = [A] + [B] for an enantiomeric mixture. The terms in curly parentheses in the right

hand side of Equation (28) are same as those for $[\alpha_{ep}]$ in Equation (13) at the same C_0 in both cases. Then Equation (28), under the condition of Equation (27), reduces to,

$$ee = \frac{[\alpha_{em}]_{K_{ht}=2K_{hm}}}{[\alpha_{ep}]} = op \quad (29)$$

indicating that, when hetero chiral monomer-dimer equilibrium constant is twice that of homo chiral monomer-dimer equilibrium constant, op and ee are equivalent.

When Equation (27) is not satisfied, concentrations of monomers and dimers have to be determined via iterative solutions to Equations (25) and (26), and determine $[\alpha_{em}]$ using,

$$[\alpha_{em}]_{K_{ht}\neq 2K_{hm}} = \frac{1}{C_0}\{[\alpha]_{m,A}\times([M_A]-[M_B]) + 2[\alpha]_{d,AA}\times([D_{AA}]-[D_{BB}])\} \quad (30)$$

Even in this situation, if $[\alpha]_{m,A} = [\alpha]_{d,AA}$ then an analogue of Equation (29) is obtained.

$$ee = \frac{[\alpha_{em}]_{K_{ht}\neq 2K_{hm}}}{[\alpha_{ep}]} = op, \text{ if } [\alpha]_{m,A} = [\alpha]_{d,AA} \quad (31)$$

This equation indicates that op = ee when SR of homo chiral dimer is equal to that of monomer, even when hetero chiral monomer-dimer equilibrium constant is not equal to twice that of homo chiral monomer-dimer equilibrium constant.

The predictions of Equations (29) and (31) can be verified by calculating $[\alpha_{em}]$ using iterative solutions to Equations (25) and (26) with selected values for K_{hm}, K_{ht}, $[\alpha]_{m,A}$ and $[\alpha]_{d,AA}$. These simulations [6] are shown in Figure 2.

It can be seen from Figure 2 that op can be greater or less than ee, depending on the relative magnitudes of K_{hm} and K_{ht} and relative magnitudes of $[\alpha]_{m,A}$ and $[\alpha]_{d,AA}$. Positive Horeau effect corresponds to op > ee (top left panel and middle two panels in Figure 2), and negative Horeau effect corresponds to op < ee (see top right panel in Figure 2).

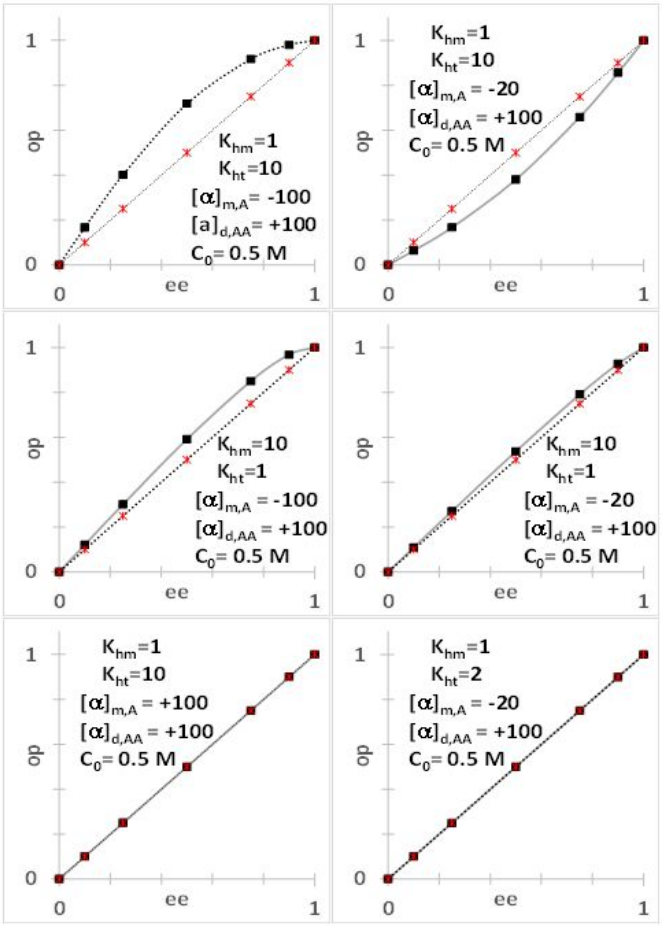

Figure 2. Simulated optical purity (op) values as a function of enantiomeric excess (ee) using Equation (30), presented as filled squares connected with thick lines. Red x marks, connected with dashed line, identify op = ee. Simulations were undertaken as described in Ref [6]. Top two and bottom two panels are replotted from Ref [6] with permission from John Wiley & Sons. Copyright (2015).

From these analyses, the following two points become clear:

(1). The Horeau effect will be observable when $K_{ht} \neq 2K_{hm}$ and $[\alpha]_{m,A} \neq [\alpha]_{d,AA}$ (see top four panels in Figure 2).

(2). The Horeau effect will *not* be observable when either $K_{ht} = 2K_{hm}$ or $[\alpha]_{m,A} = [\alpha]_{d,AA}$ (see bottom two panels in Figure 2).

Applications

Although the SR measurements on enantiomeric mixtures of **1** have led to the discovery of the Horeau

effect, **1** itself has not been used to test the predictions of Equations (29) and (31). This is because, neither the equilibrium constants nor the SRs of monomer and dimer have been determined for **1**, either experimentally or theoretically. However, there are a handful of other molecules which permitted the verification of the predictions of Equation (29) and (31). The molecules investigated for Horeau effect are: [1,1'-binaphthalene]-2,2'-diol, **3** [4]; 5-methoxy-2-{[(4-methoxy-3,5-dimethylpyridin-2-yl)methyl]sulfinyl}-1H-benzimidazole (Omeprazole), **4** [5] ; 1-(anthracen-9-yl)-2,2,2-trifluoroethanol (Pirkle's alcohol), **5** [5]; α-Hydroxy-β,β-dimethyl-γ-butyrolactone (Pantolactone), **6** [6]; Hydroxypinanone, **7** [6, 19]; (S)-(−)-6-Phenyl-2,3,5,6-tetrahydroimidazo[2,1-b]thiazole (Tetramisole), **8** [20, 21] and diethyl-2-(3-oxo-1,3-diphenylpropyl)malonate, **9 [22]**. The pertinent data available for these compounds are summarized in Table 1.

Table 1. Equilibrium constants and Horeau effect

Compound	K_{hm}	K_{ht}	Horeau effect	Reference
1	na[a]	na	yes	[2]
2	na	na	yes	[3]
3	1.3 ±0.5	3.1±1.0	no	[4]
4	14.0 ±3.5	25.3±4.0	no	[5]
5	~0.1	~0.35	no	[5]
6	6.9±0.4	13.8±0.4	no	[6, 23]
7 (in CCl_4)[b]	2.3±0.2; 2.0±0.4	na	no	[6]
7 (in $CDCl_3$)[b]	0.4±0.2; 0.75±0.04	na	no	[6]
8	na	na	??[c]	[20, 21]
9	na	na	yes	[22]

[a]na: not available; [b]the two values listed are determined from monomer and dimer infrared absorption band intensities; [c]minor deviations between op and ee were reported in Ref [21], while raw data were not provided in Ref. [20]

For compounds **1** and **2**, K_{hm} and K_{ht} are not available. The observation of op ≠ ee for **1** and **2** implies that $K_{ht} \neq 2K_{hm}$ and SR values for monomer and dimer are not equal. For compounds **3**-**6**, the homochiral and heterochiral monomer-dimer equilibrium constants satisfied the relation $K_{ht} \sim 2K_{hm}$, [4-6, 23] and accordingly Horeau effect was not observed. For **7**, [α] was found to be nearly independent of concentration and op was found to be equal to ee, both in CCl_4 and chloroform [6]. The heterochiral equilibrium constant is not available for **7**. The observation of op = ee for **7** suggests that either $K_{ht} \sim 2 K_{hm}$ or SRs for monomer and dimer equal. In case of **8**, raw data were not provided [20] to assess the level of deviations between ee and op; but an earlier reference [21] reported minor differences between op and ee. For **9**, 35% ee determined from ^{1}H NMR, using chiral shift reagent $Eu(TFC)_3$, was found to correspond to an optical purity of 57% [22]. As carboxylic groups were esterified in this compound, the Horeau effect is likely to have originated here from aggregation due to π-π stacking interactions of the phenyl groups.

The available experimental SR measurements can be associated with intermolecular hydrogen bonding interactions in carboxylic acids [2, 3] and π-π stacking interactions involving aromatic groups [22] as the likely sources for the Horeau effect.

The above summary indicates that the number of optical rotation experiments conducted with a focus on the Horeau effect is rather limited. However, there are other studies suitable for determining the likely candidates for observing the Horeau effect: (a). Most chiral samples with hydrogen bonding functional groups, such as carboxylic acids, alcohols and amines, can facilitate dimer formation in suitable solvents. By determining homochiral and heterochiral dimerization constants, and undertaking concentration dependent SR measurements for enantiomeric mixtures of these compounds, additional insights into the Horeau effect can be gained. Although the current theoretical analyses are restricted to monomer-dimer equilibria, some carboxylic acids are known to form tetramers [24]. Extension of theoretical analysis to such cases is needed. (b). transformation of an enantiomerically enriched sample to fractions with different enantiomeric compositions, in achiral chromatography is termed self-disproportion of enantiomers (SDE). Formation of homochiral and heterochiral aggregation

is thought to be responsible for the SDE phenomenon. The studies of SDE included: amines , alcohols, β-amino acids, α-amino acids, α-hydroxy acids, and amino alcohols containing trifluoromethyl group directly attached to stereogeic carbon center [25]; Other compounds studied for SDE [26] included dimethyl [(2E)-1,3-diphenyl-2-propen-1-yl] malonate, 2,2'-dimethoxy-1,1'-binnaphthalene, (4-nitrophenyl)-4-hydroxy-2-butanone, t-butyl phenyl phosphinothioic acid, N-acetyl phenylalanine, and methylphenyl alaninate; (b). J- and H- aggregates in carotenoids [27] and porphyrins [28] are known to alter the chiroptical properties; similarly, homochiral and heterochiral dimer interactions play a crucial role on the triplet excited state stabilization [29]; (d). Allosteric interactions are known to introduce conformational alterations [30] and lead to significant non-linear effects [31]. Although this is not an exhaustive list, these systems are likely candidates for observing the Horeau effect. Thus, there is a clear need for a broad series of future investigations.

Conclusions

The observations of Horeau [2] have influenced the way the specific rotations were being used to determine the enantiopurity of chiral samples, and directed the focus to evaluating the aggregation of, and associated equilibria in, non-racemic chiral samples. The consideration of homochiral and heterochiral monomer-dimer equilibria has led to understanding the conditions needed to observe (or not observe) the Horeau effect. The current survey indicates only a limited number of existing experimental optical rotation observations studying the Horeau effect. Extension of these studies to additional chiral aggregates will be useful.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

Financial support from the National Science Foundation (CHE-1464874) is gratefully acknowledged. I thank Dr. Cody Covington for developing the computer programs to simulate the Horeau effect, and Dr. Joseph Parello for translating Ref [2].

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