164. *Horeau*'s Coupling of Enantiomers Revisited. The Reversible Coupling of Enantiomers to Form Diastereoisomers in Kinetically Labile Metal Complexes

by **Werner Marty**[1], **Maurice L. Pasquier**, and **Harald Gampp***

Institut de chimie, Université de Neuchâtel, av. de Bellevaux 51, CH-2000 Neuchâtel

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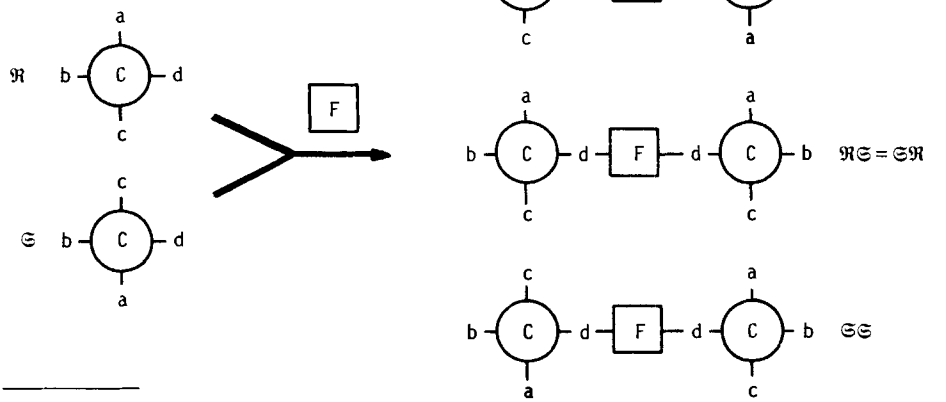
Pairs of enantiomeric molecules (ℜ, ℭ) of a substrate of unknown, but incomplete enantiomeric purity may be coupled to each other through labile coordination to a metal center M. This results in the formation of an *equilibrium* mixture of diastereoisomeric complexes, *viz. meso*-$L_nM\mathfrak{R}\mathfrak{S}$ (= *m*) and a pair of enantiomers $L_nM\mathfrak{R}\mathfrak{R}$ and $L_nM\mathfrak{S}\mathfrak{S}$ (= *e*), where L is an achiral auxiliary ligand. General expressions are presented for determining the ratio of enantiomers $[\mathfrak{R}]_0/[\mathfrak{S}]_0$ from experimental parameters, which may be obtained from NMR measurements. Effects of diastereoselectivity are specifically considered. Limiting cases (nearly pure or nearly racemic substrates, very high or no diastereoselectivity, very large or no excess of free substrate) are discussed. The cases of additional diastereoisomerism owing to different coordination geometries and of the formation of complexes with more than two substrate molecules per metal center are also investigated. The results presented can not only be used for determining the enantiomeric excess but also for designing optimal strategies for the successive resolution of partly enriched samples.

Introduction. – In a fundamental contribution, *Horeau* and coworkers [1] have considered the quantitative relationship between the diastereoisomers *m* and *e* arising in the *coupling reaction* ('duplication') of enantiomers with an achiral, bifunctional reagent F as a function of the enantiomer ratio $\alpha = [\mathfrak{R}]/[\mathfrak{S}]$ *(Scheme)*.

Scheme



[1]) Deceased Sept. 20, 1986.

The authors restricted their discussion to the case of *irreversible* formation of the diastereoisomers *m* and *e*. Two applications of this reaction scheme were recognized: *i*) the determination of the enantiomeric excess (ee) of an unknown, non-racemic substrate (ℜ, ℭ) through analysis of the product ratio [*m*]/[*e*]; *ii*) the improvement of the enantiomeric purity of partially resolved substrates through removal of the *meso*-diastereoisomer (which contains 50% of the minor enantiomer), followed by regeneration of the substrate. *Horeau* and coworkers [1] already recognized that the validity of their analysis was restricted to those cases where no diastereoselectivity is obtained in the formation of *m* and *e*. Application of their analysis, therefore, required a proof for the absence of diastereoselective discrimination in the coupling reaction with F. One case of diastereoselectivity was already presented in the original paper, *viz.* the reaction of (−)-menthylchloroformate with (±)-menthol which gave a 40:60 ratio of [*e*]/[*m*] [1][2]). However, no effort was made to solve this problem in general.

Three difficulties must be overcome in treating such cases: *i*) Experimentally, the kinetic diastereoselectivity of the coupling reaction needs to be determined. *ii*) A proof for the irreversibility is needed, since the coupling reaction and its reverse may have different kinetic diastereoselectivities such that the observed diastereoisomer ratio may not only depend on the coupling reaction. *iii*) The mathematics of the pertinent system of two concurrent, competitive reactions under second-order conditions are difficult and have not been solved so far, except for cases where the kinetic diastereoselectivities may be determined under initial rate conditions or with use of a large excess of substrate over coupling reagent.

It is probably due to these difficulties that *Horeau*'s analysis [1] has not found widespread application, not even for the frequent problem of determination of ee's. To our knowledge, three investigations [2–4] have since used this principle for determining ee, and none for the originally proposed improvement of resolutions. *Hansen* and coworkers [2] have checked the optical purity of a resolved heptalenecarboxylic-acid derivative by coupling pairs of resolved substrate molecules to form the anhydride. This represents an attractive variation of *Horeau*'s principle in that the coupled substrates are linked to each other and not through an additional bifunctional group F. Less than 0.2% of *m* anhydride was found and from this, an enantiomeric purity > 99% was estimated. The racemic heptalenecarboxylic acid gave the *e* and *m* diastereoisomers in a 3:2 ratio. Recently, *Wynberg* and coworkers [3] have presented a general procedure for determining ee's of alcohols. Samples of non-racemic alcohols were transformed into *m* and *e* phosphonates. For racemic alcohols, the diastereoisomer ratio was virtually statistical and independent of the nature of the alcohol for a variety of structures.

The diastereoisomer ratios were determined by ^{31}P-NMR spectroscopy, *i.e.* the coupling reagent served as the spectral probe. *Leitich* [4] has determined the ee of (*Z,E*)-1,5-cyclooctadiene by analysis of the [*m*]/[*e*] ratio of its thermal dimerization product. This example resembles the heptalenecarboxylic-acid derivative case [2] in that the coupled substrates are directly bound to each other. The possible interference from kinetic diastereoselectivity was recognized and ruled out by proving that the *m* and *e* dimers were

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[2]) In [1], the molar ratio of the reactants is not indicated. It is, therefore, impossible to calculate the degree of diastereoselectivity from the product ratio. However, a 1:1 ratio (observed in all but one case) of *m* and *e* at $t \rightarrow \infty$ is consistent only with the absence of kinetic diastereoselectivity.

formed at the same rate. On the other hand, we note that in those examples where evidence for kinetic diastereoselectivity was found [1] [2], no proofs for irreversibility were reported.

In this paper, we establish a quantitative relationship between reactant ($\mathfrak{R}, \mathfrak{S}$) and product ($m, e$) stereoisomer concentrations for the case of *complete reversibility* of the general coupling reaction in the *Scheme*. This relationship can, therefore, be derived on a thermodynamic basis, *i.e.* by determination of concentrations or concentration ratios after sufficiently long reaction times.

Results and Discussion. – *Metal Ions as Coupling Reagents. General Aspects.* As stated above, known applications of *Horeau*'s principle have been based exclusively on *covalent* coupling of substrate molecules. However, several reports in the literature indicate that similar coupling may also be brought about by self-association through H-bonding. Such coupling of enantiomers has been detected by NMR [5–8]. Only a few isolated cases of H-bond association appear to be known and these have been qualified as exceptional [9]. The kinetic lability of these aggregates leads to rapid exchange on an NMR time-scale and the chemical shift differences for *m* and *e* diastereoisomers vary as a function of the optical purity of the sample [7].

Coupling of enantiomeric substrates through *metal-complex formation* appears to be another, widely applicable alternative to covalent derivative formation and self-association through H-bonding [10]. It has been reported in a few cases that *m* and *e* diastereoisomers of metal complexes are distinguishable by NMR measurements [10–14]. These complexes may be kinetically inert, *i.e.* their formation reaction is *irreversible* in this case. Otherwise, ligand exchange may be sufficiently rapid such that the equilibrium between *m* and *e* is attained in short time. The distinction between labile and inert systems is merely defined by practical limits on acceptable equilibration times. An *upper limit* to equilibration rates between *m* and *e* diastereoisomers is imposed by the coalescence phenomenon, if spectral signals are used to distinguish the two species. However, the exchange broadening in the NMR may be suppressed to some extent by proper choice of temperature and solvent [15][3]). In the following analysis of the quantitative relationship between the total substrate's enantiomer ratio, $\alpha_0 = [\mathfrak{R}_0]/[\mathfrak{S}]_0$, and the product diastereoisomer ratio, $[m]/[e]$, we suppose that the experimental parameters have been accurately determined preferably by integration of base-line-separated spectroscopic signals, *e.g.* NMR lines.

The Algebraic Relationship between the Enantiomer Ratio, $[\mathfrak{R}]_0/[\mathfrak{S}]_0$ *of the Substrate and the Diastereoisomer Ratio* [m]/[e] *of the Coupling Products.* Let $\mathfrak{R}$ and $\mathfrak{S}$ be enantiomers with a single stereogenic center, which are present in an unknown ratio $\alpha_0 = [\mathfrak{R}]_0/[\mathfrak{S}]_0$. These enantiomers are then coupled according to the *Scheme,* using metal ions M^{m+} which form labile complexes as the coupling reagent F. In the most general case, we allow for the coordination of n further ligands L, other than $\mathfrak{R}$ and $\mathfrak{S}$ ($n = 0, 1, 2 \ldots$). The coupling products *m* and *e*, thus, contain the common fragment L_nM^{m+} which will be abbreviated by M in the following where L may be an auxiliary (spectator) ligand.

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[3]) It has been shown recently that the formation of kinetically labile dimers is another promising tool for ee determination: using an achiral Sn reagent 1,2-diols have been converted into dimeric dioxastannolanes, whose ^{13}C-NMR spectra are different for racemic and enantiomerically pure samples. Under fast-exchange conditions, the intensities of corresponding signals are proportional to the amount of $\mathfrak{R}$ and $\mathfrak{S}$ species in solution. Thus, in these systems a single measurement provides the value of ee [16].

In the present case of reversibly formed coupling products, the following equilibria will be established. These equilibria represent the simplest system allowing for coupling according to the *Scheme*. More elaborate systems will be treated below.

$$\left.\begin{array}{l} M + \mathfrak{R} \rightleftarrows M\mathfrak{R} \\ M + \mathfrak{S} \rightleftarrows M\mathfrak{S} \end{array}\right\} K_1 = \frac{[M\mathfrak{R}]}{[M][\mathfrak{R}]} = \frac{[M\mathfrak{S}]}{[M][\mathfrak{S}]} \tag{1}$$

$$\left.\begin{array}{l} M\mathfrak{R} + \mathfrak{R} \rightleftarrows M\mathfrak{R}\mathfrak{R} \\ M\mathfrak{S} + \mathfrak{S} \rightleftarrows M\mathfrak{S}\mathfrak{S} \end{array}\right\} K_e = \frac{[M\mathfrak{R}\mathfrak{R}]}{[M\mathfrak{R}][\mathfrak{R}]} = \frac{[M\mathfrak{S}\mathfrak{S}]}{[M\mathfrak{S}][\mathfrak{S}]} \tag{2}$$

$$\left.\begin{array}{l} M\mathfrak{R} + \mathfrak{S} \rightleftarrows M\mathfrak{R}\mathfrak{S} \\ M\mathfrak{S} + \mathfrak{R} \rightleftarrows M\mathfrak{S}\mathfrak{R} \end{array}\right\} K_m = \frac{[M\mathfrak{R}\mathfrak{S}]}{[M\mathfrak{R}][\mathfrak{S}]} = \frac{[M\mathfrak{S}\mathfrak{R}]}{[M\mathfrak{S}][\mathfrak{R}]} \tag{3}$$

From *Eqns. 1–3*, overall stability constants β_e, β_m are defined in the usual way:

$$\beta_e = K_1 \cdot K_e = \frac{[M\mathfrak{R}\mathfrak{R}]}{[M][\mathfrak{R}]^2} = \frac{[M\mathfrak{S}\mathfrak{S}]}{[M][\mathfrak{S}]^2} \tag{4}$$

$$\beta_m = K_1 \cdot K_m = \frac{[M\mathfrak{R}\mathfrak{S}]}{[M][\mathfrak{R}][\mathfrak{S}]} = \frac{[M\mathfrak{S}\mathfrak{R}]}{[M][\mathfrak{S}][\mathfrak{R}]} \tag{5}$$

The total concentrations ($[\mathfrak{R}]_0, [\mathfrak{S}]_0$) are given by *Eqns. 6* and *7*.

$$[\mathfrak{R}]_0 = [\mathfrak{R}] + [M\mathfrak{R}] + [M\mathfrak{R}\mathfrak{S}] + 2[M\mathfrak{R}\mathfrak{R}] \tag{6}$$

$$[\mathfrak{S}]_0 = [\mathfrak{S}] + [M\mathfrak{S}] + [M\mathfrak{R}\mathfrak{S}] + 2[M\mathfrak{S}\mathfrak{S}] \tag{7}$$

We suppose that the diastereoisomers resulting from the coupling reaction, *viz.* the *meso*-species $M\mathfrak{R}\mathfrak{S}(=m)$ and the pair of enantiomers $M\mathfrak{R}\mathfrak{R}$, $M\mathfrak{S}\mathfrak{S}(=e)$ may be determined quantitatively, *e.g.* by a spectroscopic method such as NMR. However, any other method of assaying these diastereoisomers without perturbation of their ratio may be employed (see below).

We shall designate $r = [m]/[e]$ the observed ratio of *m* and *e* diastereoisomers.

As has been pointed out in the *Introduction*, *r* may be influenced by diastereoselectivity in the formation of *m* and *e*, *i.e.* K_m may differ numerically from K_e. Since we are dealing with equilibrium systems, any existing diastereoselectivity must be due to thermodynamic effects alone and cannot be of kinetic origin. Thus, the extent of diastereoselectivity may be established by determining $[m]/[e]$ for a *racemic* sample where $[\mathfrak{R}]_0 = [\mathfrak{S}]_0$. We shall designate this ratio $d = ([m]/[e])_{rac}$.

As will be shown below, an excess of free substrate, in general, also influences the value of *r*, except in limiting cases, and the ratio of 'free' to coupled substrate, $h = ([\mathfrak{R}] + [\mathfrak{S}])/([m] + [e])$, needs to be determined. Also, some substrate may be present as $M\mathfrak{R}$ and $M\mathfrak{S}$, and the ratio $f = ([M\mathfrak{R}] + [M\mathfrak{S}])/([\mathfrak{R}] + [\mathfrak{S}])$ needs to be determined in this case. This can be achieved by integrating the corresponding NMR signals, in those cases where *r* and *d* may be determined by this method.

A general, algebraic relationship between the experimental parameters *r*, *d*, *h*, *f*, and α_0 has been derived (*Appendix*). This has been done in order to illustrate the difference in enantiomeric composition between 'coupled' (as measured by $r = [m]/[e]$), free, and singly bound substrate. Of the last two, only the *relative amounts* are determined, but

their enantiomeric composition can be calculated. The ratio of the enantiomers in the free, uncoupled substrate, α, as a function of the measurable quantities d and r is given by *Eqn. 8* (see *Appendix*)[4]).

$$[\mathfrak{R}]/[\mathfrak{S}] = \alpha = \frac{1}{r}(d + \sqrt{d^2 - r^2}) \tag{8}$$

It should be noted that r cannot exceed d irrespective of the degree of diastereoselectivity, since for purely statistical reasons the amount of m diastereoisomer is maximal for a racemic substrate. This is expressed in *Eqn. 9*,

$$d = \left(\frac{m}{e}\right)_{\text{rac}} \geqq r = \left(\frac{m}{e}\right)_{\text{non-rac}} \tag{9}$$

which readily allows one to identify the signals of the m and e diastereoisomers by comparing the peak intensities for racemic and non-racemic samples: the relative intensity of the m species must be smaller in a non-racemic sample. Using the composite parameter α in addition to r, d, h, and f, *Eqn. 10* is derived (*Appendix*):

$$\alpha_0 = \frac{[\mathfrak{R}]_0}{[\mathfrak{S}]_0} = \frac{\alpha^3[2 + r + h(1+f)(1+r)] + \alpha^2(2+r) + \alpha[r + h(1+f)(1+r)] + r}{\alpha^3 r + \alpha^2[r + h(1+f)(1+r)] + \alpha(2+r) + 2 + r + h(1+f)(1+r)} \tag{10}$$

In this equation, the parameters h and f always occur in a specific combination (*Eqn. 11*).

$$k = h(1+f) \tag{11}$$

Obviously, if M$\mathfrak{R}$ and M$\mathfrak{S}$ are not present in detectable amounts, $k = h$. This situation will be realized experimentally, if m and e are formed in the presence of a sufficiently large excess of free substrate, as required by the numerical values of K_1, β_e, and β_m.

The ratio α_0 is related to the enantiomeric excess ee by

$$\text{ee} = \left|\frac{\alpha_0 - 1}{\alpha_0 + 1}\right| \tag{12}$$

Combining *Eqns. 10* and *12* leads to *Eqn. 13* and after elimination of α by using *8* to *14* (see *Appendix*).

$$\text{ee} = \frac{1}{(2+k)(1+r)} \cdot \left| \frac{2(\alpha^2 - 1)}{\alpha^2 + 1} + \frac{k(1+r)}{\alpha + 1}(\alpha - 1) \right| \tag{13}$$

$$\text{ee} = \frac{\sqrt{d^2 - r^2}}{(d+r)(1+r)}\left(1 + \frac{r}{d} \cdot \frac{2 + kd}{2 + k}\right) \tag{14}$$

All these variants of the general relation (*Eqn. 10*) are rather complex, and this is due to a strong interdependence of all the experimental and derived parameters used, at least in the most general case.

Limiting Cases. Some possible simplifications of the general formulae (*Eqns. 10, 13,* and *14*) are easily foreseen, and those of potential practical interest shall be dealt with in this section.

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[4]) α is obtained as the solution of the quadratic *Eqn. A8* (*Appendix*). *Eqn. A8* has two roots, α_+ and α_-, where $\alpha_+ \cdot \alpha_- = 1$. Any of those can be chosen, which of course reflects the fact that the present analysis cannot specify which enantiomer is present in excess. *Eqns. 9* and *10* are derived for $\alpha = \alpha_+$.

1) $h \approx 0$. Quantitative substrate coupling to form *m* and *e* exclusively, using exact stoichiometric amounts of L_nM and substrate, may be achieved, if β_m and β_e are high and also much greater than K_I. Under these conditions α_0 and ee are obtained from *Eqns. 15* and *16*.

$$\alpha_0 = \frac{2\alpha^2 + r\alpha^2 + r}{r + \alpha^2 r + 2} \tag{15}$$

$$ee \simeq \frac{\sqrt{d^2 - r^2}}{d(r+1)} \tag{16}$$

This limiting case may be realized to good approximation in a variety of cases by proper choice of M, L, solvent, *etc.*

For $h \approx 0$, necessarily $k \simeq 0$ (*Eqn. 11*), *i.e.* if there is formation of M$\mathfrak{R}$ and M$\mathfrak{S}$, free ligand must be present in any system with the exact stoichiometry of the coupling reaction. The inverse is not true, since it is possible that $f = 0$ and $k \neq 0$ because of $h > 0$.

2) $h \to \infty$. Apart from accidental occurrence, this case is necessarily realized if the coupled species are very unstable, *i.e.* if β_e and β_m are very small. In this case, $\alpha \approx \alpha_0 \approx [M\mathfrak{R}]/[M\mathfrak{S}]$, since nearly all substrate is present in the free form. Provided $[M\mathfrak{R}]$, $[M\mathfrak{S}] \ll 1$ according to *Eqn. 8*, we have

$$\alpha_0 \approx \alpha \approx \frac{1}{r}(d + \sqrt{d^2 - r^2}). \tag{17}$$

3) $d = 1$. This case corresponds to the *absence of diastereoselectivity, i.e.* $\alpha = \alpha_0$ and *Eqn. 8* is transformed into *Eqn. 18*.

$$\alpha = \frac{1}{r}(1 + \sqrt{1 - r^2}) \tag{18}$$

There is no enantiomer discrimination between the 'coupled' forms *m* and *e* and all other species and, therefore, the parameters *h* and *f* need not be determined in this particular case.

4) $d \to \infty$. This case corresponds to exclusive formation of the *m* species by the minor enantiomer:

$$\text{no reaction} \left\{ \begin{array}{ccc} & \xleftarrow{\mathfrak{R}} M\mathfrak{R} \xrightarrow{\mathfrak{S}} & \\ & \xleftarrow{\mathfrak{S}} M\mathfrak{S} \xrightarrow{\mathfrak{R}} & \end{array} \right\} M\mathfrak{R}\mathfrak{S}$$

If in addition the minor enantiomer is transformed quantitatively into *m*, the amount of *m* becomes a direct measure of the ee. However, in most cases, some of the minor enantiomer is likely to be present in the free form or as M$\mathfrak{R}$ or M$\mathfrak{S}$. Since in this case, the species *e* is not formed, only *m* and free ligand, and M$\mathfrak{R}$ or M$\mathfrak{S}$ are observed. Measuring these three quantities for a *racemic* sample allows one to determine the equilibrium ratios between these three species.

For the case of negligible formation of M$\mathfrak{R}$ and M$\mathfrak{S}$, the experimental parameters *j* and j_{rac} may be defined as the ratio of *meso*-form to free substrate in an unknown non-racemic and in a racemic sample, respectively:

$$j = \frac{[M\mathfrak{R}\mathfrak{S}]}{[\mathfrak{R}] + [\mathfrak{S}]} \quad \text{and} \quad j_{rac} = \frac{[M\mathfrak{R}\mathfrak{S}]_{rac}}{[\mathfrak{R}]_{rac} + [\mathfrak{S}]_{rac}} = \frac{[M\mathfrak{R}\mathfrak{S}]_{rac}}{2[\mathfrak{R}]_{rac}}$$

A procedure analogous to the one outlined in the *Appendix* yields *Eqns. 19* and *20* from which the ratio of enantiomers is obtained.

$$\frac{\alpha}{(1+\alpha)^2} = \frac{j(2j+1)}{4j_{rac}(2j_{rac}+1)} \cdot \frac{[M]_{tot} - ([\mathfrak{R}]_0 + [\mathfrak{S}]_0)\left(2 + \frac{1}{j_{rac}}\right)^{-1}}{[M]_{tot} - ([\mathfrak{R}]_0 + [\mathfrak{S}]_0)\left(2 + \frac{1}{j}\right)^{-1}} \tag{19}$$

$$\alpha_0 = \frac{j(1+\alpha)+\alpha}{j(1+\alpha)+1} \tag{20}$$

The opposite limiting case, $d = 0$, *i.e.* stereoselective formation of the *e* diastereoisomer may exist, but it cannot be used in the present method. This is because the determination of ee is based on the determination of $[m]/[e]$, and $d = 0$ indicates that no *m* is formed.

5) High Enantiomeric Excess. The dependence of *r* on ee for different values of *d* is shown in *Fig. 1*. The curves differ appreciably at low ee but merge for high ee. This means that effects due to diastereoselectivity may be neglected at high ee only and that α_0 may be obtained from *Eqn. 18* under these conditions.

Application of the Method for Determination of ee. The complexation of Co(II) by histidine was studied by ^{1}H-NMR in D_2O [11]. Separate signals were observed for *meso* (Co(L-His)(D-His)) and enantiomeric ($Co(L\text{-}His)_2$, $Co(D\text{-}His)_2$) complexes from which it was concluded that the ligand exchange rates were less than $10^3\,s^{-1}$. Under experimental conditions where only 1:2 complexes are formed (pH > 7, 1:2 metal-to-ligand ratio) the ratio of *m* to *e* complexes for different relative amounts of D- to L-histidine

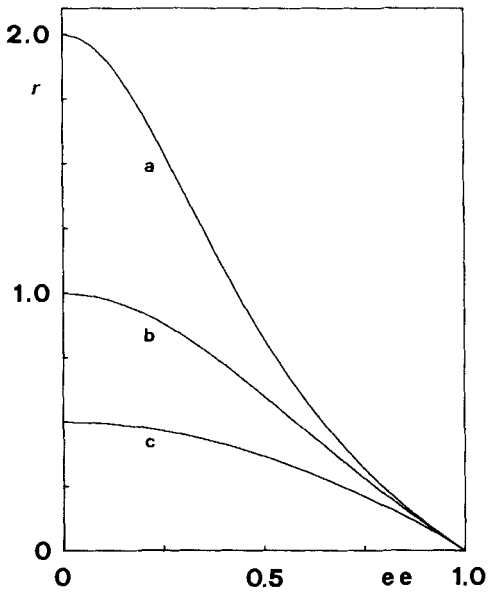

Fig. 1. *Dependence of the ratio of* meso *to enantiomeric product,* r, *on the enantiomeric excess ee for different stereoselectivities* d (Curves calculated from *Eqn. 16, i.e.* for the case where no free substrate is present). $d = 2$(a), 1(b), 0.5(c).

was determined by integrating the respective NMR lines. These measurements showed that the complexation of Co(II) by two histidines is diastereoselective, the *m* complexes being favored over the *e* complexes.

Using racemic histidine, $d = 1.59$ was found. For ratios of D- to L-histidine of 1:4 and 4:1, the values of r were 0.598 and 0.581, respectively. Since under the experimental conditions $h = 0$ (*i.e., Limiting Case 1*), the enantiomeric excess can be calculated from *Eqn. 16*. One, thus, obtains ee = 0.58 and 0.59, respectively, in good agreement with the known value of 0.60.

In our laboratory, the ee of 1-diphenylphosphino-2-propanethiol (L) was determined [10]. When racemic and enantiomerically enriched samples of the ligand are treated with substoichiometric amounts of Ni(II), all the metal is converted into the *m* and *e* diastereoisomers of *trans*-$Ni(L)_2$ [17]. The ^{31}P-NMR in CH_2Cl_2/CH_3OH 10:1 shows two singlets. The intensity ratios observed for a racemic and an enantiomerically enriched sample were 0.5 (= *d*) and 0.037 (= *h*), respectively. The uncomplexed ligand shows a singlet as well, and from its intensity $h = 0.12$ is obtained. Introducing these values into *Eqn. 14*, one calculates an enantiomeric excess ee = 0.960. In an additional experiment, a 1:1 mixture of racemic and enriched ligand was used (other experimental conditions were the same). From the observed value $r = 0.375$, ee = 0.475 was calculated, in excellent agreement with the expected value of 0.480. This shows that the equilibrium is rapidly established and no kinetic effects need to be considered.

These examples show that ee determinations can be done without using chiral standards, that the obtained results are accurate, and that the application of the presented method is straightforward.

Resolution Procedures Based on Formation of Reversibly Formed Diastereoisomeric Complexes. Eqns. 10, 13, and *14* show that there is a difference in enantiomeric composition between the complexes and the free substrate. This difference may be useful in resolution procedures. A slightly enriched sample of substrate may be treated with L_nM, and if the metal complexes can be separated from the free ligand without exchange (*e.g.* by rapid precipitation), then the recovered, free ligand may be more enriched than the original substrate. The factors determining the efficiency of this procedure are presented in graphical form *(Fig. 2)*. The obtainable enrichment increases with decreasing *h*, and this effect increases with *r*, *i.e.* as the starting sample becomes purer (*Fig. 2, A*). The effect of increasing values of *d* is shown in *Fig. 2, B;* again, the efficiency is highest at low *h*. Qualitatively, the enantiomer enrichment is highest for highly enriched samples and for coupling reagents L_nM which present a high diastereoselectivity favoring the *m* form in complex formation.

The Influence of Complex Stability and Solubility. As has been pointed out above, choice of a sufficiently high value of *h* favors the formation of the 'coupled' species over the binary complexes $L_nM\mathfrak{R}$ and $L_nM\mathfrak{S}$. Explicit knowledge of the stability constants of the 'coupled' species is not required, but quantitative data or good estimates of the stabilities facilitate the optimal choice of the experimental conditions. Note that precipitation of complexes or of free ligand is likely to alter the $[m]/[e]$ ratio and has to be avoided in any procedure for determining ee.

Equilibration Time-Scale and Proof of the Reversibility of the Coupling Reaction. For most practical purposes in ee determination, equilibration times in the range minutes to seconds may be generally acceptable. However, *complete equilibration, e.g.* of NMR

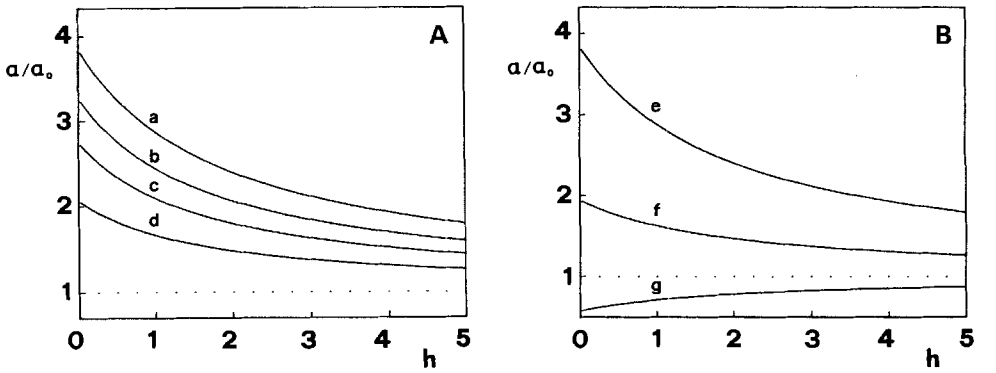

Fig. 2. *Dependence of the enantiomeric enrichment obtainable by separating coupled and uncoupled species, α/α_0, on the excess of free substrate* h (Curves calculated from *Eqns. 8* and *10*). A: $d = 4$; $r = 0.1$ (a), 0.5 (b), 1.0 (c), 2.0 (d). B: $r = 0.1$; $d = 4$ (e), 2 (f), 0.5 (g). The dotted line corresponds to a racemic mixture (A: $d = r = 4$) or to the absence of diastereoselectivity (B: $d = 1$).

samples, must be proved in each system. Recording of the spectra at different times to ensure time-independent peak ratios is reliable only, if a change is observed and may be followed to the end. If no change is seen, then the equilibration is either very fast or very slow. In such cases, addition of a known amount of substrate of appreciably different enantiomeric purity is recommended to determine the time for complete equilibration.

Conclusions. – This paper extends *Horeau*'s analysis [1] of diastereoisomeric interactions between chiral molecules. Pairs of enantiomeric molecules ($\mathfrak{R}$, $\mathfrak{S}$) of a substrate of unknown, but incomplete enantiomeric purity may be coupled to each other through coordination to a *labile metal center* M which yields an *equilibrium* mixture of diastereoisomeric complexes, *viz.* a *meso*-form (*m*) and a pair of enantiomers (*e*).

Any spectroscopic technique (or any sufficiently rapid separation technique) suitable for determining the unperturbed equilibrium ratio $r = [m]/[e]$, as well as the concentration of free substrate may be used for determining the ratio of total concentrations $[\mathfrak{R}]_0/[\mathfrak{S}]_0$, and thus the enantiomeric excess ee.

However, the following features must be considered: *i*) Possible diastereoselectivity, as measured by the parameter $d = ([m]/[e])_{rac}$, will distribute the minor isomer non-statistically between *m* and *e*. Under these conditions, existing *diastereoselectivity* is *exclusively thermodynamic*, since *m* and *e* are at equilibrium. *ii*) In any non-racemic sample, uncomplexed substrate at equilibrium with complexes *m* and *e* has an enantiomer ratio α different from α_0, unless $d = 1$. This difference in the enantiomer ratio depends on the relative amount of free ligand. Thus, the ratio $h = ([\mathfrak{R}] + [\mathfrak{S}])/([m] + [e])$ must be known.

The general expressions presented in this paper and the discussion of practically important limiting cases will allow a straightforward determination of the enantiomeric excess in many cases. Moreover, it has been shown how *Horeaus*'s method can be used to design optimal strategies for the successive resolution of partly enriched samples without the need of chiral auxiliaries.

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Appendix A. – For the special case represented in the *Scheme*, the relation between the enantiomeric ratio in an unknown mixture, $\alpha_0 = [\mathfrak{R}]_0/[\mathfrak{S}]_0$, and the observable quantities r, h, and f,

$$\alpha_0 = \frac{[\mathfrak{R}]_0}{[\mathfrak{S}]_0} = \frac{2[M\mathfrak{R}\mathfrak{R}] + [M\mathfrak{R}\mathfrak{S}] + [M\mathfrak{R}] + [\mathfrak{R}]}{2[M\mathfrak{S}\mathfrak{S}] + [M\mathfrak{R}\mathfrak{S}] + [M\mathfrak{S}] + [\mathfrak{S}]} \tag{A1}$$

$$r = \frac{[m]}{[e]} = \frac{[M\mathfrak{R}\mathfrak{S}]}{[M\mathfrak{R}\mathfrak{R}] + [M\mathfrak{S}\mathfrak{S}]} \tag{A2}$$

$$h = \frac{[\mathfrak{R}] + [\mathfrak{S}]}{[m] + [e]} = \frac{[\mathfrak{R}] + [\mathfrak{S}]}{[M\mathfrak{R}\mathfrak{S}] + [M\mathfrak{R}\mathfrak{R}] + [M\mathfrak{S}\mathfrak{S}]} \tag{A3}$$

$$f = \frac{[M\mathfrak{R}] + [M\mathfrak{S}]}{[\mathfrak{R}] + [\mathfrak{S}]} \tag{A4}$$

will be derived in the following. With $\alpha = [\mathfrak{R}]/[\mathfrak{S}]$, *Eqns. A5* and *A6* are directly obtained from the definitions of the formation constants (*Eqns. 1–5*).

$$\frac{[M\mathfrak{R}]}{[M\mathfrak{S}]} = \alpha \tag{A5}$$

$$\frac{[M\mathfrak{R}\mathfrak{R}]}{[M\mathfrak{S}\mathfrak{S}]} = \alpha^2 \tag{A6}$$

Introducing *Eqns. A5* and *A6* into *Eqns. A1–A4* gives:

$$\alpha_0 = \frac{[M\mathfrak{S}\mathfrak{S}] \cdot 2\alpha^2 + [M\mathfrak{R}\mathfrak{S}] + [M\mathfrak{S}] \cdot \alpha + [\mathfrak{S}]\alpha}{[M\mathfrak{S}\mathfrak{S}] \cdot 2 + [M\mathfrak{R}\mathfrak{S}] + [M\mathfrak{S}] + [\mathfrak{S}]} \tag{A1'}$$

$$r = \frac{[M\mathfrak{R}\mathfrak{S}]}{[M\mathfrak{S}\mathfrak{S}]} \cdot \frac{1}{1+\alpha^2} \tag{A2'}$$

$$h = \frac{[\mathfrak{S}]}{[M\mathfrak{S}\mathfrak{S}]} \cdot \frac{1+\alpha}{(1+\alpha^2)(1+r)} \tag{A3'}$$

$$f = \frac{[M\mathfrak{S}]}{[\mathfrak{S}]} \tag{A4'}$$

Substituting in *Eqn. A1'* $[M\mathfrak{R}\mathfrak{S}]$ and $[M\mathfrak{S}]$ by using *Eqns. A2'* and *A4'* gives

$$\alpha_0 = \frac{2\alpha^2 + r(1+\alpha^2) + \dfrac{[\mathfrak{S}]}{[M\mathfrak{S}\mathfrak{S}]}(1+f)\alpha}{2 + r(1+\alpha^2) + \dfrac{[\mathfrak{S}]}{[M\mathfrak{S}\mathfrak{S}]}(1+f)} \tag{A1''}$$

Finally, substituting $[\mathfrak{S}]/[M\mathfrak{S}\mathfrak{S}]$ in *Eqn. A1''* by using *Eqn. A3'* yields:

$$\alpha_0 = \frac{\{\alpha^2(2+r)+r\}(1+\alpha) + \alpha h(1+\alpha^2)(1+r)(1+f)}{\{\alpha^2 r + 2 + r\}(1+\alpha) + h(1+\alpha^2)(1+r)(1+f)} \tag{A1'''}$$

which can be rearranged into *Eqn. 10* (see text). Due to possible diastereoselectivity, α is not known in general. Therefore, an additional experiment using a racemic mixture has to be carried out (see text) which gives the quantity d (*Eqn. A7*).

$$d = \left(\frac{[m]}{[e]}\right)_{rac} = \frac{[M\mathfrak{R}\mathfrak{S}]}{[M\mathfrak{R}\mathfrak{R}] + [M\mathfrak{S}\mathfrak{S}]} = \frac{[M\mathfrak{R}\mathfrak{S}]}{2[M\mathfrak{S}\mathfrak{S}]} \tag{A7}$$

Substituting the concentrations in *Eqns. A7* and *A2'* by the respective expressions from *Eqns. 4* and *5* leads to *Eqns. A7'* and *A2''*.

$$d = \frac{\beta_m}{2\beta_e} \tag{A7'}$$

$$r = \frac{\beta_m}{\beta_e} \cdot \frac{\alpha}{1+\alpha^2} \tag{A2''}$$

Combination of *Eqns. A7'* and *A2''* finally relates α to the measured quantities r and d (*Eqn. A8*). Solving the quadratic equation for α leads to *Eqn. 8* (see text).

$$r = 2d\,\frac{\alpha}{1+\alpha^2} \tag{A8}$$

Simple arithmetics lead to *Eqns. A9* and *A10*,

$$\frac{\alpha-1}{\alpha+1} = \frac{\sqrt{d^2-r^2}}{d+r} \tag{A9}$$

$$\frac{\alpha^2-1}{\alpha^2+1} = \frac{\sqrt{d^2-r^2}}{d} \tag{A10}$$

which when introduced into *Eqn. 13* yield *Eqn. 14*.

Appendix B. – *Extensions to Other Systems.* Depending on the nature of M and the substrate, the formation of complexes may involve additional, geometrical isomers, if the substrate molecules occupy different pairs of coordination sites. Furthermore, the possibility of coordination of more than two substrate molecules may have to be considered. We do not intend to discuss these cases exhaustively, but will select two simple cases.

i) *Formation of* cis- *and* trans-*Square-Planar Species at Equilibrium.* Let M be a square planar metal center and $\mathfrak{R}$ and $\mathfrak{S}$ enantiomeric, *bidentate* ligands. (A square planar complex with one inert, bidentate ligand with two unequal donor atoms and two unidentate ligands $\mathfrak{R}$, $\mathfrak{S}$ may be subsumed in the same category.) The following equilibria have to be considered:

$$\mathrm{M} + \mathfrak{R} \underset{}{\overset{K}{\rightleftharpoons}} \mathrm{M}\mathfrak{R} \tag{B1}$$

$$\mathrm{M} + \mathfrak{S} \underset{}{\overset{K}{\rightleftharpoons}} \mathrm{M}\mathfrak{S} \tag{B2}$$

$$\mathrm{M}\mathfrak{R} + \mathfrak{R} \underset{}{\overset{K_{ce}}{\rightleftharpoons}} \textit{cis}\text{-}\mathrm{M}\mathfrak{R}\mathfrak{R} \tag{B3}$$

$$\mathrm{M}\mathfrak{R} + \mathfrak{R} \underset{}{\overset{K_{te}}{\rightleftharpoons}} \textit{trans}\text{-}\mathrm{M}\mathfrak{R}\mathfrak{R} \tag{B4}$$

$$\mathrm{M}\mathfrak{R} + \mathfrak{S} \underset{}{\overset{K_{cm}}{\rightleftharpoons}} \textit{cis}\text{-}\mathrm{M}\mathfrak{R}\mathfrak{S} \tag{B5}$$

$$\mathrm{M}\mathfrak{R} + \mathfrak{S} \underset{}{\overset{K_{tm}}{\rightleftharpoons}} \textit{trans}\text{-}\mathrm{M}\mathfrak{R}\mathfrak{S} \tag{B6}$$

(The same equilibrium constants apply to the four analogous reactions of M$\mathfrak{S}$.) The total concentrations are given by:

$$[\mathfrak{R}]_0 = [\mathfrak{R}] + [\mathrm{M}\mathfrak{R}] + [\textit{cis}\text{-}\mathrm{M}\mathfrak{R}\mathfrak{S}] + 2[\textit{cis}\text{-}\mathrm{M}\mathfrak{R}\mathfrak{R}] + [\textit{trans}\text{-}\mathrm{M}\mathfrak{R}\mathfrak{S}] + 2[\textit{trans}\text{-}\mathrm{M}\mathfrak{R}\mathfrak{R}] \tag{B7}$$

$$[\mathfrak{S}]_0 = [\mathfrak{S}] + [\mathrm{M}\mathfrak{S}] + [\textit{cis}\text{-}\mathrm{M}\mathfrak{R}\mathfrak{S}] + 2[\textit{cis}\text{-}\mathrm{M}\mathfrak{S}\mathfrak{S}] + [\textit{trans}\text{-}\mathrm{M}\mathfrak{R}\mathfrak{S}] + 2[\textit{trans}\text{-}\mathrm{M}\mathfrak{S}\mathfrak{S}] \tag{B8}$$

If the spectral resolution is sufficient, then all six 'coupled' species, *viz. cis-* and *trans-*M$\mathfrak{R}\mathfrak{S}$, and *cis-* and *trans-*M$\mathfrak{R}\mathfrak{R}$ and M$\mathfrak{S}\mathfrak{S}$ give rise to separate sets of signals. Neglecting the formation of M$\mathfrak{R}$ and M$\mathfrak{S}$, we define the observed intensity ratios, using the following notation for the sums of *cis* and *trans m* and *e* diastereoisomers:

$$\Sigma\mathfrak{R}\mathfrak{S} = [\textit{cis}\text{-}\mathrm{M}\mathfrak{R}\mathfrak{S}] + [\textit{trans}\text{-}\mathrm{M}\mathfrak{R}\mathfrak{S}] \tag{B9}$$

$$\Sigma\mathfrak{R}\mathfrak{R} = [\textit{cis}\text{-}\mathrm{M}\mathfrak{R}\mathfrak{R}] + [\textit{trans}\text{-}\mathrm{M}\mathfrak{R}\mathfrak{R}] \tag{B10}$$

$$\Sigma\mathfrak{S}\mathfrak{S} = [\textit{cis}\text{-}\mathrm{M}\mathfrak{S}\mathfrak{S}] + [\textit{trans}\text{-}\mathrm{M}\mathfrak{S}\mathfrak{S}] \tag{B11}$$

$$r^{\Sigma} = \left(\frac{\Sigma\mathfrak{R}\mathfrak{S}}{\Sigma\mathfrak{R}\mathfrak{R} + \Sigma\mathfrak{S}\mathfrak{S}}\right) \tag{B12}$$

$$d^{\Sigma} = \left(\frac{\Sigma\mathfrak{R}\mathfrak{S}}{\Sigma\mathfrak{R}\mathfrak{R} + \Sigma\mathfrak{S}\mathfrak{S}}\right)_{\mathrm{rac}} \tag{B13}$$

$$h^{\Sigma} = \left(\frac{[\mathfrak{R}] + [\mathfrak{S}]}{\Sigma\mathfrak{R}\mathfrak{R} + \Sigma\mathfrak{S}\mathfrak{S} + \Sigma\mathfrak{R}\mathfrak{S}}\right) \tag{B14}$$

The following expression can be derived:

$$\alpha_0 = \frac{\alpha^3[(2 + r^\Sigma + h^\Sigma(1 + r^\Sigma)] + \alpha^2(2 + r^\Sigma) + \alpha[r^\Sigma + h^\Sigma(1 + r^\Sigma)] + r^\Sigma}{\alpha^3 r^\Sigma + \alpha^2[r^\Sigma + h^\Sigma(1 + r^\Sigma)] + \alpha(2 + r^\Sigma) + 2 + r^\Sigma + h^\Sigma(1 + r^\Sigma)} \quad \text{(B15)}$$

This expression is analogous to *Eqn. 10*, except that the definitions of the parameters have been modified, and that $f = 0$. *Eqn. B15* suggests that ee of the substrate may be determined exactly as for the simpler system, except that the observed parameters are now the *sums* of the peak intensities for *cis*- and *trans*-diastereoisomers of the *m* and *e* species. Comparison of racemic and non-racemic samples will lead to unequivocal identification of correct pairs of peaks in cases of doubt. This analysis may obviously be extended to systems with more complex mixtures of geometrical isomers.

ii) *Tris(bidentate) Octahedral Complexes.* Let three bidentate ligands $\mathfrak{R}$ or $\mathfrak{S}$ with one stereogenic atom be coordinated at a metal center M. In this case, eight species may result:

fac-M$\mathfrak{RRR}$	*fac*-M$\mathfrak{RRS}$	*fac*-M$\mathfrak{RSS}$	*fac*-M$\mathfrak{SSS}$
1	2	3	4
mer-M$\mathfrak{RRR}$	*mer*-M$\mathfrak{RRS}$	*mer*-M$\mathfrak{RSS}$	*mer*-M$\mathfrak{SSS}$
5	6	7	8

In the NMR spectrum in an achiral solvent, these species are pairwise isochronous: 1/4, 2/3, 5/8, and 6/7. The signal for 1/4 and 5/8 are analogous to *e*, and 2/3 and 6/7 to *m*. From this follows that the ee of the substrate may be determined as in the preceding example.

REFERENCES

[1] J.P. Vigneron, M. Dhaenens, A. Horeau, *Tetrahedron* **1973,** *29,* 1055.
[2] W. Bernhard, P. Brügger, J.J. Daly, P. Schönholzer, R.H. Weber, H.-J. Hansen, *Helv. Chim. Acta* **1985,** *68,* 415.
[3] B.L. Feringa, A. Smaardijk, H. Wynberg, *J. Am. Chem. Soc.* **1985,** *107,* 4798.
[4] J. Leitich, *Tetrahedron Lett.* **1978,** 3589.
[5] T. Williams, R.G. Pitcher, P. Bommer, J. Gutzwiller, M. Uskoković, *J. Am. Chem. Soc.* **1969,** *91,* 1871.
[6] M.I. Kabachnik, T.A. Mastryukova, E.I. Fedin, M.S. Vaisberg, L.L. Morozov, P.V. Petrovskii, A.E. Shipov, *Russ. Chem. Rev.* **1978,** *47,* 821 and ref. cited therein.
[7] M.J.P. Harger, *J. Chem. Soc., Perkin Trans. 2* **1977,** 1882.
[8] A. Dobashi, N. Saito, Y. Motoyama, S. Hara, *J. Am. Chem. Soc.* **1986,** *108,* 307.
[9] J. Jacques, A. Collet, S.H. Wilen, 'Enantiomers, Racemates and Resolutions', J. Wiley & Sons, New York, 1981, p.410.
[10] M.L. Pasquier, W. Marty, *Angew. Chem., Int. Ed.* **1985,** *24,* 315.
[11] C.C. McDonald, W.D. Phillips, *J. Am. Chem. Soc.* **1963,** *85,* 3736.
[12] J.W.L. Martin, J.A.L. Palmer, S.B. Wild, *Inorg. Chem.* **1984,** *23,* 2664 and ref. cited therein.
[13] J. Otera, T. Yano, *Bull. Chem. Soc. Jpn.* **1985,** *58,* 387.
[14] M. Hoch, D. Rehder, *Inorg. Chim. Acta* **1986,** *115,* L23.
[15] B.P. Bammel, R.F. Evilia, *Inorg. Chem.* **1984,** *23,* 1574.
[16] C. Luchinat, S. Roelens, *J. Am. Chem. Soc.* **1986,** *108,* 4873.
[17] E. Pfeiffer, M.L. Pasquier, W. Marty, *Helv. Chim. Acta* **1984,** *67,* 654.