103. Stereoselectivity in Reactions of Metal Complexes

Part XIV[1])

Use of Circular Dichroism to Determine the Stereoselective Formation of $[M(his)_2]$ and $[M(PhEt\text{-}sal)_2]$ ($M = Ni^{2+}$, Cu^{2+}, his = histidine, PhEt-sal = *N*-(1-phenylethyl)salicylaldimine)

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The stereoselective formation of the 1:2 complexes $[M(his)_2]$ and $[M(PhEt\text{-}sal)_2]$ ($M = Ni^{2+}$, Cu^{2+}, PhEt-sal = *N*-(1-phenylethyl)salicylaldimine) has been determined by circular dichroism (CD) measurements. Stereoselectivity, defined as $S = K_{meso}/2K_{rac}$, has been found to be 2.48 for $[Ni(his)_2]$, corresponding to a 21% excess of the mixed species relative to the statistical amount. This value is temperature-independent between 15 and 35°. Whereas the absence of stereoselectivity in the formation of $[Cu(prol)_2]$ is confirmed, weak stereoselectivity is observed for $[Cu(his)_2]$ (2% excess of the mixed species). The CD intensity of the latter complex strongly depends on temperature and decreases by 12%, when the temperature is increased from 15 to 35°. Small but significant stereoselectivity is found for the formation of the *Schiff*-base complexes $[Ni(PhEt\text{-}sal)_2]$ and $[Cu(PhEt\text{-}sal)_2]$ in acetone with 1.0% and 2.4% excess, respectively, of the mixed species over the statistical value.

Introduction. – Stereoselectivity in the formation of binary complexes of metal ions with optically active chelating agents has been the subject of numerous studies. As in the case of the formation of 1:2 complexes with diamines [2] [3], attempts to detect stereoselectivity with most of the natural amino acids failed [4], except for histidine for which an excess of 12, 22, and 13% over the statistical amount of the mixed (*R*,*S*)-complex is found for Co^{II}, Ni^{II}, and Zn^{II}, respectively [5]. On the other hand, considerable stereoselectivity has been observed in the formation of binary complexes with amino acids having large substituents on the N-atom, as for example in the case of *N*-benzylproline [6].

The main technique used for determination of stereoselective complex formation is the comparison of acidimetric titration curves of 1:2 metal-to-ligand mixtures with the optically pure ligand as well as with an equimolar mixture of both enantiomers. Spectroscopic techniques have been used in some cases. The equilibrium situation in the Co^{II}/histidine system has been determined on the basis of NMR data [7], and the relative stabilities of some diastereoisomeric mixed ligand complexes involving amino-acid derivatives have been obtained from CD measurements [8]. In general, visible absorption spectra (VIS) are not suitable for stereoselectivity measurements of binary complexes, because the differences in the absorption spectra of the optically active and the *meso*-forms are generally too small, and even in favorable cases, the spectrum of the *meso*-form

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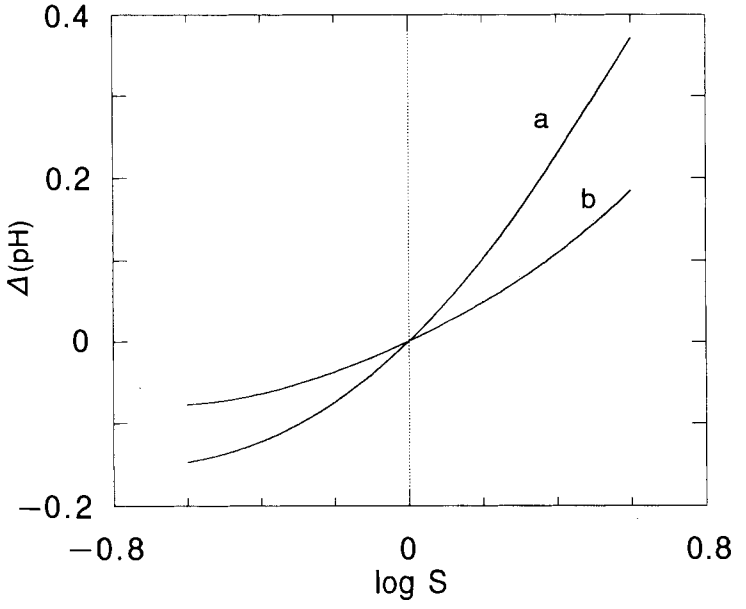


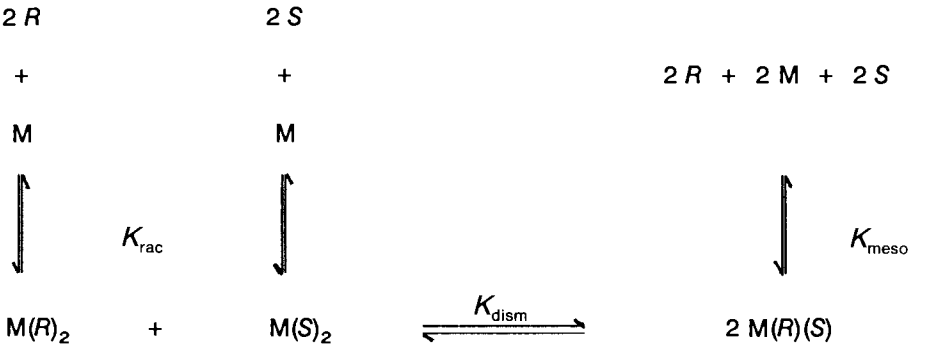
Fig. 1. *Calculated pH differences in the titration curves between optically pure and mixed complexes at 50% ML_2 formation as a function of the stereoselectivity, S.* [M] = $5 \cdot 10^{-3}$ M, $[L]_{tot} = 1 \cdot 10^{-2}$ M, $K_{meso} = 10^9$. *a*) 1 Proton, *b*) 2 protons.

cannot be determined directly. Determination of stereoselectivity by acidimetric titrations is limited by several restrictions, *e.g.* the only suitable ligands are proton donors which must be used in stoichiometric amounts and in aqueous solutions. As the interesting species are determined indirectly by the proton activity, the sensitivity of the method is limited by the precision with which proton activity can be measured. *Fig. 1* gives the calculated pH differences of titration curves at the point where 50% of ML_2 is formed and shows that these pH differences are relatively small in the selectivity range $0.25 < K_{meso}/2K_{rac} < 4.0$, corresponding to a maximum free-energy difference between the mixed and the unmixed species of *ca.* ± 3.5 kJ mol^{-1}, taking into account the statistical factor of 2. Whereas a continuous increase of the separation is observed for an increasing stability of the mixed over the unmixed species, in the other direction a limiting value of $\Delta(pH) = 0.3/n$ (n = number of displaced protons) is obtained, corresponding to a free-energy difference of $1.72/n$ kJ · mol^{-1}, due to the statistical factor in the formation of either enantiomer, [M((*R*)-L)$_2$] or [M((*S*)-L)$_2$], or the racemic mixture of both. The separation of the two titration curves is half as large for diacids relative to monoacids. If the first displaced proton of a diprotic ligand lies in the buffered part of the titration curve, as for example is the case with histidine, the separation of the two titration curves lies somewhere within the range delimited by the two curves of *Fig. 1*. From the preceding, it can also be concluded that the technique of acidimetric titration can only be applied in a limited manner for studies of the influence of environmental effects, like temperature, ionic strength, solvent, *etc.*, on the stereoselectivity of complex formation.

Here, we present a technique based on circular dichroism (CD) measurements. It consists of a continuous variation of the relative amounts of the two enantiomers of the

ligand, the total ligand concentration being constant. Quantitative formation of the 1:2 species is ensured by using the ligand in sufficiently high excess. If the measurements are performed at a wavelength at which the free ligand shows no CD activity, the signal measured is due only to $[M((R)\text{-}L)_2]$ and $[M((S)\text{-}L)_2]$ which have the same CD intensity but of opposite sign (*Scheme*). The comparison of the CD intensity of the optically pure

Scheme



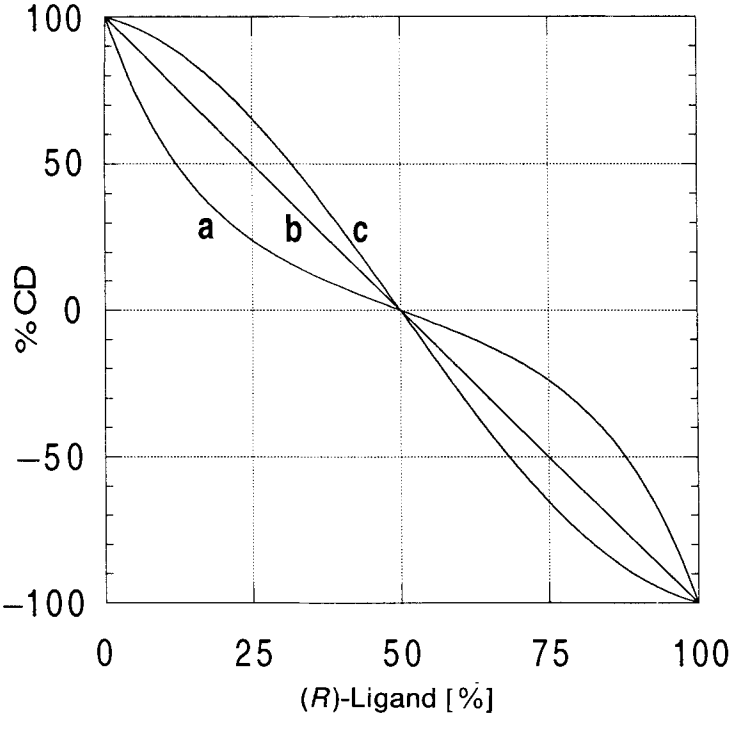


Fig. 2. *Calculated relative CD intensity as a function of the concentration ratio [(R)]/[(S)] and the stereoselectivity, S.* $[M] = 5 \cdot 10^{-3}$ M, $[L]_{tot} = 5 \cdot 10^{-2}$ M, $K_{meso} = 10^9$. *a*) S = 5, *b*) S = 1, *c*) S = 0.25.

compounds relative to those of the mixtures allows a direct determination of the ratio of the stability constants and, therefore, of the stereoselectivity $S = K_{meso}/2K_{rac}$.

Fig. 2 shows three examples of calculated curves of the relative CD intensities as a function of the concentration ratio [(*R*)]/[(*S*)] and the stereoselectivity S. In the case of S = 1 (no stereoselectivity), a straight line between the two extreme values for the two pure optically active enantiomers is obtained. Any deviation from this straight line indicates a nonstatistical distribution of the three complexed species. If the reaction is in favor of the mixed species (S > 1), the deviation from linearity steadily increases with higher selectivity, but reaches a limiting value for higher stability of the optically pure species (S < 1). If the CD signal is strong enough, the method is quite sensitive, *e.g.* $K_{meso}/2K_{rac} = 1.1$, corresponding to $\Delta G - RT\ln 2 = 0.24\ \text{kJ}\cdot\text{mol}^{-1}$ (25°), gives a significant maximum deviation of 2% m° at a [(*R*)]/[(*S*)] ratio of 80:20. In comparison, the same stereoselectivity would show a maximum separation of only 0.02 pH units in the acidimetric titration curves.

Besides the stereoselectivity, the magnitude of the deviation from linearity depends on the ratio of the two enantiomers, [(*R*)]/[(*S*)], and the excess of the ligand over the metal. As shown in *Figs. 3* and *4*, the best results are obtained for an enantiomeric ratio of 3 to 5 and a 10 to 100 fold excess of the ligand over the metal.

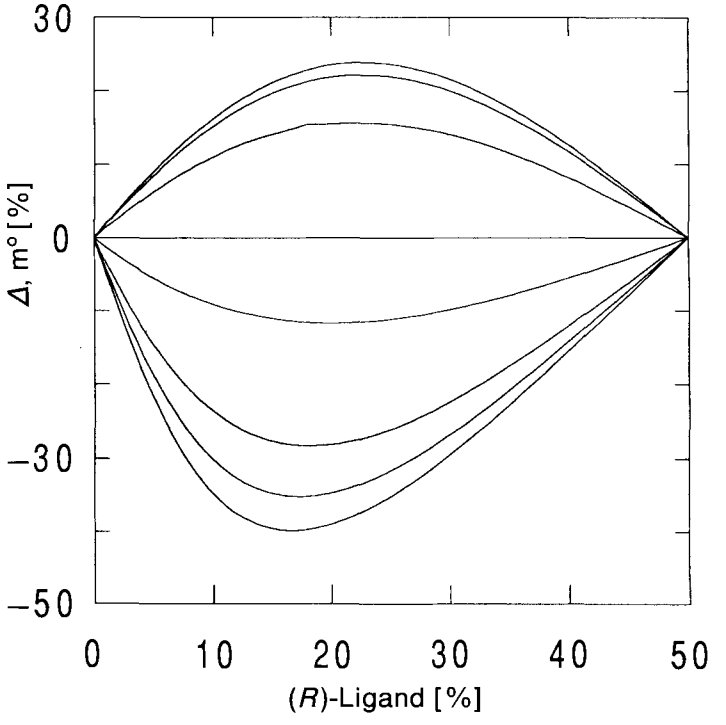


Fig. 3. *Deviation, % m°, from standard (S = 1) CD signal for various S.* $[M] = 5\cdot10^{-3}$ M, $[L]_{tot} = 5\cdot10^{-2}$ M, $K_{meso} = 10^9$. Reading from the bottom: S = 10, 7.5, 5, 2, 1, 0.25, 0.05, 0.005.

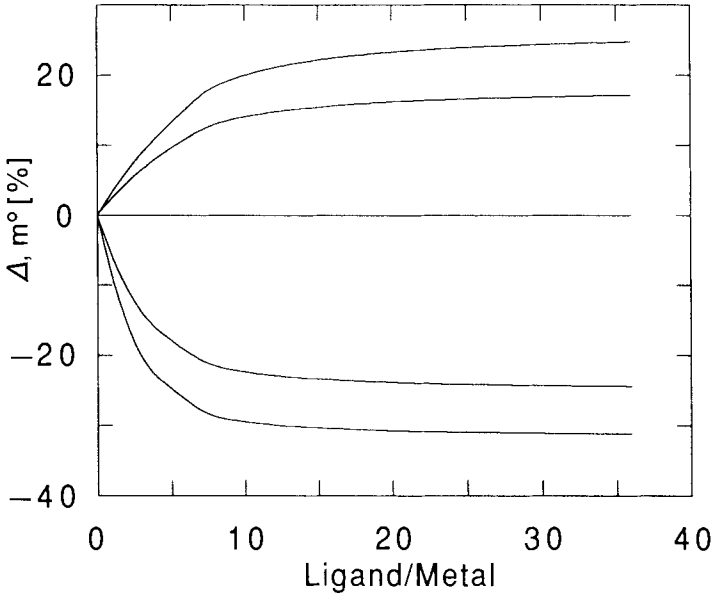


Fig. 4. *Deviation, % m°, from standard (S = 1) CD signal for [(R)]/[(S)] = 30:70 as a function of the ligand/metal ratio for various S.* [M] = $5 \cdot 10^{-3}$ M, $K_{meso} = 10^9$. Reading from the bottom: S = 10, 5, 1, 0.25, 0.05.

As the chemical properties of enantiomers of the free ligand are identical, the only chemical parameter changed for the different solutions in a series of measurements is the relative amount of the three complexes [M((*R*)-L)$_2$], [M((*S*)-L)$_2$], and [M((*R*)-L)((*S*)-L)]. Furthermore, the method is based on a direct determination of the complexed species, and seems, therefore, especially appropriate for measurements in nonaqueous solutions and for investigations of the influence on the stereoselectivity of secondary parameters such as temperature, ionic strength, *etc.* On the other hand, the method is limited to complexes where the CD spectra of the optically active complexes are sufficiently different from the spectra of the ligands.

Results. – *Amino Acids.* To test the method, we first measured the formation of metal complexes with histidine, a system for which the stereoselectivity in the formation of binary complexes is well known [5]. The measurements were made using 10^{-3} M solutions of metal ions containing a tenfold excess of the amino acid at pH 9.0 and at 0.1 ionic strength. Under these conditions, the formation of the 1:2 complexes of both metals can be considered as complete. From the relative CD intensites shown in *Fig. 5*, the stereoselectivity values obtained are S = 2.48 for Ni^{II} which corresponds to 71% of the mixed and 14.5% of each of the optically active species. This is in good agreement with the values given in the literature[2]) [5]. For Cu^{II}, S = 1.11 (53% of the mixed and 23.5% of each of the

[2]) Some confusion has arisen in the literature from the fact that the J_2 values from [5] are reproduced as the formation constants for all 1:2 complexes [9]. In fact, this is true for the optically active species only, $J_2 = K_{11}$, whereas for the racemic ligand, $2J_2 = K_{11} + K_{12}/2$. The corresponding overall stability constants from [5] for the Ni^{II} complexes are, therefore, $K_{rac} = 3.80 \cdot 10^{15}$ and $K_{meso} = 2.00 \cdot 10^{16}$, giving a selectivity factor $K_{meso}/2K_{rac} = 2.63$ (72.5% of the mixed species).

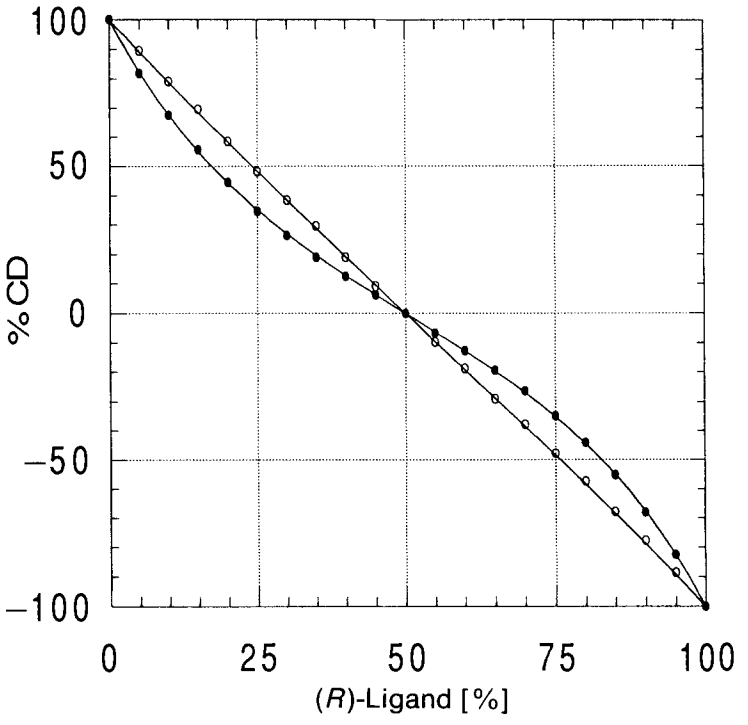


Fig. 5. *Relative CD intensity as a function of the concentration ratio [(R)]/[(S)].* [M] = $5 \cdot 10^{-3}$ M, $[L]_{tot} = 5 \cdot 10^{-2}$ M. ●: $[Ni(his)_2]$, ○: $[Cu(his)_2]$.

optically active species). A statistical distribution was previously reported for Cu^{II} [5], because such small stereoselectivity is difficult to detect by potentiometric titration.

For both metal ions, the measurements have been performed at various temperatures ranging from 15 to 35°. For Ni^{II}, neither the intensity of the spectra of the optically pure species, nor the value of the stereoselectivity change with temperature. For Cu^{II}, on the other hand, the CD intensity decreases with increasing temperature. The intensity falls by *ca.* 12% between 15 and 35°, and the maximum shifts slightly from 690 nm to 685 nm. The VIS spectrum is practically unchanged. From this observation, we assume that a temperature-dependent equilibrium between different isomeric forms of the 1:2 Cu^{II}-histidine complexes may exist in solution. As the relative CD intensity for the various [(*R*)]/[(*S*)] mixtures is not temperature-dependent, it is not clear whether or not the apparent stereoselectivity is affected by such an equilibrium.

There is some ambiguity in the literature about the question of whether or not the formation of the binary Cu^{II} complex with proline is stereoselective. Using acidimetric titrations, no stereoselectivity was detected for this system [10]. On the other hand, stereoselectivity was postulated on the basis of differences observed in the electronic absorption spectra of solutions containing the optically pure complexes or mixtures of them [6]. To clarify this question, we applied the technique of continuous variation of enantiomer ratio to this system using a tenfold excess of proline relative to Cu^{II}. A

perfectly linear relationship was observed. Stereoselectivity in this system can, therefore, be considered as absent or, if it exists, it must be less than 1%. This shows that, due to the presence of different species in the racemic mixture compared to the optically active compounds, electronic absorption spectra can be different for either statistical or non-

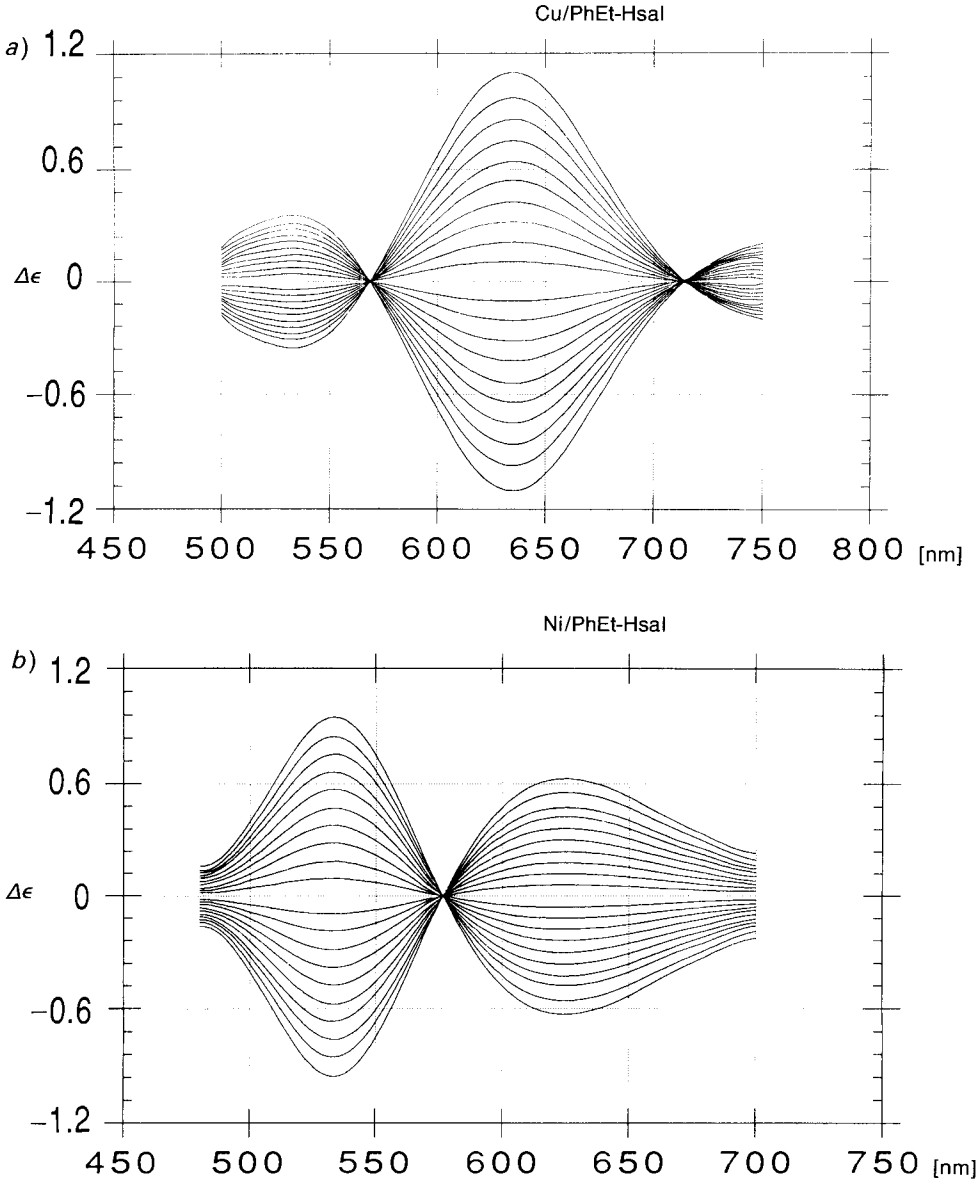


Fig. 6. *CD Spectra as a function of the concentration ratio [(R)]/[(S)].* $[M] = 10^{-3}$ M, $[L]_{tot} = 2.2 \cdot 10^{-2}$ M. *a*) [Cu(PhEt-sal)$_2$], *b*) [Ni(PhEt-sal)$_2$].

statistical distributions. Thus stereoselectivity cannot be inferred solely from differences in the electronic absorption spectra.

Schiff-*Base Ligands.* The Ni^{II} complex of the *Schiff* base *N*-(1-phenylethyl)salicylaldimine, PhEt-sal, has been used in the stereoselective cyclopropanation of styrene giving 6% ee in the product [11]. More recently, it has been shown [12] that the ligand-exchange reaction of [Ni(PhEt-sal)$_2$] with tetradentate *Schiff*-base ligands is stereoselective. Not only do the optically active species react at different reaction rates with an optically active entering ligand, *e.g.* 1,2-diamino-*N,N'*-disalicylidenepropane (26% ee), but stereochemical discrimination has been shown to occur also in ligand-substitution reactions of the optically active or the *meso*-complexes with achiral ligands, such as H_2sal(2-Me)(en) (= 2-methyl-*N,N'*-disalicylidene-1,2-diamine). The latter stereochemical discrimination can occur either by a nonstatistical distribution of the optically active and the *meso*-complexes in the reaction mixture, or by a difference in the reaction rate of one of the rate-controlling steps of the substitution process. It seemed, therefore, of interest to examine the possibility of the stereoselective formation of these *Schiff*-base complexes. *Fig. 6* shows the CD spectra of continuous [(*R*)]/[(*S*)] variations of a 22 fold excess of the ligand over the metal for Ni^{II} and Cu^{II}. From these measurements, small but significant stereoselectivity can be calculated, corresponding to S = 1.04 for Ni^{II} and 1.10 for Cu^{II}. When these results are compared to the ligand-substitution kinetics of [Ni(PhEt-sal)$_2$] with tetradentate *Schiff* bases, it is seen that the *meso*-complex [Ni((*R*)-L)((*S*)-L)] reacts 1.21 times faster with H_2sal(2-Me)(en) than with the optically active species [Ni((*R*)-L)$_2$] and [Ni((*S*)-L)$_2$]. This is significantly higher than the thermodynamic stability difference, and the observed stereochemical differentiation is, therefore, mostly due to kinetic effects. For the reaction with H_2salen (= *N,N'*-disalicylideneethane-1,2-diamine), the ratio of secondary rate constants $k_2(RS)/k_2(RR)$ calculated with mean values from [12] is 1.04. This is exactly the stereoselectivity of the formation of the two isomeric forms. On the other hand, for the reaction with H_2sal(cy)(en) (= *N,N'*-disalicylidenecyclohexane-1,2-diamine), ligand exchange is faster with the optically active forms, and the kinetic stereoselectivity is opposite to the relative thermodynamic stability. Taking into account the nonstatistical distribution of the reactants, data from [12] give a $k_2(RS)/k_2(RR)$ (= $k_2(RS)/k_2(SS)$) ratio of 0.86.

Experimental. – CD Measurements were accomplished using a *Jasco 500* spectropolarimeter. A *Haake N3* thermostat was used to maintain sample temp. within ± 0.5 K.

The H_2O-insoluble *Schiff*-base complexes used in this work were prepared as described in [12]. All other reagents used were of anal. grade.

Solns. of histidine and proline were prepared at pH 9.0 and 9.5 respectively. CD Spectra were taken between 288 and 308 K using solns. that were $5 \cdot 10^{-3}$ M in Ni^{II} or Cu^{II} and $5 \cdot 10^{-2}$ M in total (*R*)- + (*S*)-ligand. The ionic strength was 0.1 M ($NaNO_3$). Data were measured at λ_{max} = 610 nm for [Ni(his)$_2$], at λ_{max} = 690 nm for [Cu(his)$_2$], and at λ_{max} = 760 nm for [Cu(prol)$_2$].

Solns. of the *Schiff* bases were prepared in acetone. Measurements were made using 10^{-3} M solns. of the metal, containing a 22 fold excess of the corresponding ligand, at 296.5 K. The data were obtained at λ_{max} = 535 nm for Ni^{II} and λ_{max} = 635 nm for Cu^{II}.

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