Stereoselectivity in reactions of metal complexes Part XVIII*. Kinetics and stereoselectivity in electron-transfer reactions between $[Co(L)H_2O]^+$ (L = *N,N'*-[(pyridine-2,6-diyl)bis(methylene)]bis[proline] (promp) and *N,N'*-[(4-methoxypyridine-2,6-diyl)bis(methylene)]bis[proline] (MeO-promp) and optically active iron(II) complexes

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Abstract

The new optically active pentadentate ligands *N,N'*-[(4-methoxypyridine-2,6-diyl)bis(methylene)]bis[(*R*)- or (*S*)-proline], (*R*)- or (*S*)-MeO-promp, and their Co^{III} complexes have been synthesised. Electron-transfer kinetics between $[Co(L)H_2O]^+$ (L = *N,N'*-[(pyridine-2,6-diyl)bis(methylene)]bis[proline] (promp) or MeO-promp) and the optically active [Fe(*S, S*)-L'] (L' = promp, MeO-promp or *N,N'*-[(pyridine-2,6-diyl)bis(methylene)bis[alanine] (alamp)) have been measured by circular dichroism. The observed stereoselectivity is always in favour of the heterochiral diasteroisomeric pair. Mean $k_{\Delta\Lambda}/k_{\Lambda\Lambda}$ ratios of 2.0, 2.1, 1.9 and 2.4, 2.0, 1.9 were observed for $[Co(promp)H_2O]^+$ and $[Co(MeO\text{-}promp)H_2O]^+$, respectively, with the three optically active Fe^{II} complexes. Substitution in the pyridine moiety of the ligands has no influence on the stereoselectivity of the reaction. An outer sphere mechanism involving the pyridine moiety of one or both of the reacting complexes can therefore be excluded.

Key words: Cobalt complexes; Iron complexes; Polydentate ligand complexes; Electron transfer; Kinetics; Stereoselectivity

1. Introduction

Since the first observation of stereoselectivity in electron-transfer reactions between metal complexes in 1980 [2], studies of stereochemical parameters in these reactions as a means of investigation of the chiral recognition and the energetic differentiation of transition states in reactions involving metal complexes and/or metalloproteins have found increasing interest. Several representative publications resume the recent progress accomplished in the field [3–5].

Stereoselectivity in electron transfer has mainly been studied in outer sphere reactions involving inert optically active compounds and was measured by analysis of the reaction products. Few examples of stereoselectivity in inner sphere reactions have been published [6, 7].

In a preceding communication [8] we reported some results on kinetic stereoselectivity in the electron transfer reaction between inert chiral Co^{III} and labile, optically active Fe^{II} complexes, both containing ligands with the basic framework shown in Fig. 1(a). In these reactions the absolute configuration of the labile reagents was assumed to be determined by the stereochemistry of the ligands, for which a stereospecific behaviour in the formation of the corresponding Co^{III} complexes has been found [9]. Compared to examples known from the literature [3, 4], the observed stereoselectivity indicates important chiral recognition between the two reagents. Because the reacting species allow neither hydrogen bonding nor ion pair formation, the molecular recognition must be due to non-bonding interactions, and the two reacting metal centres must therefore be brought sufficiently close together when the electron transfer occurs.

To understand the observed stereoselectivity, it is important to determine the pathway by which the

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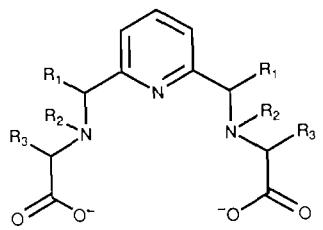
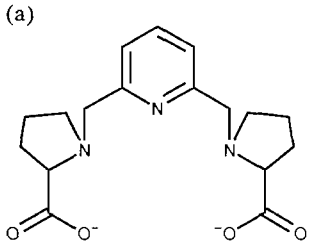


(a)



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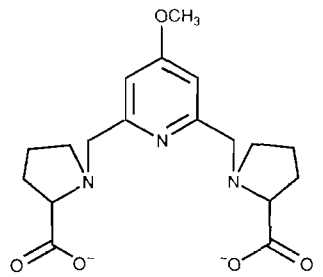

(c)

Fig. 1. (a) Basic framework of the stereospecific pentadentate ligands studied in this work; (b) promp; (c) MeO-promp

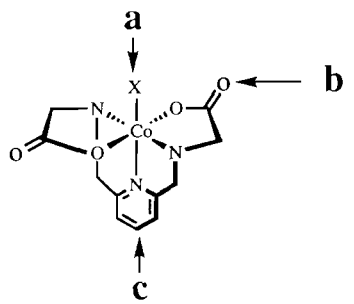

Fig. 2. Possible pathways for electron transfer between Co^{III} and Fe^{II} complexes via (a) the 6th coordinate position, (b) the carboxylate oxygen or (c) the aromatic pyridine

electron transfer between the two metal centres takes place. A transition state in which the water molecule in the sixth coordination site of the Co^{III} species acts as a bridge has tentatively been proposed to explain the stereoselectivity [8] (see Fig. 2). Nevertheless, such a mechanism is highly unusual and electron transfer between aqua ions is in general considered to occur by an outer sphere mechanism [10]. Possible pathways for electron transfer for the inert Co^{III} complex are indicated in Fig. 2. An inner sphere mechanism may involve either the group X coordinated in the sixth coordination site, H_2O in this case (a), or the carboxylate oxygens (b) by bridging to the Fe^{II}. An outer sphere mechanism, on the other hand, could result from an edge-to-edge interaction between the pyridine moieties of the two reacting complexes (c), as it was proposed for the self-exchange reaction in $[Ru(NH_3)_5py]^{3+/2+}$ [11–15].

Even though pathway (c) does not seem very likely in the light of the observed stereoselectivities [8], because of the large distance between the chiral centres of the ligands, it cannot be excluded a priori. To decide whether or not this possibility should be taken into account, we synthesised the new ligand *N,N'*-[(4-methoxypyridine-2,6-diyl)bis(methylene)]bis[(*R*)- or (*S*)-proline], MeO-promp (Fig. 1(c)) in order to compare the reactivity of its complexes with those of the ligand *N,N'*-[(pyridine-2,6-diyl)bis-(methylene)bis[(*R*)- or (*S*)-proline], promp (Fig. 1(b)). Any significant contribution of pathway (c) to the electron transfer should result in a marked difference between the two ligands, promp and MeO-promp, in the observed stereoselectivity of the reaction between their Co^{III} and Fe^{II} complexes.

2. Results and discussion

2.1. Equilibria

The constants for the various equilibria studied are listed in Table 1, along with the constants for *N,N'*-[(pyridine-2,6-diyl)bis(methylene)]bis[(*S*)-alanine] ((*S,S*)-alamp). From these values it is seen that the Co^{II} complex is less stable with the MeO-substituted ligand, which can be explained by its lower basicity. On the other hand, the coordinated water molecule in the Co^{III} complex is less acidic for MeO-promp than for promp ($pK_a = 9.28$ and 9.05, respectively), which would seem to indicate that the methoxy group contributes to increase the electron density in the coordination centre and therefore on the oxygen atom of the coordinated water molecule.

TABLE 1. Equilibrium constants, log *K*, for the systems M^{2+}/(*S,S*)-L; $T = 25$ °C, $\mu = 0.1$ (KNO_3)

Equilibrium	L		
	promp[a]	MeO-promp	alamp[b]
$H_2L/H^+ \cdot HL^-$	9.33(3)[c]	8.97(5)	8.23(2)
$HL^-/H^+ \cdot L^{2-}$	10.02(4)	9.81(2)	9.02(2)
$FeL/Fe^{2+} \cdot L^{2-}$	12 68(3)	12 66(14)	9.62(7)
$CoL/Co^{2+} \cdot L^{2-}$	15.01(7)	14.60(4)	11 70(3)
$CoL(H_2O)/CoLOH^- \; H^+$	9.05(5)	9.28(5)	

[a]Ref 9 [b]Ref. 8 [c]The uncertainty on the last digit is given in parentheses.

2.2. Kinetics

Two kinetic methods may be used to determine the presence of stereoselectivity in the reaction between a kinetically inert Co^{III} complex and a labile Fe^{II} complex of the type shown in Fig. 1: (i) UV–Vis or (ii) circular dichroism (CD) spectroscopy [8]. In the former each enantiomer of the Co^{III} complex is reacted with one enantiomer of the labile Fe^{II} complex. The second method involves reacting the *racemic* Co^{III} complex with one enantiomer of the Fe^{II} complex. Thus, in method (i), $k_{\Delta\Lambda}$ and $k_{\Lambda\Lambda}$ are determined individually, which needs a difference of at least 10% in the rate constants to prove stereoselectivity. In method (ii), on the other hand, $k_{\Delta\Lambda}$ and $k_{\Lambda\Lambda}$ are determined from a single kinetic run by the measurement of the difference between the two enantiomers of the Co^{III} complex as a function of time. This method was used for the results presented in this report. The *racemic* Co^{III} complexes were reacted with the Λ-(*S*, *S*) enantiomer of an Fe^{II} complex. The presence of an excess of ascorbic acid ensures pseudo-first order conditions by constantly reducing the Fe^{III}, and allows the reaction to go to completion. In fact, the redox potential of the couple $[Co^{III}L(H_2O)]^+/[Fe^{II}L']$ is unfavourable, and the equilibrium lies strongly on the side of the Co^{III} complex. $[Fe^{II}L']$ acts therefore as an electron transfer catalyst for the reduction of $[Co^{III}L(H_2O)]^+$ by ascorbic acid; this reaction is very slow in the absence of Fe^{II}. In order to prevent appreciable ligand exchange in the optically active reagent by the racemic ligand liberated during the reaction (the two ligands may be chemically identical or different), the optically active ligand is present in a large excess with respect to the initial concentration of the Co^{III} complex.

The evolution of the concentration with time of the two enantiomers of the Co^{III} complex, [Δ] and [Λ], can thus be expressed by their respective first order rate equations, eqns. (1), where C_0 is the initial concentration of the *rac*-Co^{III} complex, and $k'_{\Delta\Lambda}$ and $k'_{\Lambda\Lambda}$ the corresponding pseudo-first order rate constants*.

$$[\Delta] = C_0/2 \exp(-k'_{\Delta\Lambda}t)$$
$$[\Lambda] = C_0/2 \exp(-k'_{\Lambda\Lambda}t) \quad (1)$$

The second order rate constants, $k_{\Delta\Lambda}$ and $k_{\Lambda\Lambda}$, can be obtained using eqns. (2), after estimation of [FeL'], which is pH dependent, and can be obtained using the equilibrium constants given in Table 1.

$$k'_{\Delta\Lambda} = [FeL']k_{\Delta\Lambda}$$
$$k'_{\Lambda\Lambda} = [FeL']k_{\Lambda\Lambda} \quad (2)$$

*$k'_{\Delta\Lambda}$, which is identical to $k'_{\Lambda\Delta}$, corresponds to reactions between heterochiral complexes. $k'_{\Lambda\Lambda}$, which is identical to $k'_{\Delta\Delta}$, corresponds to reactions between homochiral complexes.

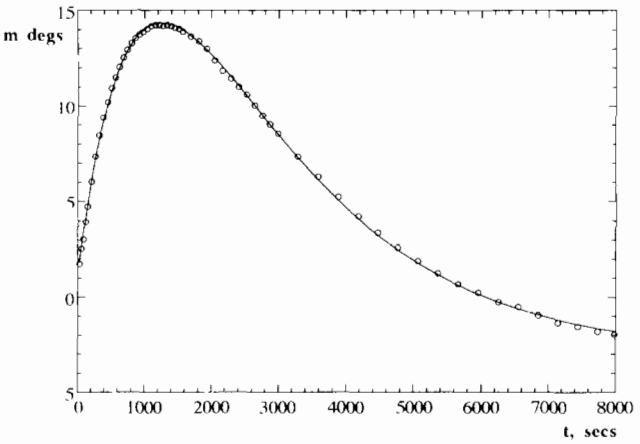

Fig. 3. Typical experimental curve for stereoselectivity determination by circular dichroism shown for the reaction between *rac*-$[Co(MeO\text{-}promp)H_2O]^+$ and [Fe(MeO-(*S*,*S*)-promp)]. *rac*-$[Co^{III}(MeO\text{-}promp)H_2O]^+ = 1.0\times10^{-3}$ M, [MeO-(*S*,*S*)-promp] $= 1.0\times10^{-2}$ M, $[Fe^{II}] = 4.0\times10^{-3}$ M, [ascorbic acid] = 0.1 M, [acetate buffer] = 0.1 M, pH = 4.0, T = 25 °C.

The observed CD signal in millidegrees ($m°$) is given by eqn. (3), where $\Delta\epsilon_\Delta$ and $\Delta\epsilon_\Lambda$ are the molar extinction coefficient differences of Δ-$[Co(R, R)L]^+$ and Λ-$[Co(S, S)L]^+$ respectively, and l is the cell path length:

$$m° = \Delta\epsilon_\Delta l33000[\Delta] + \Delta\epsilon_\Lambda l33000[\Lambda] \quad (3)$$

Since [Δ] and [Λ] are defined by eqns. (1) and $\Delta\epsilon_\Lambda = -\Delta\epsilon_\Delta$, we can write eqn. (4):

$$m° = \Delta\epsilon_\Delta l33000C_0/2\ \{\exp(-k'_{\Delta\Lambda}t) - \exp(-k'_{\Lambda\Lambda}t)\} \quad (4)$$

The individual rate constants and the stereoselectivity, $S = k_{\Delta\Lambda}/k_{\Lambda\Lambda}$, can now be determined using a standard curve fitting programme, taking into account the presence of other optically active species, e.g. $[Co^{II}L]$, formed during the reaction. The signal increases as the relative amount of the slower reacting enantiomer increases (in a positive direction if $\Delta\epsilon$ for this enantiomer is positive, and vice versa), then returns to a constant final value. A typical experimental curve is shown in Fig. 3 for the reaction between *rac*-$[Co(MeO\text{-}promp)H_2O]^+$ and Λ-[Fe(MeO-(*S*, *S*)promp)]. The faster reacting couple is Δ-$[Co(R, R)L]^+/\Lambda$-[Fe(*S*, *S*)L], and, as $\Delta\epsilon$ for Δ-$[Co(MeO\text{-}(R, R)promp)H_2O]^+$ is -1.88 at 503 nm, the wavelength used in the experiment, the observed signal increases in the positive direction and then returns to a value near zero, which corresponds to the equilibrium concentration of the Co^{II} complexes under the prevailing conditions.

One question about the exact origin of the CD signal remains to be discussed. In fact, redox mediated ligand exchange on the Co^{III} complexes could occur during the electron transfer reaction, according to the following scheme:

$$[Co^{III}((R,R)L)H_2O]^+ + [Fe^{II}(S,S)L'] \xrightarrow{k_{1R}} [Co^{II}(R,R)L] + [Fe^{III}(S,S)L']^+ \quad (I)$$

$$[Co^{III}((S,S)L)H_2O]^+ + [Fe^{II}(S,S)L'] \xrightarrow{k_{1S}} [Co^{II}(S,S)L] + [Fe^{III}(S,S)L']^+ \quad (I')$$

$$[Co^{II}(R,R)L] + H_2(S,S)L' \overset{K}{\rightleftharpoons} [Co^{II}(S,S)L'] + H_2(R,R)L \quad (II)$$

$$[Co^{II}(S,S)L] + H_2(S,S)L' \overset{K}{\rightleftharpoons} [Co^{II}(S,S)L'] + H_2(S,S)L \quad (II')$$

$$[Co^{II}(S,S)L'] + [Fe^{III}(S,S)L']^+ \xrightarrow{k_{2S}} [Co^{III}((S,S)L')H_2O]^+ + [Fe^{II}(S,S)L'] \quad (III)$$

$$Red. + [Fe^{III}(S,S)L']^+ \xrightarrow{k_3} [Fe^{II}(S,S)L'] + Ox \quad (IV)$$

By voltammetric measurements the redox potentials $E_{1/2}$(NHE) have been estimated as 0.04 ± 0.01 V for $[Co(promp)H_2O]^{+/0}$ and as 0.17 ± 0.01 V for $[Fe(promp)]^{+/0}$, respectively (pH 7, phosphate). From these values an approximate k_2/k_1 ratio of 160 can be calculated.

When the optically active ligand is present in a large excess, the rapid equilibrium (II) lies mainly on the right side, and the back reaction of (I) can therefore be neglected. On the other hand, the reoxidation reaction (III), which is the back reaction of (I') when L = L', can modify the relative concentration of $[Co((S,S)L)H_2O]^+$, the variation with time of which will be a function not only of k_{1S} but also of the ratio k_{2S}/k_3. In the case of identical ligands (L = L') the measured stereoselectivity will then be too high when the faster reacting couple is the one with different absolute configuration of the two reacting complexes, and too low (or even inversed), when the couple of complexes with identical configuration reacts faster.

The problem can in general be solved easily, when the ligands L and L' are chemically different, and when they form Co^{III} complexes with sufficiently different CD spectra, allowing measurement at a wavelength at which the complex formed by redox mediated ligand exchange has no CD activity. This can be illustrated for the reaction of *rac*-$[Co(promp)H_2O]^+$ with [Fe(*S*, *S*)alamp]. The CD spectra for the (*S*, *S*)-Co^{III} complexes of the three ligands used in this study are shown in Fig. 4. At 503 nm the CD spectrum of $[Co^{III}(alamp)H_2O]^+$ crosses the zero line, and the measured CD intensity is independent of the formation of these species by reaction (III). Nevertheless, this method requires complete ligand exchange in the labile Co^{II} species, depending on their relative stabilities and the concentration ratio of the ligands. In the case of identical ligands this procedure cannot be applied. As the reoxidation of the Co^{II} complexes is a function of the k_2/k_3 ratio, it is possible to identify separately the amount of the optically active Co^{III} complex due to the stereoselectivity and to reoxidation of the optically active Co^{II} complex by measuring the stereoselectivity as a function of the concentration of ascorbic acid. Figure 5(a) shows the calculated maximum in the difference, $([R]-[S])$, of the two enantiomeric Co^{III} complexes for different k_{1R}/k_{1S} ratios as a function of the $\log(k_2/k_3)$ ratio. The simulation is made assuming quantitative ligand exchange in the labile Co^{II} complex (eqn. (II)) and the steady state approximation for $[Fe^{III}L]^+$. It must be noticed that the real kinetic stereoselectivity, given by k_{1R}/k_{1S}, shows a limiting *%ee* value of 50%, corresponding to the case where one enantiomer is reduced whereas the other is not. For small amounts of reoxidation (< 10%) the graphic representation of max. $\%ee = f(k_2/k_3)$ is almost linear, (Fig. 5(b)), which allows an easy extrapolation to zero and the determination of the real stereoselectivity of the reaction. For the stereoselectivities observed in the systems described in this study (≈ 2), it can be seen from Fig. 5 that the contribution due to redox-mediated ligand exchange can be neglected when reaction (IV) is about 10^4 times faster than reaction (III).

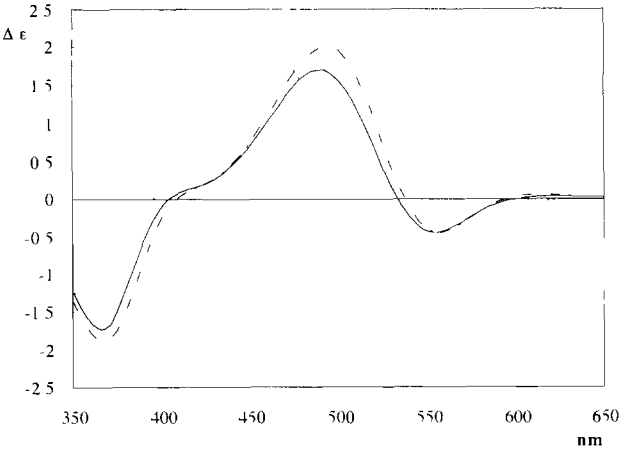

Fig. 4 Circular dichroism spectra at 25 °C of $[Co((S,S)alamp)H_2O]^+$ (– – –), $[Co(MeO\text{-}(S,S)promp)H_2O]^+$ (- - -) and $[Co((S,S)promp)H_2O]^+$ (——).

The second order rate constants and stereoselectivity for the various Co^{III}/Fe^{II} couples studied are given in Table 2. For the reaction of *rac*-[Co(promp or MeO-promp)H_2O]$^+$ with [Fe(*S*, *S*)alamp] the observed rate constants were independent of the concentration of ascorbic acid (HAsc). Since the reactions were measured at 503 nm (wavelength at which $[Co^{III}(alamp)H_2O]^+$ has no CD intensity), we expect no ascorbic acid dependence. In addition, experiments at 367 nm (see Fig. 4) gave the same stereoselectivities (1.9 and 2.0,

TABLE 2. Kinetic results for the reduction of *rac*-[Co(III)L(H_2O)]$^+$ by [Fe(II)-(*S*,*S*)-L']

L	L'	$k_{\Delta\Delta}$ (M^{-1} s^{-1})	$k_{\Lambda\Lambda}$ (M^{-1} s^{-1})	*S*
promp	alamp	33.9 ± 1.7	17.5 ± 0.9	1 9 ± 0.2
	promp	2.7 ± 0 4	1.3 ± 0.1	2 0 ± 0.2
	MeO-promp[a]	0.88 ± 0.07	0.41 ± 0.03	2.1 ± 0.2
MeO-promp	alamp	26.9 ± 1.3	13.3 ± 0 7	2.0 ± 0.2
	promp[a]	2.8 ± 0.2	1 2 ± 0.1	2.4 ± 0 2
	MeO-promp[a]	0.46 ± 0 03	0.26 ± 0.02	1 9 ± 0.2

rac-[Co^{III}L] = 1.0×10^{-3} M, [Fe^{II}] = 4.0×10^{-3} M, [(*S*,*S*)-L'] = 1.0×10^{-2} M, $0.02 \leqslant$ [HAsc] $\leqslant 0.5$ M, [acetate buffer] = 0.1 M, pH ≈ 4.0, *T* = 25 °C. [a]Extrapolated to 1/[HAsc] = 0.

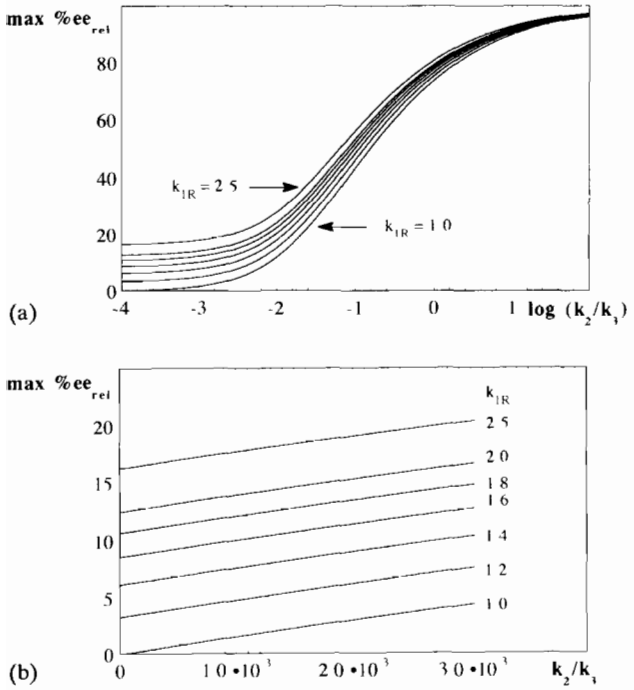

Fig. 5. Calculated maximum relative *%ee* for different k_{1R}/k_{1S} ratios as a function of (a) $\log k_2/k_3$ and (b) k_2/k_3. $k_{1S} = 1\,0$; $k_{2S} = 100$; reading from bottom, $k_{1R} = 1.0$–2.5. $\%ee_{rel} = 100([R] - [S])/C_0$, where C_0 is the total initial concentration.

respectively for promp and MeO promp) thus ruling out appreciable ligand exchange. In the case of the couple promp/promp, the observed rate constants were also independent of the ascorbic acid concentration. We conclude that there is no ligand exchange between the Co^{III} complexes for these couples.

For the other couples studied, the rate constants and observed stereoselectivities varied with the ascorbic acid concentration. Nevertheless, the maximum observed variation of the observed CD intensity was small. The difference between the lowest concentration of ascorbic acid and the value extrapolated to 1/[HAsc] = 0 did not exceed 10%. To verify that this was not due to the slow reduction of the Co^{III} complex by HAsc, we measured this reaction in the absence of Fe^{II}. Over the time span of the experiments (8 h) there was no reduction. The values given in Table 2 are those obtained by extrapolation to 1/[HAsc] = 0.

If the electron transfer was via an outer sphere mechanism with an edge-to-edge interaction between the pyridine moieties, then the presence of a methoxy group should effectively block this position. The observed rate constants and stereoselectivities should be quite altered. However, if we compare the rate constants and stereoselectivities for promp and MeO-promp with each ligand, we notice that there is practically no effect due to the methoxy group. Thus, we conclude that an outer sphere reaction, as proposed in Fig. 2(a), can be excluded.

The stereoselectivities and rate constants observed in this study, together with other results [8, 16], indicate that the electron transfer reaction mechanism is inner sphere, and that the carboxylate moiety of the Co^{III} complex may act as the bridge. For the six couples studied, the observed stereoselectivities are among the highest observed for electron transfer between chiral metal centres, and are all quite similar. If we consider the second order rate constants given in Table 2, changing the substituent on the ligand of the Co^{III} complex has little, if any, effect on the rates. However, changing the ligand of the Fe^{II} complex has a much greater effect on the rate of the reaction. The rates decrease in the order $k_{alamp} > k_{promp} > k_{MeO\text{-}promp}$. This is the inverse order of the complex formation constants and may therefore be the expression of the binding ability of the Fe^{II} centre to the carboxylate group in the precursor complex.

3. Experimental

3.1. General

Optical rotations were measured on a Perkin-Elmer 241 polarimeter; CD measurements were made using a Jasco J-500 spectropolarimeter; UV–Vis spectra were obtained from a Uvikon 820 spectrophotometer; ^1H

NMR spectra were obtained from a Bruker AMX 400 (^{1}H: 400 MHz) spectrometer.

3.2. Syntheses

N,N'-[(Pyridine-2,6-diyl)bis(methylene)]bis[(*S*)-alanine], (*S,S*)-alamp, was made as in ref. 9. *N,N'*-[(pyridine-2,6-diyl)bis(methylene)]bis[(*R*)- or (*S*)-proline] dichlorohydrate, (*R,R*)- or (*S,S*)-promp·2HCl, aqua {*N,N'*-[(pyridine-2,6-diyl)bis(methylene)]bis[(*R*)- or (*S*)-proline]} cobalt(III) perchlorate, [Co(*R,R*)- or (*S,S*)-promp)H_2O]ClO_4 were synthesised as described in ref. 10.

3.2.1. N,N'-[(4-Methoxypyridine-2,6-diyl)-bis(methylene)]bis[(S)-proline] chlorohydrate, MeO-(S,S)-promp·HCl

An aqueous solution of 3.05 g (0.03 mol) *S*-proline is neutralised by a stoichiometric amount of NaOH. 2.2 g (0.01 mol) of 2,6-bis(dichloromethyl)(4-methoxy)pyridine (obtained according to ref. 17) in 30 ml of distilled methanol are added dropwise to 50 ml of a constantly stirred methanolic suspension of sodium *S*-prolinate at reflux. The pH is maintained at 9.5 by addition of a methanolic solution of 2 M NaOH (phenolphthalein) and refluxed for 24 h. The mixture is cooled, neutralised with HCl and evaporated to dryness. The residue is dissolved in 500 ml water and adsorbed on a cation exchange column (Dowex 50X-8, H^+). The column is washed with H_2O until neutral, and the product eluted with 0.1 M NaOH. All the fractions containing MeO-promp (R_f=0.25, TLC analysis (silica gel BuOH:AcOH:H_2O 12:6:6) and UV spot) are collected and evaporated to dryness. 1.9 g of an oily residue are obtained and dissolved in a minimum amount of H_2O. Two equivalents of conc. HCl are added and the chlorohydrate crystallises at 0 °C from an ethanol/acetone mixture. After two recrystallisations, 0.43 g of MeO-(*S, S*)-promp was obtained. Yield 12%. $[\alpha]^{rt}$ (λ): −84.5° (365), −22.1° (578), c=0.27, H_2O. ^{1}H NMR (400 MHz, DMSO, reference TMS) 2.01 (m, 6H, CH_2 pyrrolidine ring); 2.30 (m, 2H, CH_2 pyrrolidine ring); 3.05 (m, 2H, pyrrolidine ring); 2.50 (m, 2H, pyrrolidine ring); 3.87 (s, 3H, −OCH_3); 4.05 (m, 2H, C*H–); 4.28–4.41 (dd, 4H, py-CH_2–N); 7.14 (d, 2H, py).

3.2.2. N,N'-[(4-Methoxypyridine-2,6-diyl)-bis(methylene)]bis[(R)-proline] chlorohydrate, MeO-(R,R)-promp·HCl

Synthesised as described in Section 3.2.1 using 2.44 g (0.02 mol) (*R*)-proline and 1.75 g (0.01 mol) 2,6-bis(dichloromethyl)(4-methoxy)pyridine. After ion exchange column chromatography, Dowex 50 (H^+), 1.52 g of ligand were obtained as a yellowish oil (crude yield 45%). All efforts to crystallise the ligand yielded very few crystals, which were analysed only by NMR. R_f (butanol/H_2O/CH_3COOH 12:6:6)=0.25. ^{1}H NMR: (400 MHz, D_2O, reference DSS) 2.22 (m, 6H, CH_2 pyrrolidine ring); 2.59 (m, 2H, CH_2 pyrrolidine ring); 3.38 (m, 2H, pyrrolidine ring); 3.85 (m, 2H, pyrrolidine ring); 3.93 (s, 3H, –OCH_3); 4.39 (m, 2H, C*H–); 4.54–4.61 (dd, 4H, py-CH_2–N); 7.12 (d, 2H, py). The *racemic* mixture is obtained by mixing equimolar amounts of the (*R,R*) and (*S,S*) enantiomers, followed by recrystallisation.

3.2.3. Aqua {N,N'-[(4-methoxypyridine-2,6-diyl)-bis(methylene)]bis[(S)-proline]}cobalt(III) perchlorate, [Co(MeO-(S,S)-promp)H_2O]ClO_4

2.66 g (7.32 mmol) of MeO-(*S,S*)-promp, in 150 ml H_2O are added to a vigorously stirred solution of 2.72 g (7.53 mmol) $Na_3[Co(CO_3)_3\cdot 3H_2O]$ and 0.12 g of activated charcoal (Riedel-de-Haën), at 50 °C. The pH of the mixture is maintained at 6.5 for 5 h with glacial acetic acid. The activated charcoal is eliminated and the mixture adsorbed on a Sephadex column (SP C25, Na^+). The neutral fraction is eluted with water and the cationic complex, eluted with 1% $NaClO_4$, is desalted on a column of Sephadex SG-10. The desalted fraction is evaporated almost to dryness, heated until completely redissolved and left to crystallise at room temperature. After two crystallisations in H_2O, 1.14 g of red crystals were obtained. Yield 29%. $[\alpha]^{rt}$ (λ): −1459.2° (365), −135.4° (578), c=0.027, H_2O. ^{1}H NMR (400 MHz, DMSO) 2.04 (m, 6H, CH_2 pyrrolidine ring); 2.37 (m, 2H, CH_2 pyrrolidine ring); 2.49 (m, 2H, pyrrolidine ring); 3.00 (m, 2H, pyrrolidine ring); 3.67 (m, 2H, C*H–); 3.96 (s, 3H, −OCH_3); 4.50–4.69 (AB system, 4H, py-CH_2–N); 7.28 (s, 2H, py).

3.2.4. Aqua {N,N'-[(4-methoxypyridine-2,6-diyl)-bis(methylene)]bis[(R)-proline]}cobalt(III) perchlorate, [Co(MeO-(R,R)-promp)H_2O]ClO_4

Synthesised as described in 3.2.3, from 1.84 g (5.06 mmol) of crude MeO-(*R,R*)-promp and 1.83 g (5.21 mmol) $Na_3[Co(CO_3)_3\cdot 3H_2O]$. After three recrystallisations in H_2O, 0.82 g of red crystals were obtained. Yield 30%. $[\alpha]^{rt}$ (λ): +1433.4° (365), +124.2° (578), c=0.027, H_2O. ^{1}H NMR (400 MHz, D_2O) 1.78 (m, 2H, CH_2 pyrrolidine ring); 2.05 (m, 2H, CH_2 pyrrolidine ring); 2.24 (m, 4H, pyrrolidine ring); 2.59 (m, 2H, pyrrolidine ring); 3.18 (m, 2H, pyrrolidine ring); 3.92 (dd, 2H, C*H–); 3.98 (s, 3H, –OCH_3); 4.80–4.92 (AB system, 4H, py-CH_2–N); 7.28 (s, 2H, py). The *racemic* mixture is obtained by mixing equimolar amounts of the (*R,R*) and (*S,S*) enantiomers, followed by recrystallisation.

3.3. Potentiometric measurements

All solutions were prepared with bidistilled H_2O. Titration curves were measured at 25.0±0.1 °C, under

N_2 using 0.01 M NaOH as titrant. $[L^{2-}] \approx 2.5 \times 10^{-3}$ M for the acidity constant measurements, and $[M^{2+}]$ and $[L^{2-}] \approx 1.5 \times 10^{-3}$ M, for the complex formation measurements, $\mu = 0.1$ (KNO_3). The dissociation and equilibrium constants were determined using the program SCOGS [18].

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