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Chiral recognition of amino esters by a ruthenium porphyrin complex: kinetics of the exchange process determined by ^{1}H NMR

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Abstract

The synthesis of a (carbonyl) (valine methyl ester) ruthenium(II) picket-fence complex bearing optically active α-methoxy-α(trifluoromethyl)phenylacetyl residues on both sides of the porphyrin plane (α,β,α,β-isomer) is described. For various amino esters, chiral recognition was observed for the complexation of the ligand with up to 52% enantiomeric excess for *tert*-leucine methyl ester. The dissociation rate constants of the two enantiomers of valine methyl ester were determined by ^{1}H NMR using magnetization transfer experiments, showing that the origin of the enantioselectivity in favour of the (L)-valine (ca. 2.6:1) resides in the difference between the kinetics of the axial ligand dissociation of the two enantiomers.

1. Introduction

The selective complexation of amino acids by synthetic host compounds has been the focus of an increasing number of publications. These studies have made essential contributions towards the understanding of non-covalent interactions involving amino acids. Some of the recently reported synthetic hosts rely on metalloporphyrin complexation through hydrogen bonding with amino acids. This phenomenon was nicely recognized by Ogoshi et al. who used multifunctional and chiral porphyrins as model receptors for chiral recognition.[1] Two metal ions, Rh and Zn, were studied in detail as interaction sites. As porphyrin multifunctional receptors, zinc was found to be advantageous over rhodium due to its weak coordinating interaction, allowing the other weak interactions inside the porphyrin pocket to have a greater influence. Some other reports have also been devoted to the use of metal porphyrins in chiral recognition.[2–5]

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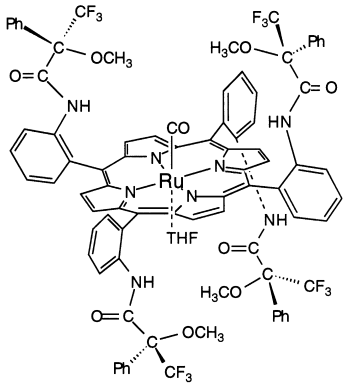

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Figure 1. Chiral complex

We have shown earlier[5] that the interactions of various amino esters with chiral ruthenium porphyrins were weakly selective in the absence of a simultaneous oxidation reaction. Reasons for this are that the host–guest interaction was mainly of a steric nature and the absence of hydrogen bonding in the chiral recognition. This paper illustrates how axial ligand dissociation can, on the basis of chiral carbonyl ruthenium porphyrins as hosts, lead to a large increase in the chiral recognition ability. The present investigation examines, in detail, the reactions of amino esters with a chiral carbonyl ruthenium porphyrin. Mixed-ligated (carbonyl) (amino ester) Ru(II) complexes were obtained with chiral recognition. The kinetics of axial ligand dissociation for the two enantiomers of valine methyl ester (Val-OMe) were also determined by ^{1}H NMR using magnetization transfer experiments. The study showed that the origin of the enantioselectivity in favour of the (L)-valine (ca. 2.6:1) resides mainly in the difference between the dissociation rate constants of the two enantiomers.

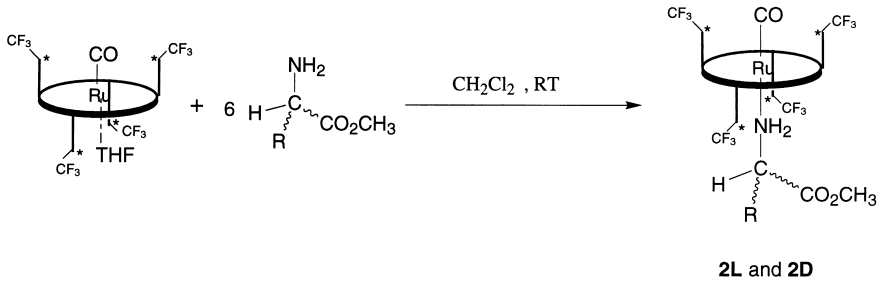
2. Results and discussion

In order to more rationally control the chiral recognition, we have re-examined a symmetric *meso*-tetraarylporphyrin P* bearing four chiral groups, derived from Mosher's acid, on the porphyrin (the α,β,α,β-isomer was used for this study).[6] The ruthenium complex **1** (Fig. 1) was prepared by treatment of the optically active porphyrin with $Ru_3(CO)_{12}$ in *o*-dichlorobenzene at 170°C as reported previously.[6] In order to obtain a six-coordinate (carbonyl) ruthenium derivative, tetrahydrofuran was added as the sixth ligand to the resulting solution before purification. The presence of the ruthenium–carbonyl bond is confirmed by the IR spectrum which displays a typical absorption at 1970 cm^{-1}. The presence of a CO axial ligation in these porphyrins decreases the symmetry of the molecule, compound **1** having two different faces. Thus, the ^{19}F NMR signal due to equivalent CF_3 groups in the chiral unmetallated porphyrin (D_2 symmetry) is split into two signals on lowering to C_2 symmetry in **1**, with the C_2 axis normal to the porphyrin plane.

2.1. Chiral recognition of amino esters using ^{19}F and ^{1}H NMR as a probe

The addition of 6 equiv. of racemic valine methyl ester to complex **1** results in the formation of two diastereoisomers: the mixed-ligated complexes (P*)Ru(CO)($NH_2CH(CO_2Me)^iPr$) **2L** and **2D** (Scheme 1). Due to C_2 symmetry, the ^{19}F spectrum of each isomer has two types of fluorine groups

and the ^{19}F spectra of the mixture of the two isomers exhibited four magnetically inequivalent fluorine groups. To obtain the stereochemical identity of each isomer, the same reaction was carried out with pure (L)- and (D)-valine methyl esters.



Scheme 1.

By a procedure similar to that described above, complexation of racemic alanine methyl ester, valine methyl ester, *tert*-leucine methyl ester and tyrosine methyl ester also gave the mixed-ligated complexes (P*)Ru(CO)($NH_2CH(CO_2Me)R$) (with R=Me, ^{i}Pr, ^{t}Bu and *p*-OH-Phe). The determination of the chiral recognition was possible by integrating the signals obtained in ^{19}F NMR. The analysis of the ^{1}H NMR spectra also allowed the determination of the level of chiral recognition by integration of the upfield shifted signals of the ligands (as the NMR probe we used the methyl groups of the side chain in alanine, valine and *tert*-leucine methyl ester, and the *o*-phenyl protons in tyrosine). Data are listed in Table 1.

Firstly, it appears that the stereoselectivity favours the formation of the (L)-isomer. Secondly, the highest value of the ee is obtained with *tert*-leucine methyl ester (52%). Thirdly, the reaction is quite sensitive to the nature of the amino ester: a very weak asymmetric induction (8%) was observed with the tyrosine ester. These diamagnetic compounds are well-characterized by the usual spectroscopy methods (IR, UV–visible, mass spectroscopy).

2.2. ^{1}H NMR spectrum of (P*)Ru(CO)((L)-$NH_2CH(CO_2Me)^{i}Pr$) **2L**

To get more information on the interactions between the ligand and the chiral porphyrin, we analyzed the ^{1}H NMR spectrum of the complex (P*)Ru(CO)($NH_2CH(CO_2Me)^{i}Pr$) **2L** (Fig. 3) prepared from **1** and (L)-valine methyl ester. The spectrum shows the general features described previously for metalloporphyrin–amino acid derivatives.[2] Protons of the amine group of the coordinated amino ester are different (δ=−5.55 and −4.09 ppm), showing the absence of nitrogen inversion due to complexation, and strongly shielded ($\Delta\delta=\delta_{bound}-\delta_{free}$=−7.10 and −5.64 ppm, respectively) due to the ring current effect of the porphyrin. The shielding decreases from the C_α to the C_β groups (for example, $\Delta\delta$=−6.59 and −2.43 ppm, respectively, for $C_\alpha H$ and $C_\beta H$), and the lower shift is observed for the ester chain ($\Delta\delta$=−1.22 ppm

Table 1
Chiral recognition of amino esters with complex **1**

Complex	Amino acid methyl ester	Chiral recognition (%)
1	Alanine	18
1	Valine	45
1	tert-Leucine	52
1	Tyrosine	8

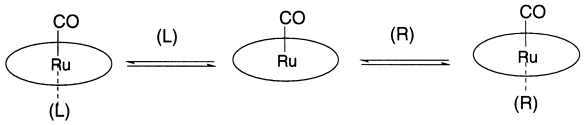


Figure 2.

for the methyl group). No ligand exchange occurs on the ^{1}H NMR chemical shift time-scale at room temperature.

2.3. Complexation dynamics

The chiral recognition observed on complexation of amino esters, which is, at first, surprising given the lack of enantioselectivity exhibited in the synthesis of the complex (P*)Ru(valine methyl ester)$_2$ from the bis(acetonitrile) species,[5] prompted us to do some additional studies. One explanation for the chiral recognition could be the kinetics of the axial ligand rate dissociation: no ligand exchange was observed in the bis(amino ester) derivative.[5] In contrast, exchange of pure (L)-valine methyl ester ruthenium carbonyl complex **2L** with pure (D)-valine methyl ester at room temperature in dichloromethane (12 equiv.) leads to the formation of the other isomer **2D** with 78% yield after a few minutes. For this reason, we undertook the determination of the dissociation rate constants of the complexes **2L** and **2D** by magnetization transfer experiments. In the presence of an excess of ligand, the ligand exchange proceeds by a dissociative mechanism, with a five-coordinate transition state (Fig. 2).

The first ^{1}H NMR magnetization transfer experiments on **2L** and **2D** were carried out at 298 K, but no detectable effect on the difference spectra after irradiation of the methyl resonance of the free ligand was observed. However, chemical exchange was evident at 323 K from the measurement of magnetization transfer: pre-irradiation at the frequency of one of the methyl resonances (δ=0.92 ppm) of the C_β group of free (L)-valine methyl ester at a power level sufficient to abolish the resonance in the spectra caused a decrease in the intensity of the corresponding methyl resonance (δ=−0.89 ppm) of the valine-ligated ruthenium complex (Fig. 3). Hence the ligand is cycled at this temperature between free and complexing forms by virtue of ligand exchange.

Saturation transfer NMR experiments can also be used to measure first-order rate constants in reversible reactions.[7] Consider the simple chemical reaction:

$$A \rightleftharpoons B$$

where A and B have unique identifiable magnetizations. If the species B is saturated, and the magnetization of A $M_A(t)$ is measured, one can write:[7]

$$\frac{dM_A(t)}{dt} = \frac{M_0 - M_A(t)}{T_1(A)} - kM_A(t) \quad (1)$$

with M_0=$M_A(0)$ and T_1(A) is the spin lattice relaxation time of A. The constant k represents the rate constant from A to B; in our case k is the dissociation constant.

The amount of magnetization in A (M_A) after prolonged saturation of B is described by a steady-state situation with ($dM_A(t)/dt$=0), which leads to:

$$k = \frac{(\Delta M_A/M_0)}{(1 - \Delta M_A/M_0)T_1(A)} \quad (2)$$

with ΔM_A=M_0−M_A. In this method, the spin-lattice relaxation time of the non-saturated resonance is assumed to be known. Since this latter value is not directly accessible at 323 K, we used the method

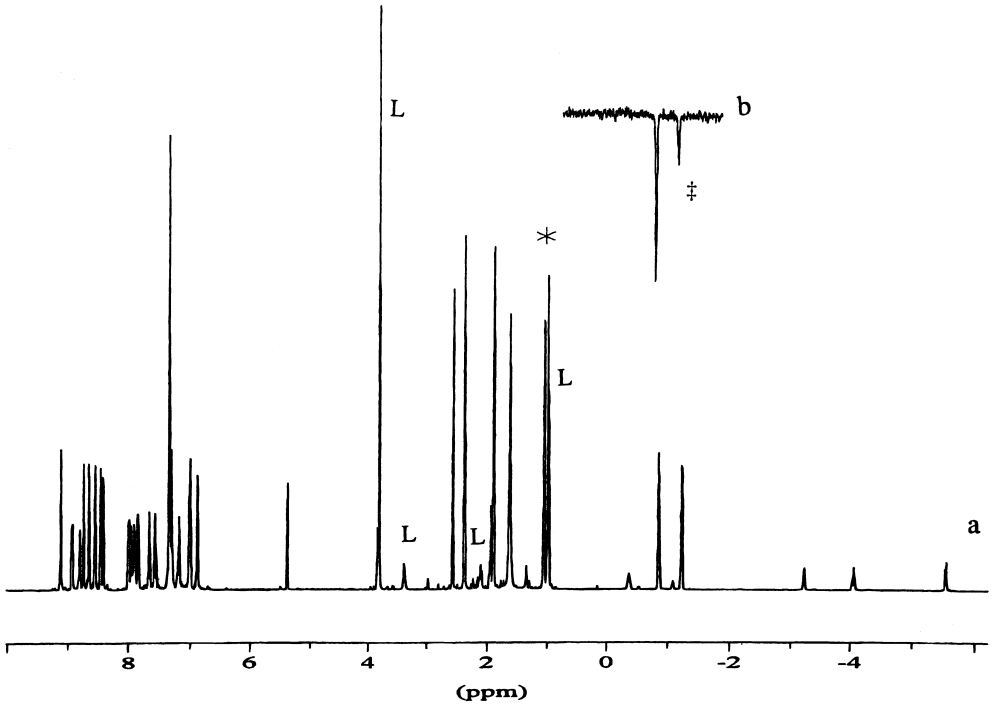


Figure 3. (a) ^{1}H NMR spectrum of **2L**; (b) difference spectrum of magnetization transfer experiment with (L)-valine methyl ester. *, irradiated signal; L, ligand excess; ‡, signal corresponding to undesirable magnetization transfer due to partial saturation of the second methyl group of the free ligand

Table 2
Relaxation time T_{obs} and dissociation rate constants k of complexes **2L** and **2D**

Complex	T_{obs} (s)	k (s^{-1})
2L	0.446	0.15
2D	0.408	0.36

described previously by Mann.[8] Determination of the relaxation time (T_{obs}(A)) of the methyl group of the ligated amino ester by an inversion recovery experiment while saturating the corresponding signal of the free ligand allows the calculation of k through the relation:

$$k = \frac{(\Delta M_A / M_0)}{T_{obs}(A)} \tag{3}$$

The T_{obs}(A) values and exchange rates derived from this method are given in Table 2.

These data are close to the constant found for the dissociation of *tert*-butylpyridine in a porphyrin ruthenium carbonyl complex (0.09 s^{-1}).[9] More importantly, they also reveal that the dissociation rate constant for the (D)-enantiomer of valine methyl ester is higher (k_D/k_L=2.4) than the dissociation rate constant for the (L)-enantiomer. This led to the prediction of a chiral recognition for the (L)-enantiomer with an enantiomeric excess of 41%, which is in accordance with the analysis of the ^{19}F and ^{1}H NMR of the mixture of the two diastereoisomers recorded at 323 K giving an enantiomeric excess of 45% ((L)/(D)=2.6). Accordingly, the origin of the chiral recognition resides mainly in the kinetics of axial

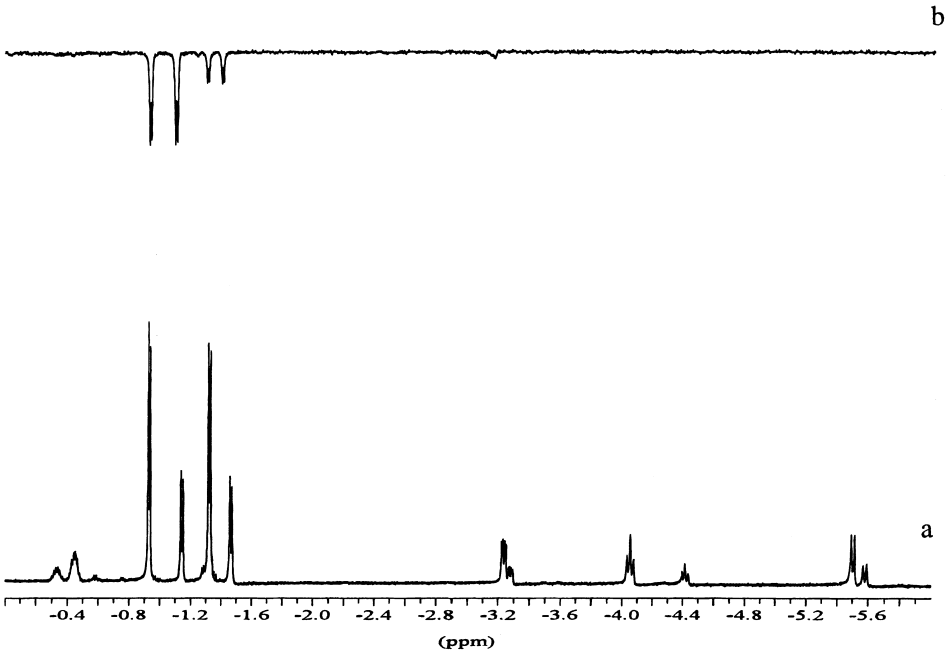


Figure 4. (a) ^{1}H NMR spectrum of the racemic mixture (**2L**+**2D**) obtained after addition of an excess of racemic valine methyl ester to **1**; (b) difference spectrum of magnetization transfer experiment with racemic valine methyl ester

ligand dissociation. These results also explain the lack of selectivity in the formation of the complex (P*)Ru(Val-OMe)$_2$,[5] in which no ligand exchange occurs. The results also agree with the work of Marchon et al. on the chiral recognition of amine and amino alcohol with cobalt porphyrins.[4,10] The difference between the dissociation rate constants of the two enantiomers of valine methyl ester may be attributed to differences in the hydrogen bonding between the NH group of the chiral pickets and the carbonyl of the ester of the amino ester. Such interactions were indeed proposed previously by us in a chiral porphyrin ruthenium bis((L)-valine methyl ester) complex on the basis of its crystal structure.[5]

In view of these results, we can also take advantage of the fact that assignments are known for both diastereoisomers and thus magnetization transfer spectroscopy can also be used in the presence of a racemic ligand. The spectra of the diastereomeric mixture (**2L**+**2D**) obtained by the addition of an excess of racemic valine methyl ester to **1**, and the difference spectrum observed upon saturation of the side chain methyl signal of racemic free valine methyl ester (δ=0.92 ppm), are shown in Fig. 4. The amount of magnetization transfer is similar for the two diastereoisomers **2L** and **2D** (δ=−0.89 and −1.03 ppm, respectively). Since we are now dealing with the racemic ligand, the amount of transfer for each isomer is proportional to the dissociation rate constant and to the concentration of this isomer.[7] In these reactions, the relative changes of the free ligand concentrations are neglected by assuming (D)=(L). This simplification is valid in our system since the exchange reaction proceeds with a large excess of ligands. Consequently, the ratio of saturation transfer to the two diastereoisomeric complexes (**2L** and **2D**) must reflect the ratio of their association rate constants. Thus, this experiment provides the quantitative control and indirect evidence to show that ligand association rates are similar for the two valine enantiomers.

3. Conclusion

Taken together these results indicate that the chiral recognition of amino esters by a chiral ruthenium porphyrin is not governed by ligand association to the metal but by ligand dissociation. We believe this NMR method should have large applicability to other ligand exchange reactions although the magnetization transfer technique cannot be considered as a general method, since ligand exchange must occur within a narrow timespan (typically 0.1–20 s^{-1}).

4. Experimental

4.1. General procedures

NMR spectra were recorded in $CDCl_3$ on a Bruker DPX 200 or DMX 500 spectrometer and chemical shifts were referenced to internal TMS. Dichloromethane was distilled over phosphorus pentoxide. The porphyrin P* was synthesized as described previously.[6] The corresponding ruthenium carbonyl complex was obtained by refluxing the porphyrin in *o*-dichlorobenzene with Ru_3CO_{12}.[6] Amino acid derivatives were purchased from Sigma, and their hydrochloride salts were neutralized with a 2N aqueous solution of sodium hydroxide.

4.2. Chiral recognition of amino acid derivatives with carbonyl complexes

Chiral complex **1** (5.6 μmol) was dissolved in deuteriated chloroform (0.5 ml), and a solution of 33 μmol (6 equiv.) of amino acid methyl ester in neutralized chloroform (0.7 ml) was added. The mixture was immediately analyzed by NMR.

4.3. *(P*)Ru(CO){(NH$_2$)CH(CO$_2$Me)^{i}Pr}* ***2L***

Valine methyl ester (4.1 mg, 33.0 μmol) was added at room temperature to 9.3 mg of **1** (5.6 μmol) in dichloromethane (2 ml). After 5 min of stirring, the product was purified on acid alumina (dichloromethane), yielding 7.6 mg of **2L** (76%). ^{1}H NMR ($CDCl_3$, δ): −5.55 (d, 1H, 8.8 Hz, NH), −4.09 (t, 1H, 8.5 Hz, NH), −3.28 (m, 1H, CH*), −1.26 (d, 3H, 7.0 Hz, CH_{3^iPr}), −0.89 (d, 3H, 6.7 Hz, CH_{3^iPr}), −0.39 (m, 1H, $CH_{^iPr}$), 1.86 (s, 3H, OCH_3), 1.87 (s, 3H, OCH_3), 2.33 (s, 6H, OCH_3), 2.52 (s, 3H, CO_2CH_3), 6.82–7.25 (m, 20H, Ph pickets), 7.54 (td, 2H, 0.9 Hz, 7.6 Hz, H-5 of *meso* Ph), 7.64 (td, 2H, 0.9 Hz, 7.3 Hz, H-5 of *meso* Ph), 7.80–8.00 (m, 8H, H-5+H-4 of *meso* Ph), 8.38 (d, 2H, 4.9 Hz, H_{pyrr}), 8.43 (s, 2H, NHCO), 8.52 (d, 2H, 4.9 Hz, H_{pyrr}), 8.61 (d, 2H, 4.9 Hz, H_{pyrr}), 8.71 (d, 2H, 4.9 Hz, H_{pyrr}), 8.77 (dd, 2H, 0.9 Hz, 7.3 Hz, H-3 of *meso* Ph), 8.90 (dd, 2H, 0.9 Hz, 7.9 Hz, H-3 of *meso* Ph), 9.09 (s, 2H, NHCO); ^{19}F NMR ($CDCl_3$, δ): −69.16 (s, 6F, CF_3), −69.84 (s, 6F, CF_3); IR (KBr, cm^{-1}): 1950 (CO), 1735 (CO_2CH_3), 1710 (NHCO); VIS (CH_2Cl_2, λ_{max}, nm): 413 (Soret), 532. FABMS (*m/z*): calcd for $C_{91}H_{73}F_{12}N_9O_{11}Ru$: 1797.431; found: 1797.431.

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