Kinetic resolution of esters *via* metal catalyzed methanolysis reactions

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Some chiral lanthanide complexes of the Schiff base adducts of: a) bis(2-pyridylcarboxaldehyde) and (1*R*),(2*R*)-*trans*-1,2-diaminocyclohexane (Pyr-R,R′-chxn: **3**); b) 6-methyl-2-pyridylcarboxaldehyde and (1*R*),(2*R*)-*trans* 1,2-diaminocyclohexane (MePyr-chxn, **4**); and c) 2,6-pyridyldicarboxaldehyde and (1*R*),(2*R*)-*trans*-1,2-diaminocyclohexane ((Pyr-R,R′-chxn)$_2$, **5**) have been screened for their utility to promote kinetic resolution *via* metal catalyzed alcoholyses of the *p*-nitrophenyl esters of chiral D- and L-Boc-protected glutamine and phenylalanine. Solvents were varied to optimize the kinetic selectivity values, defined as k_2^L/k_2^D or k_2^D/k_2^L, for the methanolysis and in some cases, ethanolysis of these substrates. At ambient temperature the greatest selectivity was found for the ethanolysis of Boc-Gln-OPNP, catalyzed by **3**:Yb^{3+}:($^-$OEt) ($k_2^L/k_2^D = 7.2$). The greatest selectivity for Boc-Phe-OPNP is $k_2^D/k_2^L = 3.9$ for its methanolysis promoted by **5**:La^{3+}:($^-$OMe). A kinetic method is introduced for the determination of both D and L rate constants for catalyzed alcoholysis from a single kinetic experiment. The activation parameters $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ were determined for the metal catalyzed methanolysis and ethanolysis of the Boc-Gln-OPNP substrates, and selectivity factors were found to increase at lower temperatures. A low temperature time course for the ethanolysis of racemic Boc-Gln-OPNP catalyzed by **3**:Yb^{3+}:($^-$OEt) at −15 °C indicated that after 3 hours 60% residual D-enantiomer was observed having an enantiomeric excess of >95% ee. The activation parameters for the ethanolysis of the same substrate catalyzed by (Pyr-R,R′-chxn)$_2$:La^{3+}:($^-$OEt) predict a $k_2^D/k_2^L =$ 40.4 at −40 °C with a large ee of >99% with ~80% of L isomer remaining at that temperature which has been experimentally confirmed.

Introduction

Kinetic resolution of racemates is an emerging tool for the separation of enantiomers[1] although it has an inherent problem in that the yield of a given enantiomeric product necessarily decreases with time due to the buildup in concentration of the less reactive enantiomer of the starting material. This is particularly so when the chiral kinetic discrimination between the L and D substrates (defined as the kinetic selectivity, k_L/k_D or k_D/k_L) is not large. Several successful kinetic resolutions are known using man-made catalysts[2] and the use of enzymes for the purpose of selective hydrolysis has been investigated for many years.[3] Although transesterification reactions are well-known[4] and recent work has provided the mechanistic intricacies of metal ion catalyzed transesterifications,[5] the use of this technique for kinetic resolution of esters is still very under-developed.[6–11]

Our recent extensive mechanistic investigations of the rapid methanolysis reactions of both activated and non-activated esters in the presence of [La^{3+}($^-$OCH$_3$)]$_2$, Eu^{3+}($^-$OCH$_3$) and the Zn^{2+}($^-$OCH$_3$)-complex of 1,5,9-triazacyclododecane[5] suggested that these metal ion/alkoxides, when complexed to chiral ligands, might provide useful catalysts for the kinetic resolution of esters and related compounds. Herein we describe our proof-of-principle studies of the kinetic resolution of *p*-nitrophenyl esters of the D and L *N*-*tert*-butoxycarbonyl derivatives of glutamine (Boc-Gln-OPNP, **1**) and phenylalanine (Boc-Phe-OPNP, **2**) promoted by various metal complexes of the bis(2-pyridyl carboxaldehyde) Schiff base of (1*R*),(2*R*)-*trans*-1,2-diaminocyclohexane[12] (Pyr-R,R′-chxn:M, **3**:M).

In addition, we have screened some metal ion complexes of two other Schiff base variants, namely those of 6-methyl-2-pyridylcarboxaldehyde and (1*R*),(2*R*)-*trans*-1,2-diaminocyclohexane[13] (MePyr-chxn:M, **4**:M) and the macrocyclic tetra-Schiff base formed from 2,6-pyridyldicarboxaldehyde and (1*R*),(2*R*)-*trans*-1,2-diaminocyclohexane ((Pyr-R,R′-chxn)$_2$:M, **5**:M). Herein we report the results of these studies along with the rate constants k_L and k_D for the catalyzed reactions of the enantiomers at room temperature. We also present a useful method involving a single kinetic experiment to determine the k_L and k_D rate constants for a given ester from which one can readily calculate the ee *vs.* percent conversion curves. Finally, in two cases we have determined the activation parameters for the catalyzed transesterification and from these predicted, and subsequently experimentally verified, enantiomeric excesses (ee's) of greater than 99% at selected reduced temperatures.

Experimental

Materials

Methanol (99.8% anhydrous), sodium methoxide (0.5 M solution in methanol), Boc-L-glutamine 4-nitrophenyl ester (98%+), Boc-D-glutamine 4-nitrophenyl ester (98%+), Boc-L-phenylalanine 4-nitrophenyl ester (98%+), Boc-D-phenylalanine

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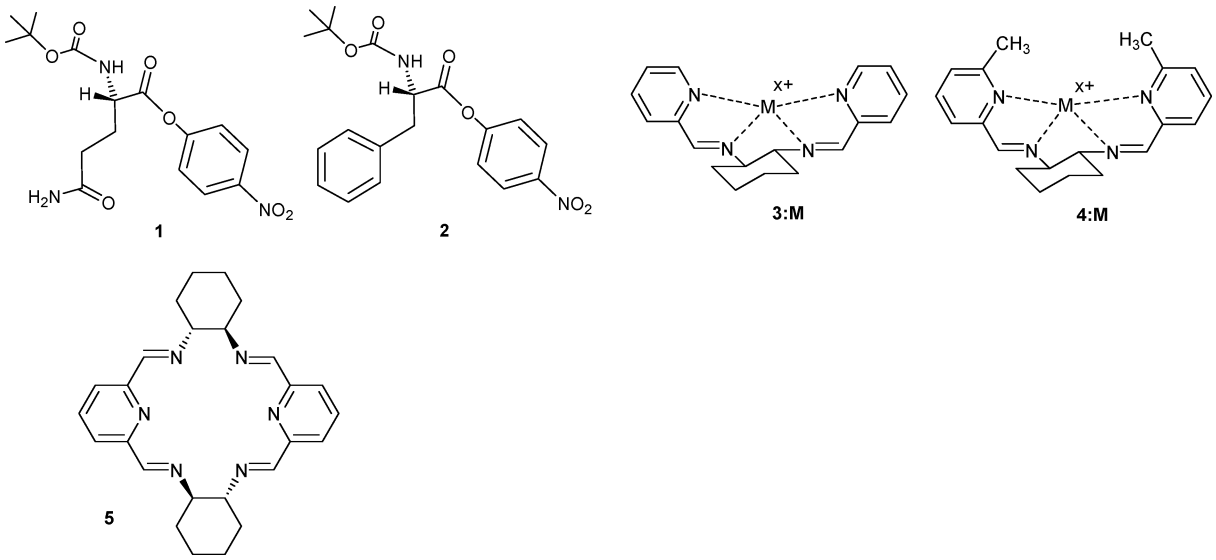

4-nitrophenyl ester (98%+), 6-methyl-2-pyridinecarboxaldehyde, 2-pyridinecarboxaldehyde and (+)-and (−)-*trans*-1,2-cyclohexanediamine (99%) were obtained from Aldrich and used as received. $M^{x+}(^{-}OTf)_x$ salts, where M = Zn, Yb, Tm, Nd, La, Eu, Ho were all obtained from Aldrich. Anhydrous ethanol was obtained from Commercial Alcohols, Brampton, Ontario. Pyr-chxn and MePyr-chxn were prepared as reported,[12,13] as was ligand **5**, termed here (Pyr-R,R′-chxn)$_2$.[14]

General methodology for determination of enantiomeric excess by kinetic studies

Stock solutions (50 mmol dm^{-3}) of the catalyst $M^{x+}(^{-}OTf)_x$ where M = Zn, Yb, Tm, Nd, La, Eu, Ho (50 mmol dm^{-3}), ligand (50 mmol dm^{-3}), and NaOMe (25 mmol dm^{-3}) were prepared in anhydrous methanol. Stock solutions (4 mmol dm^{-3}) of each enantiomer of the substrate (Boc-Gln-OPNP and Boc-Phe-OPNP) were prepared in anhydrous acetonitrile.

For each kinetic run the catalyst was formulated *in situ* by the addition of 25 μL of each $M(OTf)_x$, ligand and NaOMe stock solution and subsequently 50 μL of the stock solution of substrate to methanol such that the final volume was 2.5 mL. The **5**:La^{3+}-complex formation was relatively slow as judged by the increase in catalytic rate constant as a function of time, so the freshly made complex solutions were allowed to stand at room temperature overnight prior to use. The reaction rates were followed at 324 nm (for the formation of *p*-nitrophenol) using a Cary Bio-100 spectrophotometer with the cell compartment thermostated at 25.0 ± 0.1 °C. First order rate constants (k_{obs}) were evaluated from fits of the absorbance *vs.* time profiles to a standard exponential model. Specifically, two identical sample solutions in 1 cm cuvettes were prepared. To one sample the L enantiomer was added and the reaction was allowed to go to completion to determine the first order rate constant for its disappearance (k_L). Subsequently an aliquot of the stock solution of the D enantiomer was added to the same cuvette and a first order rate constant for its disappearance (k_D) was similarly obtained. For the other sample solution, the D enantiomer was added followed by the L enantiomer and two first order rate constants corresponding to k_D and k_L were obtained. The rate constants for each enantiomer were then averaged to give the reported rate constant. This methodology controls for variations between prepared samples and effects due to the order of addition of the enantiomers but has an estimated 2% error attributed to dilution of the catalysts in the subsequent experiments which is incorporated into the standard deviations reported.

The single kinetic run method to obtain both the k_D and k_L was conducted as per the following example. Two UV/vis cuvettes, each containing 0.1 mmol dm^{-3} Pyr-R,R′-chxn:$Yb^{3+}(^{-}OCH_3)$ catalyst, were prepared as described above. To one cuvette was added 25 μL of the enantiomerically pure D-Boc-Gln-OPNP substrate (4.0 mmol dm^{-3} in acetonitrile), and the cuvette was placed into the sample chamber of a dual beam UV/vis spectrophotometer. To the second cuvette was added 25 μL of a stock solution of racemic substrate (4.0 mmol dm^{-3} in acetonitrile) after which it was placed in the reference cell position. The resulting biphasic kinetic traces were analyzed to determine k_L and k_D by NLLSQ fitting the absorbance *vs.* time data to eqn (1);

$$Abs_t = Abs_0 + 0.5(\Delta Abs)e^{-kLt} - 0.5(\Delta Abs)e^{-kDt} \quad (1)$$

where $\Delta Abs = Abs_\infty - Abs_0$.

Determination of activation parameters

Following the general methodology outlined above, the k_{obs} constants for transesterification of each enantiomer of Boc-Gln-OPNP were obtained in MeOH and EtOH solvent at four to five temperatures between 25 °C and 5 °C with the Pyr-R,R′-chxn:$Yb^{3+}(^{-}OR)$ catalyst, and four to seven temperatures between 40 °C to 10 °C for the (Pyr-R,R′-chxn)$_2$:La($^{-}$OR) catalyst. Three reactions of each substrate were followed at each temperature and the corresponding k_{obs} values were averaged to give the values reported in Tables 5 and 6. The k_2 rate constants were then fit to a standard Boltzman equation $k = ATe^{(-\Delta H/RT + \Delta S/R)}$ based on a $1/k$ weighting: the activation parameters, $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ are given in Table 7.

General methodology for determination of enantiomeric excess by HPLC

A Hewlett Packard Series 1050 HPLC using a Chiralcel OD-H column (Daicel Chemical Industries) was used for the determination of the enantiomeric excess produced by **5**:$La^{3+}(^{-}OEt)$, Pyr-R,R′-chxn:$Yb^{3+}(^{-}OEt)$ and Pyr-S,S′-chxn:$Yb^{3+}(^{-}OEt)$ catalyzed reactions of a racemic mixture of L- and D-Boc-Gln-OPNP (formulated by adding equal amounts of the authentic enantiomers). All chromatograms were run with a mobile phase of 10% isopropanol–90% hexanes at 2.00 ml min^{-1} and monitored at a wavelength of 270 nm. The retention times for the starting materials and catalysts were determined from authentic samples. A 25 μL aliquot of a 4 mmol dm^{-3} solution of the commercial D-Boc-Gln-OPNP substrate was found to contain about 6–7% of the corresponding L-enantiomer as an impurity.

In a typical experiment to monitor the enantiomeric excess of the reaction as a function of time, a reaction vial equipped with a rubber septum was charged with $Yb(OTf)_3$ (5 μL, 50 mmol dm^{-3}), ligand Pyr-R,R′-chxn (5 μL, 50 mmol dm^{-3}), NaOEt (5 μL, 25 mmol dm^{-3}) and an internal standard of toluene (50 μL, 1.63 mol dm^{-3}) in 0.5 mL of ethanol. An identical reference vial was prepared with substrate but no catalyst. The vials were placed in the freezer in $CaCl_2$–acetone bath held at a temperature of −15 °C. After 15 minutes of cooling, the reaction was initiated by adding the racemic Boc-Gln-OPNP substrate (50 μL, 10 mmol dm^{-3}) to each vial. After addition of substrate the final volume in each vial was 0.635 mL, with final concentrations of 3.9×10^{-1} mmol dm^{-3} $Yb(OTf)_3$, 3.9×10^{-1} mmol dm^{-3} Pyr-R,R′-chxn, 2.0×10^{-1} mmol dm^{-3} NaOEt, 8×10^{-1} mmol dm^{-3} of the racemic Boc-Gln-OPNP substrate and 0.13 mol dm^{-3} toluene. Immediately after the addition of substrate, a 10 μL aliquot of the reference mixture without catalyst was injected to provide a time zero point. Subsequent injections of 10–25 μL aliquots from the reaction vial containing catalyst were made at 25 minute intervals. For experiments run at −40 °C, **5**:$La^{3+}(^{-}OEt)$ catalyst mixtures at the concentrations described above were prepared in six vials which were placed in a freezer at −40 °C. At three times, duplicate reactions were stopped with the addition of $HClO_4$ (7.8×10^{-1} mmol dm^{-3}) and LiCl (3.9 mmol dm^{-3}) for future HPLC analysis. The relative concentrations of each residual starting enantiomer were determined based on the peak areas of the L and D enantiomers corrected by dividing the peak area of interest by that of the internal standard. The ee was calculated using eqn (2), where A_L and A_D are the corrected peak areas of the L and D enantiomers.

$$\text{ee}\ (\%) = 100\left[\frac{A_L - A_D}{A_L + A_D}\right] \qquad (2)$$

Results and discussion

Shown in Fig. 1 and 2 are plots of the k_{obs} values *vs.* [Pyr-R,R-chxn:Yb^{3+}:0.5($^{-}OCH_3$)] for the catalyzed methanolysis reaction of L- and D-Boc-Gln-OPNP and L- and D-Boc-Phe-OPNP. Similar plots (not shown) are obtained for the reaction of L- and D-Boc-Gln-OPNP promoted by La^{3+}:(Pyr-R,R′-chxn)$_2$ in the presence of 0.5 eq. of $NaOCH_3$. Previous work[5] established that the active forms of these and related complexes contain one methoxide per metal ion, but the use of the 0.5 eq. buffers the medium at the

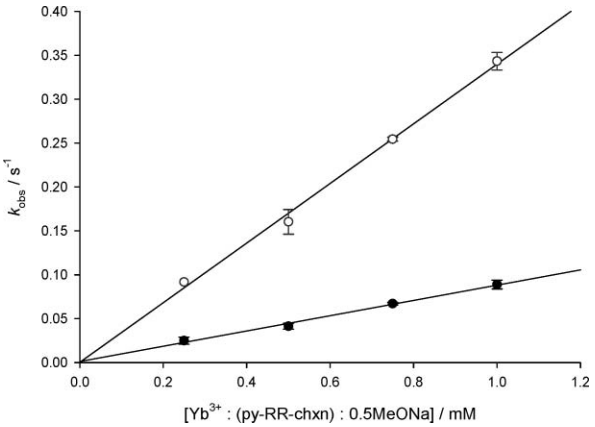

Fig. 1 Plots of k_{obs} *vs.* [Pyr-R,R′-chxn:Yb^{3+}:0.5(NaOMe)] for methanolysis of D-Boc-Gln-ONp (●) and L-Boc-Gln-ONp (○) (0.05 mmol dm^{-3}) in methanol at 25 °C.

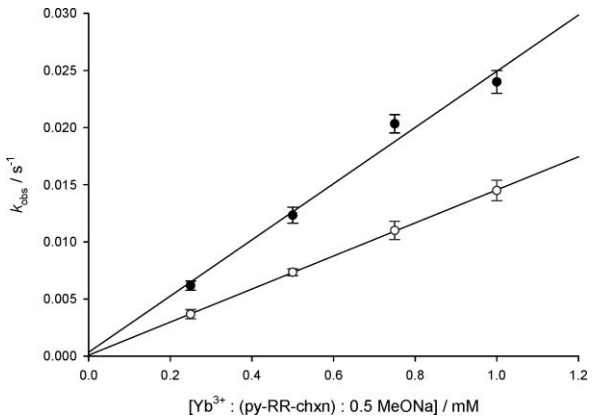

Fig. 2 Plots of k_{obs} *vs.* [Pyr-R,R′-chxn:Yb^{3+}:0.5(NaOMe)] for methanolysis of D-Boc-Phe-ONp (●)and L-Boc-Phe-ONp (○) (0.05 mmol dm^{-3}) in methanol at 25 °C.

$_s^spH$[15] corresponding to the pK_a of the catalyst system when the [Pyr-chxn:M^{3+}:($HOCH_3$)]/[Pyr-chxn:M^{3+}:($^{-}OCH_3$)] ratio is unity. The fact that the plots in Fig. 1 and 2 are linear with intercepts of zero rules out the involvement of free methoxide in the production of the *p*-nitrophenol product and also rules out involvement of higher order species such as dimers.

Given in Table 1 are the second order rate constants for methanolysis of the L and D substrates promoted by $La^{3+}(^{-}OCH_3)$, $Eu^{3+}(^{-}OCH_3)$, and $Yb^{3+}(^{-}OCH_3)$ complexes of Pyr-R,R′-chxn as well as the La^{3+}-complex of **5** in pure methanol at 25 °C. The gradients of the lines in Fig. 1 and 2 are taken as the second order (k_2) constants, although we know that only half of the complex is present as the active CH_3O^{-}-containing form. At ambient temperature, none of the three complexes is particularly enantioactive with the Boc-Phe-OPNP substrate and all the selectivity values, defined as k_2^L/k_2^D, are less than unity. On the other hand, the k_2^L/k_2^D ratios are all greater than unity with the Pyr-R,R′-chxn:Ln^{3+} complexes for the Boc-Gln-OPNP substrate, while the **5**:La^{3+} catalyst has the opposite preference where k_2^L/k_2^D is <1 for reasons that are not clear.

We introduce here a faster way to screen the catalytic activity by which one can determine both the k_D and k_L constants and selectivity factors for a given catalyst in a single reaction. This

Table 1 Second order rate constants (k_2) for the methanolysis of L- and D-Boc-Phe-OPNP and Boc-Gln-OPNP catalyzed by Pyr-R,R′-chxn:Ln^{3+}:0.5($^-OCH_3$) and by **5**:(Pyr-R,R′-chxn)$_2$:0.5($^-OCH_3$) complexes at 25 °C[a]

	Substrate					
	Boc-Phe-OPNP			Boc-Gln-OPNP		
Catalyst	k_2^L/dm^3 mol^{-1} s^{-1}	k_2^D/dm^3 mol^{-1} s^{-1}	k_2^L/k_2^D[b]	k_2^L/dm^3 mol^{-1} s^{-1}	k_2^D/dm^3 mol^{-1} s^{-1}	k_2^L/k_2^D[b]
Pyr-R,R′-chxn:La^{3+}:($^-OCH_3$), ^{s}pH = 8.3	7.5	10.8	0.70 (18% ee, 43% L)	31.5	27.0	1.17 (8% ee, 37% D)
Pyr-R,R′-chxn:Eu^{3+}:($^-OCH_3$), ^{s}pH = 6.5	4.9	6.4	0.77 (13% ee, 42% L)	63.8	25.0	2.6 (44% ee, 55% D)
Pyr-R,R′-chxn:Yb^{3+}:($^-OCH_3$), ^{s}pH = 6.5	14.5	24.6	0.50 (25% ee, 47% L)	340	89	3.8 (58% ee, 62% D)
5:La^{3+}:($^-OCH_3$), ^{s}pH = 8.8	2.5	7.0	0.35 (47% ee, 56% L)	2.8	7.8	0.36 (47% ee, 56% L)

[a] k_2 defined from the gradient of the plot of k_{obs} *vs.* [ligand:M^{3+}:0.5($^-OCH_3$)]. [b] ee values and residual yield of predominant stereoisomer calculated at optimal catalytic conversion (OCC) using eqn (3)–(5)

is similar to the 'quasi-racemate' method for determining small kinetic isotope effects,[17] which we have adapted to dual-beam UV/vis spectrophotometry. In the typical example, illustrated here with the methanolysis of Boc-Gln-OPNP promoted by the Yb^{3+}:($^-OCH_3$) complex of Pyr-R,R′-chxn, the reference and sample cells of the spectrometer are respectively charged with equal amounts of the racemic and enantiomerically pure substrates, along with identical amounts of catalyst and the absorbance difference *vs.* time curve (Fig. 3) is monitored until the completion of the reaction. Characteristically these have an 'up/down' or 'down/up' behaviour depending on which enantiomer reacts more rapidly, and if both react at the same rate, then there is no rise/fall behaviour. The k_L and k_D rate constants are easily obtained from NLLSQ fits of the Abs *vs.* time curve to the expression in eqn 1. For the example chosen here, $k_L = 0.028$ s^{-1} and $k_D = 0.0068$ s^{-1} and the $k_L/k_D = 4.1$, which is experimentally the same as what was obtained from the single run experiments in Table 1, row 3. The ΔAbs *vs.* time curve in Fig. 3 also visually provides the time (t_{OCC}) at which the rates of catalytic conversion of the D and L isomers are the same (vertical dashed line) which we will define here as the 'optimal catalytic conversion (OCC)'. The exact equations for the determination of t_{OCC} and the [residual D] and [residual L] isomers at that time are given as:

$$t_{OCC} = \ln(k_L/k_D)/(k_L - k_D) \quad (3)$$

$$[L]/[L_0] = \exp(-k_L t_{OCC}) \quad (4)$$

$$[D]/[D_0] = \exp(-k_D t_{OCC}) \quad (5)$$

The ee at t_{OCC} is defined as: ([L] − [D])/([L] + [D])100. These values are given in Tables 1–6 along with the percentage of the dominant enantiomer remaining at the OCC.

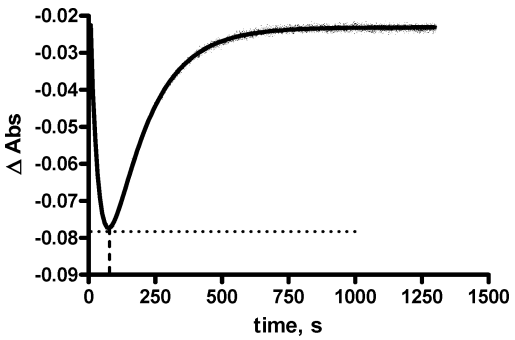

Fig. 3 A ΔAbs *vs.* time plot for the methanolysis of D-Boc-Gln-OPNP and racemic Boc-Gln-OPNP (0.04 mmol dm^{-3} in sample and reference cell respectively) promoted by 0.1 mmol dm^{-3} Pyr-R,R′-chxn:Yb^{3+} in the presence of 0.05 mmol dm^{-3} $NaOCH_3$. Dashed vertical line defines the time (~65 s) where the catalyzed rates of conversion of the D- and L-isomers are equal (t_{OCC}).

The effect of changing the metal ion and ligand to metal ion ratio was investigated in methanol with 0.5 mmol dm^{-3} of metal ion (added as the corresponding triflate), one or two equivalents of Pyr-R,R′-chxn and 0.25 mmol dm^{-3} of added $NaOCH_3$. The same series of reactions was investigated in a solvent comprising 90% CH_3CN–10% methanol and the results are also presented in Table 2. Of the various metal ions Yb^{3+} and Tm^{3+} have the greatest selectivity factors, and although increasing the ligand/M^{x+} ratio from one to two may increase, decrease or have no effect on the reaction rate in selected cases, this does not seem to have any profound effect on the selectivity factors. Only in the case of Nd^{3+} does the change in the solvent to 9 : 1 acetonitrile increase the rate and the selectivity factor appreciably: in all other cases the k_L/k_D ratio drops or remains constant. The same thing is seen for La^{3+}:(Pyr-R,R′-chxn)$_2$ where the 9 : 1 acetonitrile : methanol solvent system increases the selectivity factor to 3.5 from 2.8 in methanol.

Some additional screening was done to investigate the effect of 9 : 1 solvent : methanol compositions on the selectivity factor for the Yb^{3+}:($^-OCH_3$) complex of Pyr-R,R′-chxn with L- and D-Boc-Gln-OPNP using THF, ether, dichloromethane, 1,2-dichloroethane and toluene. Only THF and toluene with 2 : 1 ligand : Yb^{3+} ratio gave selectivity factors approaching those in methanol, the respective values being 3.9 and 3.4.

Table 2 Observed first order rate constants for the catalysis methanolysis of 4×10^{-5} mol dm^{-3} L- and D-Boc-Gln-OPNP in methanol and 90% acetonitrile–methanol promoted by 0.5 mmol dm^{-3} of metal ion, one or two equivalents of Pyr-R,R′-chxn and 0.25 mmol dm^{-3} of added $NaOCH_3$

M^{x+}	Lig : M^{x+}	$10^3k_L/s^{-1}$	$10^3k_D/s^{-1}$	k_L/k_D	ee, with residual yield[b]
Yb^{3+}	1 : 1	155.1	40.8	3.8	58%, 62% D
CH_3OH	2 : 1	192.0	40.5	4.7	65%, 66% D
9 : 1(A : M)[a]	2 : 1	163	41.2	4.0	60%, 63% D
Tm^{3+}	1 : 1	102.0	27.2	3.8	58%, 62% D
CH_3OH	2 : 1	170.5	45.2	3.8	58%, 62% D
9 : 1(A : M)[a]	1 : 1	152.0	53.2	2.9	48%, 57% D
9 : 1(A : M)[a]	2 : 1	201.8	71.3	2.8	47%, 57% D
Nd^{3+}	1 : 1	24.7	12.3	2.0	33%, 50% D
CH_3OH	2 : 1	12.0	7.0	1.7	26%, 47% D
9 : 1(A : M)[a]	1 : 1	28.3	12.7	2.3	38%, 52% D
Zn^{2+}	1 : 1	21.2	11.0	1.9	31%, 49% D
CH_3OH	2 : 1	21.0	9.5	2.2	37%, 52% D
9 : 1(A : M)[a]	1 : 1	52.5	33.8	1.6	22%, 45% D
9 : 1(A : M)[a]	2 : 1	52.5	34.3	1.5	21%, 45% D

[a] 90% acetonitrile–methanol solution. [b] ee values and residual yield of predominant stereoisomer calculated at optimal catalytic conversion (OCC) using eqn (3)–(5).

Complex 4

As one expects a more sterically demanding complex might lead to greater chiral discrimination, we undertook single run kinetic studies of the rates of methanolysis of the $Yb^{3+}(^-OCH_3)$ and $La^{3+}(^-OCH_3)$ complexes of MePyr-chxn. The results in Table 3 indicate, that only in the cases of the Yb^{3+} complexes in the presence of 2 ligands is there an appreciable selectivity and under these conditions the reactions are markedly slower in the presence of a single equivalent of ligand. This probably means that the complexes are not fully formed when the ligand/M^{3+} ratio is 1. Even so, the dramatic reduction in reaction rate, coupled with a poorer selectivity than was realized with Pyr-R,R′-chxn:Yb^{3+} and La^{3+}:(Pyr-R,R′-chxn)$_2$, made us discontinue study with ligand **4**.

Comparison of selectivity factors in methanol, ethanol and n-propanol

As our earlier results indicated that the metal ion catalysts are generally active in other light alcohols such as ethanol and propanol, we compared the selectivity factors obtained in these three solvents. For this series of reactions the k_L and k_D constants were obtained in a single cell containing 0.5 mmol dm^{-3} each of Yb^{3+} (introduced as its triflate) and of Pyr-R,R′-chxn, and 0.25 mmol dm^{-3} of added $NaOCH_3$ which immediately equilibrates to form the NaOR of the ROH solvent. Into this cell was added 0.05 mmol dm^{-3} of L-Boc-Gln-OPNP, and its transesterification reaction was followed to completion. To the same cell was then added 0.05 mmol dm^{-3} of the D isomer of Boc-Gln-OPNP, and this reaction was again followed to completion. The entire process was repeated with a fresh solution of the catalyst formulated in the same way, and the reaction of the D and then L isomer of the substrate was followed to completion. Given in Table 4 are the averages of the various first order rate constants determined in this way, and it can be seen that the selectivity factors are highest in ethanol. For (Pyr-R,R′-chxn)$_2$:La^{3+} with 0.5 eq. of added methoxide, the second order rate constants in ethanol for transesterification of L- and D-Boc-Gln-OPNP are $k_2{}^L = 2.0$ dm^3 mol^{-1} s^{-1} and $k_2{}^D = 11.1$ dm^3 mol^{-1} s^{-1} for a stereoselectivity factor of 5.5.

Table 4 First order rate constants for the alcoholysis reaction of L- and D-Boc-Gln-OPNP promoted by 0.5 mmol dm^{-3} Pyr-R,R′-chxn:Yb^{3+}:0.5($^-$OR) in various alcohols at $T = 25$ °C

Solvent	$10^3k_L/s^{-1}$	$10^3k_D/s^{-1}$	k_L/k_D	ee, with residual yield[a]
MeOH	155 ± 10	40.8 ± 1.0	3.8	58%, 62% D
EtOH	51.5 ± 1.5	7.2 ± 0.4	6.9	75%, 73% D
PrOH	6.4 ± 1.9	2.0 ± 0.7	3.2	52%, 59% D

[a] ee values and residual yield of predominant stereoisomer calculated at optimal catalytic conversion (OCC) using eqn (3)–(5).

Table 3 First order rate constants for methanolysis of substrates promoted by $Yb^{3+}(^-OCH_3)$ and $La^{3+}(^-OCH_3)$ complexes of ligand **4** in MeOH, $T = 25$ °C, $[M^{3+}] = 0.5$ mmol dm^{-3}, $[^-OCH_3] = 0.25$ mmol dm^{-3}

Subst.	M	Lig : M	$10^3k_L/s^{-1}$	$10^3k_D/s^{-1}$	k_L/k_D	ee with residual yield[a]
1	Yb	1 : 1	31.0	27.0	1.1	7%, 39% D
		2 : 1	19.3	8.5	2.3	38%,52% D
	La	1 : 1	26.2	26.3	1	0.2%,37% D
		2 : 1	35.8	34.0	1	2.6%,38% D
2	Yb	1 : 1	0.30	0.28	1.1	3.4%,38% D
		2 : 1	0.20	0.13	1.5	21%,45% D
	La	1 : 1	7.8	7.5	1	1.9%,38% D
		2 : 1	8.3	9.0	0.9	4.0%,35% L

[a] ee values and residual yield of predominant stereoisomer calculated at optimal catalytic conversion (OCC) using eqn (3)–(5).

Activation parameters for the methanolysis and ethanolysis reactions of L- and D-Boc-Gln-OPNP promoted by Pyr-R,R′-chxn:Yb^{3+}:($^-$OR) and (Pyr-R,R′-chxn)$_2$:La^{3+}:($^-OCH_3$)

Although none of the complexes provided excellent selectivity at 25 °C, any difference in the activation enthalpies ($\Delta H^{\ddagger}$) for the catalytic transesterification of the D and L isomers must be manifested in a changing k_L/k_D ratio as a function of temperature, with the magnitude of the change being a reflection of the $\Delta\Delta H^{\ddagger}$ (L *vs.* D). Knowledge of the activation parameters for the catalyzed reactions is essential for calculating the temperature where the best compromise between ee and maximal residual enantiomer is realized. The activation parameters were determined in methanol and ethanol following the procedures described in the previous sections. Given in Tables 5 and 6 are the observed first order rate constants of the catalyzed reactions along with the selectivity factors at various temperatures. The errors limits are computed as the maximum deviation from the mean of two or three determinations of the constant. When the first order rate constants are divided by the [active catalyst][18] ([Pyr-R,R′-chxn:Yb^{3+}:($^-$OR)] = 0.25 mmol dm^{-3} or[Pyr-R,R′-chxn)$_2$:La^{3+}:($^-$OR)] = 0.1 mmol dm^{-3} in ethanol and 0.05 mmol dm^{-3} in methanol), the so-produced second order rate constants (k_2) can be used to compute the activation parameters for the catalyzed transesterifications of L and D Boc-Gln-OPNP given in Table 7.

Table 5 First order rate constants for the alcoholysis of L- and D-Boc-Gln-OPNP (4×10^{-5} mol dm^{-3}) promoted by active catalyst (0.25 mmol dm^{-3} Pyr-R,R′-chxn:Yb^{3+}:($^-$OR), (**3**:Yb^{3+}:($^-$OR))) in ethanol and methanol at various temperatures[a]

T/°C	10^3k_L/s^{-1}	10^3k_D/s^{-1}	k/k_D	ee with residual yield[b]
EtOH				
25	51.5 ± 1.5	7.2 ± 0.4	7.2	75%, 73% D
20	36.9 ± 2.4	4.6 ± 0.1	8.5	78%, 74% D
10	13.9 ± 1.0	1.9 ± 0.1	7.3	76%, 73% D
5	11.0 ± 0.8	1.0 ± 0.2	11.0	83%, 79% D
MeOH				
25	155 ± 10	40.8 ± 1.0	3.8	58%, 62% D
20	115 ± 1	31.0 ± 0.7	3.7	58%, 62% D
10	70.7 ± 2.0	17.3 ± 0.3	4.1	60%, 63% D
5	52.6 ± 1.8	11.1 ± 1.0	4.7	65%, 66% D

[a] Error limits are given as maximum deviation from the mean of 2 or 3 independent runs for each constant. [b] ee values and residual yield of predominant stereoisomer calculated at optimal catalytic conversion (OCC) using eqn (3)–(5).

Table 6 First order rate constants for the alcoholysis of L- and D-Boc-Gln-OPNP (0.04 mmol dm^{-3}) promoted by active catalyst (0.1 mmol dm^{-3} in ethanol and by 0.05 mmol dm^{-3} (Pyr-R,R′-chxn)$_2$:La^{3+}:($^-$OR), (**5**:La^{3+}:($^-$OR)), in methanol) at various temperatures[a]

T/°C	10^3k_D/s^{-1}	10^3k_L/s^{-1}	k_D/k_L	ee with residual yield[a]
EtOH				
40	3.8 ± 0.2	1.95 ± 0.1	2.0	32%, 50% L
35	2.7 ± 0.2	1.1 ± 0.1	2.4	42%, 54% L
30	2.5 ± 0.1	0.95 ± 0.07	2.6	55%, 44% L
25	1.9 ± 0.3	0.69 ± 0.02	3.0	56%, 47% L
MeOH				
40	17.0 ± 0.2	9.3 ± 0.3	1.8	29%, 48% L
35	12.0 ± 0.9	5.7 ± 0.7	2.1	36%, 51% L
30	9.7 ± 1.1	4.4 ± 0.9	2.2	38%, 52% L
25	7.8 ± 0.7	2.8 ± 0.3	2.8	47%, 56% L
20	4.9 ± 0.6	1.4 ± 0.3	3.5	56%, 61% L
15	3.59 ± 0.02	0.82 ± 0.02	4.3	62%, 65% L
10	2.5 ± 0.1	0.54 ± 0.01	4.6	64%, 66% L

[a] ee values and residual yield of predominant stereoisomer calculated at optimal catalytic conversion (OCC) using eqn (3)–(5).

Table 7 Activation parameters for the ethanolysis and methanolysis of L- and D-Boc-Gln-OPNP promoted by Pyr-R,R′-chxn:Yb^{3+}:($^-$OR), **3**:Yb^{3+}:($^-$OR) and (Pyr-R,R′-chxn)$_2$:La^{3+}:($^-$OR), **5**:La^{3+}:($^-$OR)[a]

System	ΔH/kJ mol dm^{-3}		ΔS/J mol dm^{-3} K^{-1}	
3:Yb^{3+}:($^-$OR)	L	D	L	D
MeOH	33.9 ± 1.0	39.3 ± 1.4	−73.7 ± 3.6	−66.0 ± 4.8
EtOH	54.3 ± 2.4	67.6 ± 3.8	−16.4 ± 8.4	−4.4 ± 12.4
5:La^{3+}:($^-$OR)	L	D	L	D
MeOH	69.0 ± 2.4	47.7 ± 2.3	23.7 ± 7.9	−39 ± 8
EtOH	67.3 ± 3.9	45.4 ± 3.3	−9.1 ± 12.0	−73 ± 11

[a] Error limits are given as maximum deviation from the mean of two or three independent runs for each constant.

The activation parameters refer to the overall catalyzed process which we have shown previously[5] with $La^{3+}{}_2(^-OCH_3)_2$ and a 1,5,9-triazacyclononane:Zn^{2+}($^-OCH_3$) complex, involves the steps shown in eqn (6) and (7) with a pre-equilibrium catalyst and substrate binding followed by the formation of an anionic tetrahedral intermediate (T_O^-) that is stabilized by complexation. With good leaving groups such as *p*-nitrophenoxy, the breakdown of the tetrahedral intermediate is fast,[5] so the k_1 step for formation of the metal-stabilized intermediate is rate limiting. Thus, for the metal catalyzed alcoholyses operative here, the activation parameters refer to the overall second order rate constant given as $k_2{}^{obs} = K_b k_1$. At 25 °C the transesterification reactions in ethanol for the D and L isomers with both catalysts are about three to five times slower than the corresponding reactions in methanol but the selectivities are larger in ethanol. In both alcohols, the selectivity factors with the catalysts get larger as the temperatures drop, indicating that one can reduce the temperature to a point that this would be a viable kinetic resolution technique for selected substrates.

$$M^{x+}\left(^-OCH_3\right) + RCO_2R' \underset{}{\overset{K_b}{\rightleftharpoons}} RCO_2R':M^{x+}\left(^-OCH_3\right) \quad (6)$$

$$RCO_2R':M^{x+}\left(^-OCH_3\right) \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \left(CH_3O^-T_o\text{-}\right):M^{x+} \xrightarrow{k_2} P \quad (7)$$

In order to demonstrate experimentally that the enantiomeric excesses of the reaction do improve markedly at low temperature, we determined, using HPLC, the time course for disappearance of each enantiomer of a racemic Boc-Gln-OPNP mixture (8×10^{-1} mmol dm^{-3}) in the presence of each of the chiral Pyr-R,R′-chxn:Yb^{3+}($^-$OR) and Pyr-S,S′-chxn:Yb^{3+}($^-$OR) complexes (3.9×10^{-1} mmol dm^{-3}) in EtOH at −15 °C over the course of three hours. Given in Fig. 4 is the time course promoted by the Pyr-R,R′ complex showing the residual amounts of the D and L isomers and the enantiomeric excesses in the total product mixture as a function of time. After three hours, essentially all the starting L-isomer has reacted while about 60% of the enantiomerically pure D-isomer is left (experimental ee after 180 min is 97%) A similar plot (not shown) obtained with the Pyr-S,S′-chxn:Yb^{3+}($^-OCH_3$)

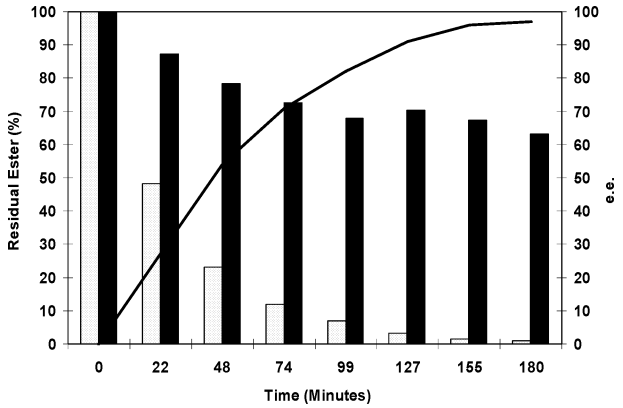

Fig. 4 Time course for the ethanolysis of racemic Boc-Gln-OPNP promoted by Pyr-R,R′-chxn:Yb^{3+}($^{-}OCH_3$) at −15 °C : solid bar, residual D-isomer; dotted bar, residual L-isomer; solid line, enantiomeric excess.

complex reveals a correspondingly fast reaction of the D-isomer, with about 54% of the residual enantiomerically pure L-isomer remaining after about 195 minutes, ee ~100%).

As a final demonstration of the accuracy of prediction of ee for the ethanolysis of a racemic Boc-Gln-OPNP mixture at reduced temperature, the activation parameters for the reaction of the D and L enantiomers with (Pyr-R,R′-chxn)$_2$:La^{3+}:($^{-}$OEt) given in Table 7 were used to find an optimum temperature and [catalyst] at which the compromise of high ee and maximum amount of residual substrate are achieved in a conveniently accessible reaction time. An appropriate compromise was calculated to be at −40 °C with 1 mmol dm^{-3} catalyst and the computed plots of residual D and L isomer concentrations, ee and ΔAbs. *vs.* time are given in Fig. 5.

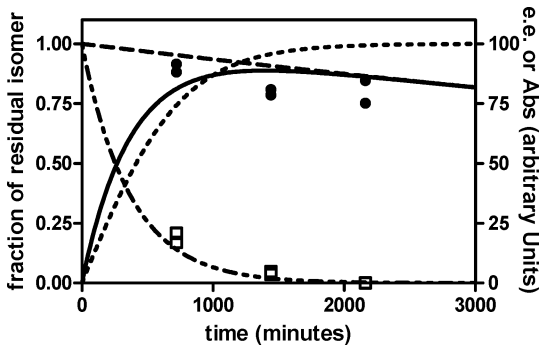

Fig. 5 Time course for various parameters arising from the ethanolysis of D-Boc-Gln-OPNP and (1.0 mmol dm^{-3}) and *rac*-Boc-Gln-OPNP, each promoted by 1.0 mmol dm^{-3} (Pyr-R,R′-chxn)$_2$:La^{3+}:($^{-}$OEt) in ethanol at −40 °C. Plots are constructed using first order rate constants calculated from activation parameter values ($k^D = 4.53 \times 10^{-5}$ s^{-1}, $k^L = 1.12 \times 10^{-6}$ s^{-1}). Shown are the ee (dotted line, right axis), and the residual fractions of D and L enantiomers *vs.* time (···, ---, left axis). Solid line is the computed ΔAbs. *vs.* time plot where the right *y*-axis represents the maximum absorbance expected for cleavage of one isomer. □ and ● symbols are duplicates of experimentally observed amounts of residual of D and L isomers at times 720, 1440 and 2160 min.

The computed data indicate that at −40 °C the $k_2^D/k_2^L = 40.4$ and at 2200 minutes the predicted ee is >99%, with 84% of residual L isomer remaining. We confirmed this prediction by running the reaction at −40 °C in six vials, quenching the reaction in duplicate vials at 720, 1440 and 2160 minutes by the addition of an excess of perchloric acid and LiCl, and analyzing the reaction mixtures by HPLC. The observed experimental points for residual D and L isomers are placed on Fig. 5 as □ and ● symbols. The experiment confirms the prediction that a so-constituted catalytic mixture run for 36 hours at −40 °C yields ~79% of the L isomer with an enantiomeric excess of >99%.

Conclusion

We have described a study of the use of some chiral lanthanide metal ion complexes to effect kinetic resolutions *via* transesterification of the nitrophenyl esters of N-Boc protected amino acids of glutamine and phenylalanine under mild conditions of essentially neutral 'pH' (in alcohol). The choice of the *p*-nitrophenyl esters is dictated by the ease with which the kinetics can be determined by UV/visible spectrophotometry. Only the La^{3+} complex of ligand **5** ((Pyr-R,R′-chxn)$_2$) is moderately effective at room temperature for selective cleavage of the phenyl alanine derivative (k_L/k_D = 0.26). The best selectivity for the glutamine derivative comes from the Yb^{3+}:Pyr-R,R′-chxn complex in ethanol where the k_L/k_D ratio is 11 at 5 °C, but activation parameter analysis indicates that a far better selectivity can be achieved with both catalysts at lower temperatures. The activation parameters allow one to predict an optimum reaction condition for a given concentration of catalyst where maximum values of the ee and residual unreacted enantiomer can be achieved in a conveniently accessible time. In a selected example we showed that a catalyst having an unimpressive $k_2^D/k_2^L = 3$ at 25 °C is predicted to have a $k_2^D/k_2^L = 40.4$ at −40 °C and we experimentally confirmed a predicted large ee of >99% with ~80% of the L isomer remaining.[19]

In order to more conveniently screen the catalytic systems at various temperatures, we have presented a simplified kinetic method where the rate constants for both enantiomers can be determined in a single experiment. Application of this methodology allows rapid determination of the activation parameters of the reactions for a given catalyst with each of the two enantiomers. This is essential for calculation of a temperature where one can obtain high enantiomeric excesses in reasonable times with appreciable amounts of the less reactive isomer remaining.

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19 The fact that an enantioactive catalyst shows little selectivity at a given experimental temperature does not necessarily indicate that it is a poor catalyst at all temperatures. This can only be verified by activation parameter analysis using Eyring or Arhenius plots. If the gradients for these plots, which define the $\Delta H^{\ddagger}$ for the catalyzed reaction of each isomer are very close to each other, then the selectivity will be the same at all accessible temperatures. On the other hand, if the gradients are substantially different, the two plots will generally cross at the isokinetic temperature. The selectivity value, and in fact the D(*R*) *vs.* L(*S*) selectivity itself, then depends on how close and on which side of the isokinetic temperature the experiment is run.