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Enantioselective Hydrogenation of α–keto Esters over Cinchona-Pt/Al_2O_3 Catalyst. Kinetic Evidence for the Substrate-Modifier Interaction in the Liquid Phase.

József L. Margitfalvi , Mihály Hegedüs and Ernô Tfirst

Central Research Institute for Chemistry of the Hungarian Academy of Sciences, Budapest, 1025 Pusztaszeri ut 59-67, Hungary.

Abstract: The hydrogenation of ethyl pyruvate was studied over cinchonidine-Pt/Al_2O_3 catalyst. Contrary to earlier results it has been found that the initial enantiomeric excess extrapolated to zero conversion is close to zero. Based on kinetic analysis the results are considered as indirect evidence for the substrate-modifier interaction taking place in the liquid phase. The above interaction leads to the formation of a weak substrate-modifier complex. The formation of the complex in the liquid phase is the key step to control both the rate acceleration and the induction of enantio-differentiation in the hydrogenation of α–keto esters in the presence of cinchona-Pt/Al_2O_3 catalysts. The character of interactions in the substrate-modifier complex is discussed. By using molecular modelling the possible form of the complex is also given.

INTRODUCTION

The enantioselective hydrogenation of α-keto esters over cinchona-Pt/Al_2O_3 catalysts is one of the most widely studied heterogeneous catalytic asymmetric hydrogenation reactions. With respect to this reaction the most disputed issue is related to the nature of interactions responsible for the rate acceleration (r.a.) and the enantio-differentiation (e.d.) steps[1-11]. In this respect there are two possibilities: the r.a and e.d. steps are controlled either by (i) modifier-active phase (Pt) interaction or (ii) modifier-substrate interactions taking place in the liquid phase.

In the existing models, i.e. both in the template[1,2] and the ligand acceleration models[3,4], the modifier-metal interaction was favoured, however the exact chemical nature of interactions was not discussed. In the model proposed recently by Augustine *et al.* Pt-modifier interaction was also suggested[5]. Recently, based on computer modelling and molecular mechanics calculations new ideas were proposed with respect to the nature of interactions involved in both the r.a and e.d. steps[6-8], however the modifier-metal interaction is still favoured.

In contrast to that we suggested that in both the r.a. and the induction of e.d. modifier-substrate interactions taking place in the liquid phase are involved[9-11]. In this respect it is very important to note that cinchona alkaloids are widely used to induce enantio-differentiation in different homogeneous reactions[12]. It is

noteworthy that the ability of cinchona alkaloids to induce enantio-differentiation strongly increases if the substrates have a conjugated double bond system[12].

RESULTS AND DISCUSSION

Kinetic results: There is one serious contradiction in the earlier results[1-4]: initial reaction rates, but with enantiomeric excesses obtained at relatively high conversion have been used for kinetic analysis[1-4]. It is also proposed that under optimum reaction conditions the initial enantiomeric excess is maintained in the whole conversion range[3,4], slight decrease of the enantiomeric excess was observed at low concentration of modifier[9]. In our studies, in order to obtain reliable reaction kinetic data, the whole conversion range was investigated[9-11]. In this contribution we shall focus on the analysis of the e.e. vs. time dependencies obtained in the conversion range of 0-70 %.

In contrast the earlier suggestions and experimental data[1-4] we have found that in the enantioselective hydrogenation of ethyl pyruvate (EtPy) over cinchonidine-Pt/Al_2O_3 catalyst the enantiomeric excess vs. time (conversion) dependencies have a monotonic increase type behaviour and the enantiomeric excess extrapolated to zero conversion is close to zero as shown in Figure 1. Similar enantiomeric excess vs. time (conversion) dependencies were obtained in our earlier studies[9-10] under transient condition and recently by Singh *et al*[13]. In the light of these results the validity of earlier models[1-4] is strongly questioned as *in all of the existing models it has been accepted that the enantiomeric excess is independent of the conversion.*

The monotonic increase type behaviour of the enantiomeric excess vs. time (conversion) dependencies can be attributed either to (i) the formation of certain species responsible for the enantio-differentiation during the hydrogenation reaction or (ii) the reaction kinetics. In this contribution we shall provide evidence that the form of the enantiomeric excess vs. time (conversion) dependencies can be attributed to the reaction kinetics derived from the reaction mechanism.

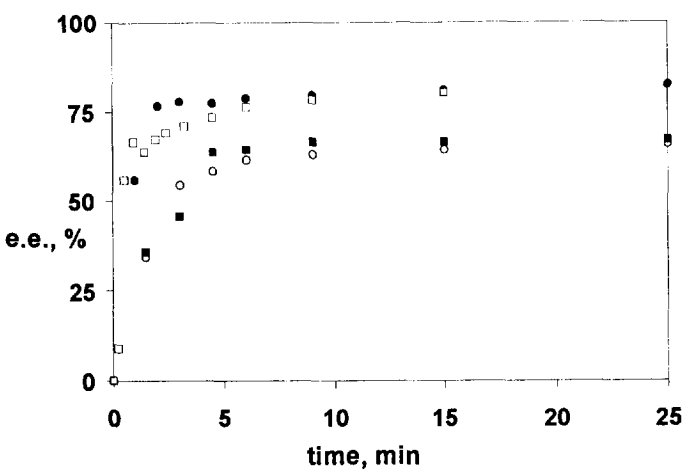


Figure 1. Typical form of the enantiomeric excess vs. time dependencies.
■ - $[CD]_{o,premixed}$: 8.3 x 10^{-4} M, EtPy premixed in ethanol; ○ - $[CD]_{o\ premixed}$: 2.0 x 10^{-4} M, EtPy injected into ethanol; □ - $[CD]_{o\ inj.}$: 0.2 x 10^{-4} M, EtPy premixed in toluene;
● - $[CD]_{o,premixed}$: 8.3 x 10^{-4} M, EtPy premixed in toluene.

Reaction scheme and kinetic modelling: The elucidation of the origin of the monotonic increase behaviour of the enantiomeric excess vs. time (conversion) dependencies required kinetic analysis of the hydrogenation of ethyl pyruvate (EtPy) over cinchona-Pt/Al_2O_3 catalyst. In the kinetic analysis a simplified reaction scheme was used. The reaction scheme reflects our earlier proposal, i.e. the induction of enantio-differentiation is attributed to the substrate-modifier interaction taking place in the liquid phase[9-11]. Due to the substrate-modifier interaction a week substrate-modifier complex, [X] can be formed in the liquid phase. The hydrogenation of the above complex leads to the preferential formation of (R)-ethyl lactate, while the hydrogenation of the free substrate (EtPy) gives the racemate. The simplified reaction scheme for the enantioselective hydrogenation of α–keto esters over cinchona-Pt/Al_2O_3 catalyst can be written as follows:

Substrate	+ H_2	----Pt----k_R---->	(R)-lactate			(1a)
Substrate	+ H_2	----Pt----k_S---->	(S)-lactate		$k_R=k_S=k$	(1b)
Substrate	+ CD	---k_1---------->	[X]			(2a)
[X]		---k'_1---------->	CD + Substrate		$K=k_1/k'_1$	(2b)
[X]	+ H_2	---Pt------k'---->	(R)-lactate + CD		k'>k	(3)

Reactions (2a), (2b) and (3) strongly resemble the corresponding steps in enzyme catalysed reactions[14]. The formation of the substrate-modifier complex, [X] takes place in a fast equilibrium reaction ($k_1>>k'_1$). In this scheme, due to the rate acceleration effect, the enantioselective step is much faster than the racemic one (k'>k): Note that the rate acceleration induced by cinchonidine is always instantaneous[9-11].

The number of elementary steps and reactions involved in the enantioselective hydrogenation of EtPy is more than those given in the simplified reaction scheme. For the sake of simplicity neither the adsorption equilibrium of the modifier, substrate, [modifier-substrate] complex, products and by-products nor the side reactions are included into the simplified reaction scheme.

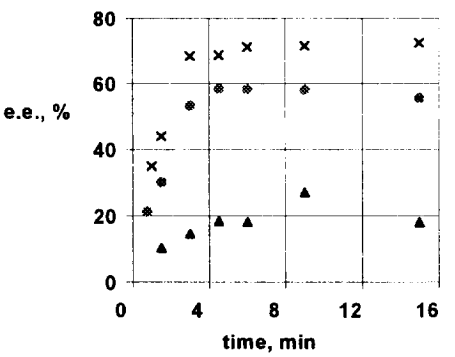


Figure 2. The increasing part of the enantiomeric excess vs. time dependencies obtained at different concentration of modifier.

[EtPy]= 1.0 M; Modifier concentrations, M: Λ - 6.8×10^{-6} ; ● - 3.4×10^{-5} ; **X** - $2.0 \times$ $^{-4}$.

By analysis of the system of differential equations describing the formation of (R) and (S)- ethyl lactate in reactions (1-3) some features of the enantiomeric excess vs. time dependencies can be investigated. The above analysis shows (see Appendix I) that the enantiomeric excess vs. time dependence should have a monotonic increase type form and the enantiomeric excess at zero conversion should be zero. Details of this analysis is given in Appendix I. These results indicate that the monotonic increase type character of the enantiomeric excess vs. time (or conversion) dependencies shown in Figure 1. and obtained in other studies [9-11,13] is the specific feature of this reaction. The observed character of these dependencies is strongly related to the reaction kinetic behaviour. Our analysis also shows that this form of dependencies appears due to the complex formation between the modifier and the substrate and the involvement of the substrate-modifier complex in the enantioselective hydrogenation reaction leading to the preferential formation of (R)-lactate. As emerges from the mathematical analysis (see Appendix I) the slope of the enantiomeric excess vs. time dependencies is proportional to the concentration of modifier. Experimental data given in Figure 2. give a strong support for our mathematical analysis, at low concentration of modifier the slope is proportional to the initial concentration of CD. At higher concentration of CD the reaction is very fast and the sampling technique used does not allow obtention of reliable samples in the increase part of the enantiomeric excess vs. time dependence.

We consider that despite the simplicity of our reactions scheme the kinetic modelling resulted in a very important information: *the initial enantiomeric excess is zero and the slope of the monotonic increase part is proportional to the modifier concentration.*

The role of by-products: In our earlier studies different side reactions and by-products were observed during the enantioselective hydrogenation of EtPy (i.e. in the presence of CD)[9-11, 15-18]. The side reactions or the by-products are as follows:

(1) semi-ketal formation form the solvent (alcohols) and substrate,
(2) semi-ketal formation from CD (via the OH group of CD) and substrate,
(3) transesterification (formation of methyl pyruvate and methyl lactate from ethyl pyruvate in methanol),
(4) deuterium exchange (formation of $CDH_2COCOOCH_3$ and $CD_2HCOCOOCH_3$ in CD_3OD),
(5) oligomerization of the substrate,
(6) formation of by-products from the oligomers and modifier,
(7) hydrogenated derivatives of CD (with the involvement of the vinyl and quinolyl group of CD).

Due the large number of side reactions and by-products formed during the enantioselective hydrogenation of EtPy it is impossible to create a generalized reaction scheme or to give a general kinetic model, which could describe the enantiomeric excess vs. time dependencies in the whole conversion range. It is considered that the poisoning of the Pt sites by-products and the loss of the active forms of CD during the hydrogenation reaction has the strongest effect on the overall kinetic behaviour including the enantiomeric excess vs. time dependence[9-11].

The role of metal: With respect to the role of metal we do not exclude the adsorption of modifier on the Pt sites, however we rule out both the formation of an ordered modifier overlayer[1,2] over Pt and the full

coverage of the Pt sites by modifier[6]. The weak adsorption of free modifier onto the Pt leads to the hydrogenation of the vinyl group[1-4,16,17], while the strong adsorption results in the hydrogenation of the quinoline ring, too[17]. The hydrogenation of the vinyl group has almost no influence on the overall behaviour, however the hydrogenation of the quinoline group leads to the complete loss of e.d.[17]. We suggest that in this catalytic system the key role of the metal is (i) to provide adsorbed hydrogen for the hydrogenation reactions and (ii) to be relatively inactive in the hydrogenation of the quinoline ring of the alkaloid. The latter issue is essential to control the enantio-differentiation step.

The origin of the enantio-differentiation step: Based on our results we suggest that the enantio-differentiation step takes place in the liquid phase. In this step the key issue is the formation of substrate-modifier complex. The formation of substrate-modifier complex is further supported by experimental evidence obtained in our earlier studies[9-11,16-18].

The fact that the enantiomeric excess and the form of the enantiomeric excess vs. conversion dependencies was strongly influenced by the initial substrate concentration[9-11,18] indicates that the substrate itself should be involved in the *control* of the e.d. step. The NMR spectra of CD in CD_3OD showed that the C(9) proton has a characteristic doublet at 5.65 ppm. In the presence of 0.15 M methyl pyruvate (MePy) a slight shift of the doublet to 5.85 ppm and a new small singlet was observed at 6.0 ppm. Upon increasing the concentration of MePy to 0.6 or 1.0 M the doublet vanished and only the new singlet at 6.0 ppm was found. More noticeable shift of the C(9) proton, up to 6.3-6.4 ppm with a formation of a singlet was observed in neat CD_3COOD or if small amount of CD_3COOD was added into the solution of CD in C_6D_6. These NMR results suggest that the torsional angle between the hydrogen atoms at C(8) and C(9) carbon atom of CD has been changed resulting in a new conformer of CD. The NOESY spectra of CD in CD_3COOD supported the above change of conformation[19]. In the above conformation changes of CD the quinuclidine and/or the quinoline ring is rotated around the C(9)-C(8) and/or the C(9)-C(4') axises of CD, respectively.

It should also be mentioned that in methanol and ethanol at low substrate concentration (0.1 -0.2 M) the enantiomeric excess was low (around 45-50 %), while at high substrate concentration (0.6 M or higher) the enantiomeric excess was around 70 % [8-11]. In the cinchona-Pt/Al2O3 catalytic sysytem the role the conformational changes of CD in the induction of enantio-differentiation was not suggested in earlier studies[1-11]. Conformational transion of chinine was postulated in a homogenous system, i.e. in the addion reaction of aromatic thiols to cyclic α,β- unsaturated ketones carried out in the presence of chinine[22].

We also consider that the quinoline part of the modifier is very important, it is also involved in the formation of the substrate-modifier complex. The quinoline ring provides a specific "shielding effect" often required for the chiral induction. The role of the quinoline part of the modifier in the enantio-differentiation step was completely neglected in earlier studies[1-8]. It was suggested that the quinoline ring is only involved in the adsorption of the modifier onto the metal. In this respect it is important to note, that if the quinoline ring of the alkaloid is fully hydrogenated the enantiomeric excess can be completely lost[17]. Recently, it was shown that the replacement of the quinolyl ring of the modifier for phenyl or pyridyl ring also leads to the complete loss of e.d.[8], i.e. the phenyl or pyridyl ring is too small to provide the "shielding effect".

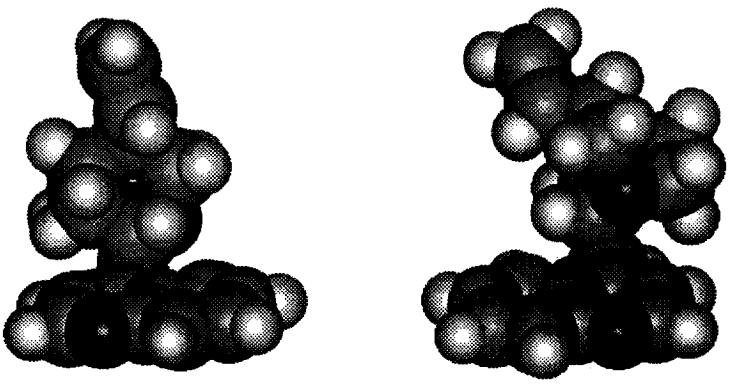
The importance of the "shielding effect" was demonstrated recently in asymmetric Diels-Alder reaction and hydrogenation reaction of acrylates and pyruvates, respectively[20,21]. Both substrates are very similar, both have a conjugated π-bond system. It is not excluded that the presence of the above conjugation is the key

structural factor responsible for the induction of e.d. by cinchona alkaloids even in the presence of supported metals.

Based on these observations we suggest that the π-orbitals of the quinoline ring might be involved in the stabilization of the substrate via π–π overlapping with its conjugated double bond. On the other hand the modifier should interact with the substrate via the quinuclidine nitrogen. The latter interaction is stronger than the π–π overlapping mentioned above, however, the π–π overlapping might be sufficient to introduce a specific shielding effect, which is needed for the enantio-differentiation step. The simultaneous π–π overlapping between the quinoline ring and the conjugated double bound in the α–keto esters and the donor-acceptor interaction between the quinuclidine nitrogen and the keto group can take place if CD changes its conformation from the open form to the closed one[18]. Figure 3. shows the open and closed forms of cinchonidine obtained by molecular mechanics calculations (additional two conformations may exist by rotation of the quinoline ring by 180 °). The change of the conformation of CD from open to closed requires 3-5 kcal/mole[6,19,22]. In the closed form the lone electron pair of the quinuclidine nitrogen is oriented above the quinoline ring. More detailed results on the conformation analysis will be published elsewhere[19].

It is commonly accepted that the mode of adsorption of the substrate on the Pt surface controls the formation of (R) or (S)-lactate [1-4]. The two possible mirror image forms of the adsorbed substrate (form R and form S) are shown in Figure 4. The adsorption of the substrate in form R leads to the formation of (R) - lactate, while the formation of (S)-lactate requires the adsorption in form S.

We consider that in this enantioselective hydrogenation reaction the modifier-substrate interaction should be involved in the control of the mode (or form) of adsorption of the substrate. Based on literature data[20,21] and the discussions made above we suggest that the role of modifier is to provide a specific shielding effect. Due to this shielding effect the substrate can adsorb on the platinum surface only by its unshielded site as shown in Figure 5. Cinchona alkaloids can provide a shielding effect in their closed form shown in Figure 3.



open form closed form

Figure 3. Open and closed conformations of cinchonidine.

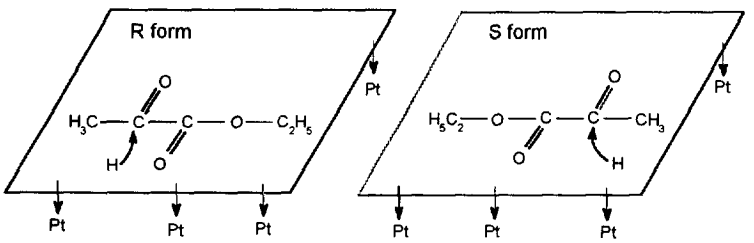


Figure 4. The two possible mirror image forms of the adsorption of α-keto esters on platinum leading to the formation of (R) and (S) products, respectively.

The possible shielded forms of the substrate-modifier complex involved in the induction of enantio-differentiation were determined by molecular mechanics calculations. In computer modelling and molecular mechanics calculations four different shielded forms of the substrate-modifier complex were calculated.

The adsorption of the substrate-modifier complex in R1 form (front site R form, i.e. in the form shown in Fig. 5.) onto the Pt surface, after the subsequent hydrogenation step leads to the preferential formation of (R) - lactate. The rotation of the substrate around the Z axis by 180° also leads to a substrate-modifier complex (R2 or back site R form), which after hydrogenation gives (R)-lactate. The rotation of the substrate in form R1 around the Y axis by 180° results in the S1 (or front site S) form, while the rotation of the S1 form around Z axis by 180 ° would give the S2 (or back site S) form. The above four forms of the substrate-modifier complex obtained by molecular mechanics calculation are shown in Figure 6. Complexes (R1, R2) and (S1, S2) shown in Figure 6 are responsible for the formation of (R)- and (S)-ethyl lactate, respectively. In complexes R1 and S2 the position of the substrate for adsorption is more favorable than in the corresponding R2 and S1 complexes. In complexes R2 and S1 the plane of the substrate is almost parallel to the plane of the quinoline ring. The complex R1 seems more favorable than the corresponding S1 as in the former complex the quinuclidine nitrogen can attack the carbon atom of the keto carbonyl group. In complex S1 there is no such type of interaction between the alkaloid and the substrate.

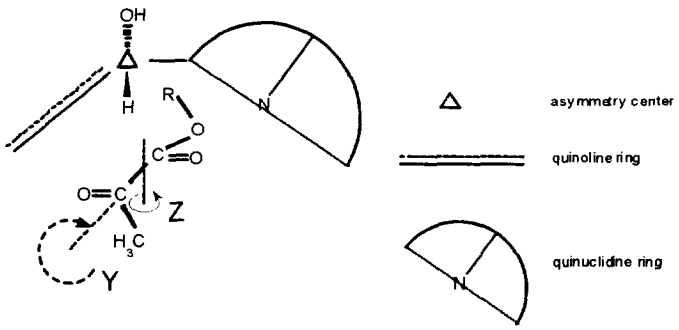


Figure 5. The shielded form of the substrate-modifier complex (a simplified scheme).

Figure 6. provides additional information as it also demonstrates that the concavity[23] of the modifier plays an important role in stabilization of the substrate-modifier complex in shielded form. The lack of induction of e.d. observed upon replacing the quinolyl part of the modifier for phenyl and pyridyl ring[8] can also be rationalized by the loss of concavity of the modifier. Further computer modelling and molecular mechanics calculations with the involvement of platinum will be needed to elucidate the exact nature of the enantio-differentiation step.

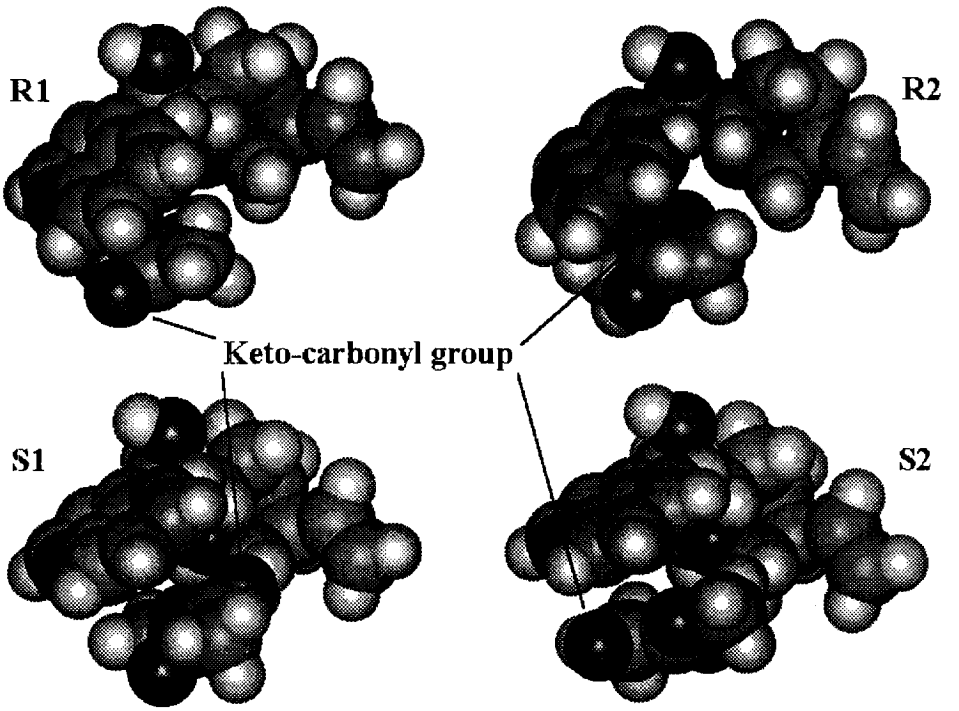


Figure 6. Computer modelling of the four shielded forms of the substrate-modifier complex. Complexes (R1, R2) and complexes (S1, S2) are responsible for the formation of (R) - and (S) - lactate, respectively.

EXPERIMENTAL

Hydrogenation: Ethyl pyruvate [EtPy] (Fluka), cinchonidine [CD] (Fluka) and Pt/Al_2O_3 catalysts (Engelhard E 4759, 5 %w Pt, D_{Pt} = 25 %) was used. The hydrogenation of EtPy was carried out in a 300 cm^3 SS autoclave equipped with an injection chamber for separate introduction of either the CD or EtPy. Upon using this technique part of the side reactions catalyzed by cinchonidine can be eliminated. Cinchonidine was injected in t=0 minute by high pressure hydrogen. Reaction conditions: temperature=23 °C, hydrogen pressure= 50 bar, $[EtPy]_o$ = 0.1-1.0 M, catalyst = 0.125g. Prior to the reaction the catalyst was rereduced in a hydrogen atmosphere at 400 °C and after cooling in a nitrogen atmosphere it was slurried into the solvent without any contact with air. Before the reaction the solvents used were carefully dried and purged with an inert gas. Prior to use EtPy was distilled under vacuum. GC analysis was carried out on a modified cyclodextrine coated capillary column (Advenced Separation) resulting in complete separation of (R)- and (S)-ethyl lactate and EtPy. The enantiomeric excess was calculated as e.e., %= ([R]-[S])/([R]+[S]) x 100 %.

Molecular Modelling: For the molecular modelling study the HyperChem program was used with the MM+ forcefield and the Polak-Ribiere (conjugate gradient) method. Minimum energy conformation of the substrate was determined, and a conformational analysis was performed for the modifier by molecular mechanics minimization with rigid quinoline and quinuclidine parts. Minimum energy calculations were performed for the whole modifier-substrate system from different starting positions. (Fig. 6 shows the most stable conformations calculated by MM+ forcefield.)

NMR measurements: NMR spectra were recorded on Varian VXR400 and Bruker AM300 spectrometers. The solvent used were: C_6D_6, CD_3OD, CD_3COOD. The concentration of CD was $1\text{-}10^{-3}$ M.

APPENDIX I

Let us consider the following reaction scheme:

$$S + H_2 \xrightarrow{k} P_R \quad , \qquad (1a)$$

$$S + H_2 \xrightarrow{k} P_S \quad , \qquad (1b)$$

$$S + M \xrightarrow{k_1} X \quad , \qquad (2a)$$

$$X \xrightarrow{k_1'} S + M \quad , \qquad (2b)$$

$$X + H_2 \xrightarrow{k'} P_R + M \quad , \qquad (3)$$

with starting concentrations:

$$[S(0)] = S^{(0)} \quad , \qquad (4a)$$

$$[M(0)] = M^{(0)} \quad , \qquad (4b)$$

$$[H_2(0)] = H_2^{(0)} \quad , \qquad (4c)$$

$$[P_R(0)] = 0 \quad , \qquad (4d)$$

$$[P_S(0)] = 0 \quad , \qquad (4e)$$

$$[X(0)] = 0 \quad . \qquad (4f)$$

In scheme (1-3) S is the substrate, M is the modifier, P_R is the (R)-product, P_S is the (S)-product, X is the modifier-substrate complex. As far as the modifier is injected into the reaction at t=0 the initial concentration of X is zero, $[X(0)]=0$. Concentrations of these materials at time t can be expressed in terms of Taylor series in the following way:

$$[S(t)] = S^{(0)} + S^{(1)} t + S^{(2)} t^2 + \ldots \quad , \qquad (5a)$$

$$[M(t)] = M^{(0)} + M^{(1)} t + M^{(2)} t^2 + \ldots \quad , \qquad (5b)$$

$$[H_2(t)] = H_2^{(0)} + H_2^{(1)} t + H_2^{(2)} t^2 + \ldots \quad , \qquad (5c)$$

$$[P_R(t)] = P_R^{(1)} t + P_R^{(2)} t^2 + \ldots \quad , \qquad (5d)$$

$$[P_S(t)] = P_S^{(1)} t + P_S^{(2)} t^2 + \ldots \quad , \qquad (5e)$$

$$[X(t)] = X^{(1)} t + X^{(2)} t^2 + \ldots \quad . \qquad (5f)$$

Substituting (5a-f) into material balances, $S^{(1)}$, $M^{(1)}$, ... , $X^{(1)}$, $S^{(2)}$, $M^{(2)}$, ... , $X^{(2)}$, ... can be determined successively as functions of $S^{(0)}$, $M^{(0)}$ and $H_2^{(0)}$, where $S^{(0)}$, $M^{(0)}$ and $H_2^{(0)}$ are the initial concentration of the substrate, modifier and hydrogen, respectively. Similarly, the enantiomeric excess can be expressed in the following form:

$$\text{e.e.} = (P_R(t) - P_S(t)) / (P_R(t) + P_S(t)) = e^{(0)} + e^{(1)} t + e^{(2)} t^2 + \ldots \quad . \qquad (6)$$

Performing calculations we obtain:

$$e^{(0)}=0 \qquad (7a)$$

$$e^{(1)}= ((k' k_1) / (4 k)) M^{(0)} \qquad (7b)$$

$$e^{(2)}=- e^{(1)} (e^{(1)} - (1/6) k_1 M^{(0)} + (1/3) k' H_2^{(0)} - (1/3) k H_2^{(0)} + (1/3) k_1' + (1/3) k_1 S^{(0)} + (1/3) k S^{(0)}) \qquad (7c)$$

From eqns. (7a-c) it follows that the e.e. vs. time dependence starts from the origin of the coordinate system, the first derivative is a function of the concentration of the modifier, and the second derivative is negative (if k'>k). If concentration $[H_2(t)]$ is forced to be constant ($H_2^{(0)}$) during the process, the last term in $e^{(2)}$ ($(1/3)kS^{(0)}$) disappears.

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