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ARTICLE TYPE

Bridging racemic lactate esters with stereoselective polylactic acid using commercial lipase catalysis

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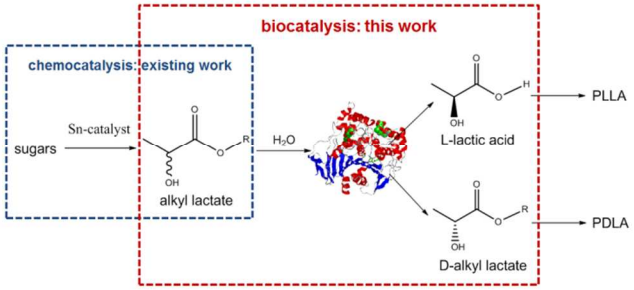
A productive and enantioselective hydrolysis of racemic mixtures of lactate esters with commercial *Candida rugosa* lipase was performed. This step contributes to a novel envisioned route for stereoselective PLA production by combining recent chemocatalytic developments with this biocatalytic contribution, foreseeing two separate L- and D-lactate enantiomer streams. A study of the hydrolysis kinetics identified an unexpected rate determining step at the origin of an unprecedented ester reactivity order.

Introduction

Lactic acid (LA) is a common renewable chemical with multiple applications in the food, cosmetic and pharmaceutical industry.[1, 2] A particularly fascinating and emerging field is its use as solvent and building block to prepare chemicals and polymers of commercial value.[3-7] Polylactic acid (PLA), a polyester which fulfills the definitions of both "renewable" and "biodegradable", has been recognized as one of the most promising bio-plastics[8-10] with an outspoken potential as sustainable alternative for certain petroleum-based plastics.[4] Next to the commodity polymer market, PLA is useful in various medical applications such as drug coatings, sutures and prostheses due to its biocompatibility and controllable degradability.[11] The global PLA production increases annually and is projected to amount up to 800,000 ton in 2020.[12]

Commercial PLA production involves ring-opening polymerization of lactide, the cyclic dimeric form of lactic acid.[13, 14] Stereoisomerism, as described first by van 't Hoff,[15] is paramount to the PLA quality. LA, obtained via bacterial fermentation of sugar, has the L-configuration and as a consequence, L-lactide is the building block of commercial poly-L-lactic acid (PLLA).[16, 17] Meso-lactide, having one L- and one D-configuration, is undesired because its incorporation in stereo-pure PLLA leads to inferior thermal and mechanical properties.[18, 19] Poly-D-lactic acid (PDLA), derived from D-lactide, behaves identically to PLLA. More importantly, blends of PLLA and PDLA contain homo-stereocomplex forms with a peculiar crystal structure providing a superior thermal and mechanical performance.[20-22] The availability of separate L- and D-lactide feed streams is thus of utmost importance, not only for large scale stereocomplex PLA production, but also to create medical grade PLA (e.g. for drug delivery) with a controllable hydrolytic biodegradation rate by applying a controlled ratio of L- to D-lactide. While L-LA is the natural isomer in the commercial fermentation process, D-LA is not abundantly available. It comes at astronomic prices today despite recent efforts and developments.[23, 24] The current production cost of L-LA is too high to foresee a global PLLA breakthrough mainly because of (*i*) the low volume productivity, *viz*. 0.3 to 5 g/L.h,[25-28] despite its high yield starting from glucose (around 90%)[1, 29-31](*ii*) the costly multiple purification and separation steps of L-LA from the fermentation broth, and (*iii*) the formation of one ton of gypsum waste per ton L-LA, resulting from acid neutralisation.[2, 31] As this salt waste is probably the main bottleneck, recent research was focused in the development of acid tolerant microorganisms, but lactic acid yields and productivities are low.[31-33] Another advancement was the development of electrodialysis membranes, as a useful tool to eliminate the salt waste, but resulting in an overall more complex process system. The above mentioned issues might compromise the genuine greenness of L-LA synthesis, especially with the large production scale outlook ahead. We therefore envision an alternative synthesis route leading to separate L- and D-LA streams from common sugars by combining the best of chemo- and biocatalysis (Scheme 1).



Scheme 1 Tentative route for stereoselective PLA by combining a chemocatalytic production of racemic lactates from sugars with an enzymatic enantioselective hydrolysis

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The newly proposed strategy involves a sequence of a chemocatalytic conversion of the sugars to racemic alkyl lactates, currently under intense investigation,[1] followed by an enzymatic enantioselective hydrolysis. The chemocatalytic route relies on a recent breakthrough yielding LA (in water) and its esters (in alcohol) from sugars [34-42] in presence of robust, solid Al or Sn containing catalysts [43-47] such as Snβ zeolite [36, 39, 48] and Sn modified silica/carbon hybrids.[46, 49] This alternative route with less work-up could be a future commercial route to lactic acid and its esters, provided that one could deal with the racemic LA mixture. Being racemic, the chemically derived lactate ester feed indeed has the desired composition to create both L- and D-lactide at comparable prices. However, direct processing of the racemic mixture with state-of-the-art technology would lead mostly to unwanted meso-lactide, apart from equimolar amounts of L-lactide and D-lactide. Considering the need for pure L- and D-lactide streams, a separation of the lactate racemate into pure enantiomers is compulsory. Chromatographic methods are time-consuming and expensive[50-52] and although chemical resolution by reacting lactic acid racemates with L-brucine is a well-known separation technique, it is generally characterized by a low efficiency.[53] More efficient and cheap separation methods should be applied to utilize the racemic feed as PLA polymer precursor. Enzymatic kinetic resolution has proven to be successful in obtaining enantiopure compounds.[54-63]

Herein we report the enantioselective hydrolysis of racemic α-hydroxy compounds like the aforementioned alkyl lactates with *Candida rugosa* lipase (CRL). The racemic ester substrates are available in high yields via heterogeneous catalysis in alcoholic media (scheme 1), while no catalyst deactivation was observed in contrast to the chemocatalytic synthesis of LA in water.[36, 40, 46] Moreover, the esters are easier to handle in purification procedures, and in the context of biocatalysis, they offer the advantage over the free acid that significantly less buffer is needed. These arguments motivate the enzymatic resolution method by means of ester hydrolysis. Besides, while multiple reports of kinetic resolutions are focused on the synthesis of one key enantiomer, the goal here is to directly provide the two processable streams of opposite enantiomers, only requiring a common ester/acid separation. Ultimately, L-LA is further converted directly to L-lactide with the current process technology,[13] while D-lactate ester is readily hydrolyzed and further processed similarly or even processed directly to D-lactide.[64]

Lipases are the biocatalyst of choice to assist the enantioselective hydrolysis step. They have verified time-on-stream stability, substrate specificity, and high enantioselectivity in mild reaction conditions with multiple applications in the food, pharmaceutical and agrochemical industries.[58, 62, 65-67] Moreover, lipases work without cofactors and they are produced extracellularly. This results in current industrial sales prices around €500/kg enzym for commercial lipase formulations of CRL, their production cost typically being a factor two to three lower.[68] With the novel fermentation techniques ahead for lipase production, the enzyme price should not be a show stopper for its use in stereoselective PLA synthesis (see supporting information).[69-72] Frequently applied in organic synthesis, lipases have been demonstrated to be particularly valuable in kinetic resolutions of alcohols, carboxylic acids, esters, and amines[56, 57, 73-77] but examples on resolutions of α-hydroxy esters are very rare.[78, 79]

Experimental

Reactions were carried out in 10 mL thick glass walled crimp cap vials. In a typical experiment a known amount of ester (Sigma-Aldrich or derived from lactide) (e.g. 0.4 g in the case of MLA) and e.g. 0.08 g enzyme preparation (Sigma-Aldrich) was added together with 7 mL phosphate buffer (pH = 7.2). A non-interfering internal standard (1,4-dioxane (Acros)) was used. A magnetic stirring bar was added and the vial was closed and placed in a copper heating block at a fixed temperature (e.g. 45 °C). Samples were taken at certain moments in time. Enantiomers of MLA, ETLA, *n*PrLA, MHBA, MGA, EGA and *n*PrGA were analyzed by chiral gas chromatography (GC) on a 25 m WCOT fused silica CP-Chirasil-DEX CB (Agilent) capillary column. The E-value (enantiomeric ratio) was determined using following formula: $E = \ln[1-c(1+ee_p)]/\ln[1-c(1-ee_p)]$.[80] The synthesis of lactate esters was performed via alcoholysis of lactides (generously provided by Purac) as described in the supporting information.

Results and discussion

Screening

In an initial phase, commercial lipase preparations were screened for their activity and enantioselectivity towards the hydrolysis of racemic methyl lactate (MLA). The screening was carried out in dilute conditions in analogy with reported procedures.[55, 78, 81-83] In the mild aqueous conditions, only LA and methanol were analyzed as product. Reactions were buffered and performed at room temperature to avoid non-stereoselective background hydrolysis. Table 1 summarizes the catalytic data of different lipases at nearly the same degree of total ester conversion.

Table 1 Screening of different commercial lipase preparations in the enantioselective hydrolysis of MLA in water.[a]

Entry	Enzyme	Time [h]	Conv.(L) [%][b]	Conv.(D) [%][b]	ee_p [%][c]	Pur. [%][d]
1	CRL	46	73.8	2.8	92.8	96.4
2	CALB	2	36.3	42.4	-7.9	46.1
3	PPL	191	60.0	22.0	39.7	69.9
4	BCL	561	46.0	31.4	17.8	58.9
5	LM	224	61.6	19.8	45.4	72.7

[a] Hydrolysis at 25 °C with enzyme preparation (abbreviations in full in text) (0.02 g in the case of CRL and CALB; 0.15 g in the case of PPL, BCL and LM), 0.135 M MLA, 7 mL 0.014 M phosphate buffer (pH = 7.2). [b] Determined by chiral GC (see experimental and supporting information). [c] enantiomer excess of L-LA on product side. [d] Molar enantiomeric purity on product side (see supporting information).

Candida rugosa lipase (CRL, **Entry 1**) outperforms all other enzymes with respect to enantioselectivity. CRL preferably hydrolyzes the L-MLA isomer with a product enantiomeric excess ee_p of 93% at very high conversion of the L-isomer of MLA. This corresponds with a molar enantiomeric purity on the

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product side of 96.4%, which is a measure for the ultimate purity of the corresponding lactides and PLA polymers. *Candida antarctica* lipase B (CALB, **Entry 2**), which was used in the immobilized form, has by far the highest activity, but its enantioselectivity is very poor and slightly in favor of D-LA formation. The three other commercial lipases *Porcine pancreas* lipase (PPL, **Entry 3**), *Burkholderia Cepacia* lipase (BCL, **Entry 4**) and lipozyme (LM, **Entry 5**) were used in excessive amounts for prolonged reaction times due to their very low activities in standard conditions.

Improving the hydrolytic productivity

Because of the high enantiomeric excess of CRL, attempts were made to maximize its volume productivity (expressed in $g.L^{-1}h^{-1}$) without compromising the excellent enantioselectivity. This is essential, because productivity is a highly important measure for industrial implementation.[84] Attempts were made by inclining substrate, enzyme and buffer concentration, while maintaining the same ratio of MLA to enzyme, together with an increase in temperature. The effects on the volume productivity are illustrated with catalytic data in Table 2.

Table 2 Effects of temperature and concentration on the productivity and enantioselectivity of *Candida rugosa* lipase.[a]

Entry	Substr. [M]	Time [h]	Temp. [°C]	Conv.(L) [%][b]	Prod. [$gL^{-1}h^{-1}$]	ee_p [%][b]	Pur. [%][d]
1	0.14[c]	46	25	73.8	0.2	92.8	96.4
2	0.55	23	25	75.0	1.9	91.8	95.9
3	0.27	6	45	72.8	3.3	91.5	95.8
4	0.55	8	45	65.7	4.4	90.9	95.5
5	1.10	16	45	63.8	4.1	88.7	94.4
6	0.55	6	55	49.3	4.8	74.7	87.4

[a] Reactions carried out with 0.08 g enzyme preparation (unless stated otherwise) with constant MLA to buffer ratio. [b] Determined by chiral GC (see experimental and supporting information). [c] 0.02 g enzyme preparation was used. [d] Molar enantiomeric purity on product side (see supporting informaton).

The results show a higher conversion rate with increasing substrate concentration without loss in enantioselectivity (**Entry 2** *vs.* **Entry 1**). The productivity is 0.22 and 1.95 $g.L^{-1}h^{-1}$ for the conversion of 0.14 M and 0.55 M MLA respectively with an ee_p value above 90% in favor of L-lactic acid formation. By increasing the reaction temperature to 45 °C (**Entry 3**), 65.7% conversion of L-MLA was reached within 8 hours corresponding to a productivity of 4.4 $g.L^{-1}h^{-1}$, indicating the enzyme is still stable at this temperature. The enantioselectivity remains high indicating that the uncatalyzed background hydrolysis is negligible at 45 °C. A raise to 55 °C (**Entry 6**) lowered the enantioselectivity, *viz*. from 91 to 75%, while the productivity was only slightly higher. This lower ee_p is explained by a significant contribution of non-stereoselective background hydrolysis. A reaction at 65 °C is not stereoselective and very slow suggesting CRL deactivation at this reaction temperature (data not shown). A careful comparison of **Entry 3** with **Entries 4** and **5**, reveals a maximum productivity and high enantioselectivity at 45°C and MLA concentration of 0.55 M or higher. Surprisingly, no significant reduction in enantioselectivity was observed for the concentrated conditions, *viz*. 0.55 M and 1.10 M MLA. These concentrations may be considered very high and industrially practical,[84] when compared to those reported for the enzymatic synthesis of enantiopure α-hydroxy compounds as well as for several other kinetic resolutions, [54, 73, 81-83, 85] typically ranging between 0.001 M and 0.3 M. The productivity and enantioselectivity is high due to the irreversibility of the hydrolysis in excess of water and the straightforward conditions of the biocatalytic system (absence of co-substrates and side reactions). Figure 1 illustrates for instance the evolution of L-LA production as a function of time for 0.55 M MLA at 45 °C in the presence of CRL (triangles).

Mechanistic discussion

A wide range of chiral esters and acids are nicely mapped in literature with respect to the enantioselectivity in respectively hydrolysis and esterification reactions and a predictive rule was established for CRL based on this data set. A true focus on α-hydroxy esters is however rather exceptional. Note that this rule is less certain when dealing with crude CRL,[86] which consists of multiple isoforms differing in their enantioselectivity (see supporting information).[87-89] Moreover, studying a variety of the substrate scope is a useful tool to gain insight into the catalytic reactivity trends.[90] Both the effects of variations at the acyl side, *viz*. R' (Me and Et) directly connected with the chiral α-carbon and at the alkyl side R (Me, Et and *n*Pr) were studied (see Table 2). To make a fair kinetic comparison, we limited our hydrolysis study to water-soluble α-hydroxy esters. Note that the chiral products of some substrates, *viz*. methyl α-hydroxy butyrate (MHBA), have been suggested to be promising polymer precursors themselves.[91, 92] The biocatalytic hydrolysis results are summarized in Table 3.

Table 3 Hydrolysis of various α-hydroxy esters.[a]

Entry	R; R'	Time [h]	Conv.(L) [%][b]	Prod. [$g.L^{-1}h^{-1}$][c]	ee_p [%][b]	Pur. [%][d]
1a	CH_3;CH_3	8	65.7	4.4	90.9	95.5
1b	CH_2CH_3; CH_3	2.3	76.1	18.1	88.7	95.4
1c	$CH_2CH_2CH_3$; CH_3	1.5	55.0	33.0	26.4	63.2
2a	CH_3; CH_2CH_3	4	84.3	12.3	>95	98.2
3a	CH_3; H	30	14.4[e]	0.19	-	-
3b	CH_2CH_3; H	26	25.7[e]	0.39	-	-
3c	$CH_2CH_2CH_3$; H	24	29.4[e]	0.48	-	-

[a] Hydrolysis at 45 °C, 0.55 M substrate, 0.057 M phosphate buffer (pH = 7.2) and 0.08 g CRL.[b] Determined by chiral GC (see experimental and supporting information). [c] See supporting information. [d] Molar enantiomeric purity on product side (see supporting information).[e] Conversion here defined as total conversion of glycolate due to achirality.

No significant difference in ee_p-values of MLA (**Entry 1a**) and ethyl lactate (EtLA) (**Entry 1b**) were obtained, while the enantioselectivity seriously decreases for the propyl lactate ester (*n*PrLA) (**Entry 1c**). A similar selectivity pattern was reported for the hydrolytic kinetic resolution of β-borylated carboxylic esters with CALB.[93] The L-enantiomer is preferred for the three lactate

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esters, which is according to the predictive Kazlauskas rule assuming OH as medium sized substituent and CH_3 at the α-carbon as large sized substituent (see scheme in Table 3).

The enantioselectivity significantly increases with elongation of the acyl side of the ester, *viz*. R' = Et as in the case of MHBA (compare **Entries 1a** and **2a**). This observation is in agreement with the established empirical rule, which suggests that the size of the substituents is crucial for the enantioselectivity of CRL:[78, 79, 86, 87, 94-98] a larger size difference between R' and OH, results in a higher enantioselectivity due to a larger difference in free energy between the transition states of the two enantiomers.

The lipase catalyzed hydrolysis is in principle a base-catalyzed mechanism, *viz.* starting with a nucleophilic attack of the serine oxygen to the carbonyl carbon of the ester. Therefore it was highly unexpected for this enzymatic reaction to reveal a higher hydrolysis rate with increasing alkyl length, *viz.* with electron donating property (or basicity),[99] as it contradicts the reactivity of esters for the classic base-catalyzed hydrolysis.[100-102] Indeed, the hydrolysis of MLA, ETLA and *n*PrLA by action of OH^- has been studied and the authors observed a rate decrease with increasing alkyl length of the released alcohol (see inset of Figure 1).[102, 103] The difference in reaction rate is also apparent by comparing the kinetic profiles of MLA (triangle), ETLA (squares) and *n*PrLA (diamonds) (Figure 1).

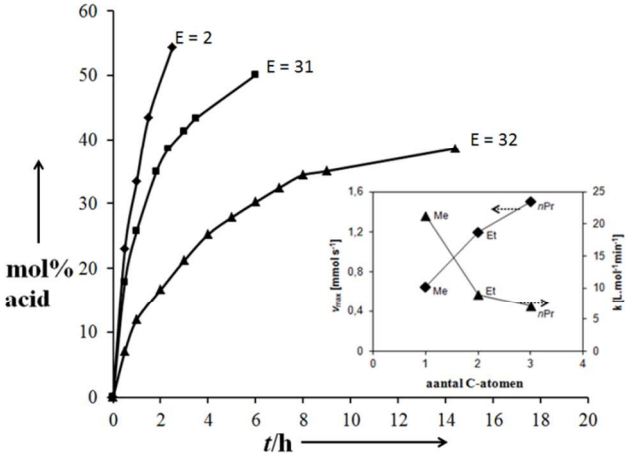


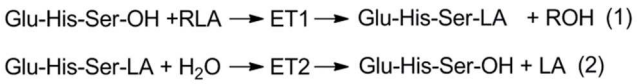
Fig.1 Production of lactic acid in time and E-value (see experimental part), starting from MLA(▲), EtLA (■) and *n*PrLA (♦) using 0.08 g CRL, 0.55 M of lactate ester and 7 mL of a 0.057 M phosphate buffer. Inset: reversed reactivity pattern for alkyl lactates (R = Me, Et, *n*Pr) in enzymatic (♦) and classic base (▲) catalyzed hydrolysis.[102]

Significantly high volume productivities with ETLA and PrLA instead of MLA, *viz*. 18.1 and 33.0 $g.L^{-1}h^{-1}$ respectively versus 4.4 $g.L^{-1}h^{-1}$ (MLA), were calculated from the graphs. In these conditions, around 50mol% of lactic acid is reached starting from ETLA in 6 hours, creating the desired equimolar ester/acid composition, with a molar enantiomeric purity of 93%.

One hypothesis to explain the reverse reactivity might rely on a more pronounced inhibitory effect of the formed methanol on the enzyme when compared to ethanol and *n*-propanol.[104-108] An enzymatic hydrolysis of *n*PrLA was therefore carried out in the same conditions of Table 3, but now in presence of 0.061 g of methanol, which equals the quantity released in a reaction with MLA if 50% of the total amount of lactate ester is converted. As no significant influence on the hydrolysis rate was observed, alcohol product poisoning is excluded.

To further elaborate the reversed rate order, kinetic parameters were measured according to Michaelis-Menten kinetics, which is appropriate to apply for our reaction system.[109] The K_M and v_{max} values of crude CRL for the different lactate esters (with R = Me, Et and *n*Pr) are depicted in the supporting information. The v_{max} is found to increase with increasing length of R in the lactate ester, as illustrated in the inset of Figure 1. In the applied conditions of Table 3 and Figure 1, *viz*. 0.55 M, the reaction is thus carried out well above K_M and thus near the maximum hydrolysis rate of the enzyme (see supporting information). This is beneficial, as the enzyme is „saturated" with substrate and thus works at maximum capacity. The above observed rate order with the three lactate esters is therefore determined by v_{max}, but now the question arises which step determines v_{max}.

A detailed study of the individual steps of the catalytic cycle discloses a valid explanation of the intriguing reactivity pattern, *viz*. MLA << ELA < *n*PrLA. Ester hydrolysis by CRL is believed to proceed according to a two-step mechanism: transesterification (equation (1)) and hydrolysis (equation (2)). First the active serine site of the catalytic triad is acylated, involving the formation of the first tetrahedral intermediate (ET1). During this acylation, the corresponding alcohol is released, caused by a nucleophilic attack of the serine to the carbonyl carbon. The second step is the deacylation of the enzyme. This step involves the formation of the second tetrahedral intermediate (ET2), caused by the introduction of a water molecule. Finally, the corresponding acid is released, recovering the catalytic triad in the original state.[110]



In the applied hydrolytic conditions, the first step, with the removal of the alcohol, is in principle irreversible, thus determining the enantioselectivity.[86, 87, 111] The acylation step is often suggested to be rate-determining, the hydrolysis rate thus being in favor of the ester with the best leaving group, *viz.* the shortest alcohol.[87, 112] This is not according to our findings in case of α-hydroxy esters: *n*PrLA has the highest reactivity.

A true understanding of the reversed reactivity pattern is only possible by considering all elementary reaction steps of the catalytic cycle. The extended mechanistic proposal is presented in Figure 2. Step (1) of the mechanism is regarded as the association of enzyme (E) and substrate (S), forming an enzyme-substrate (ES) complex, as described for the mechanistically identical serine proteases.[113-115] The initial step is largely determined by the K_M-value, whereas v_{max} (and thus our rate order) is determined in the subsequent steps. As the ES complex is identical for the three lactate esters in step (5) to (8), the rate determining step is determined either in step (2), (3) or (4) (Figure 3). Step (2) presents a nucleophilic attack of the serine to

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the carbonyl carbon, with the formation of the tetrahedral intermediate and stabilization of the negative oxygen by hydrogen bonds in the oxyanion hole, comprised of a Gly and Ala residue. According to the classic base-catalyzed hydrolysis, the formation of such tetrahedral intermediate, is rate-determining.

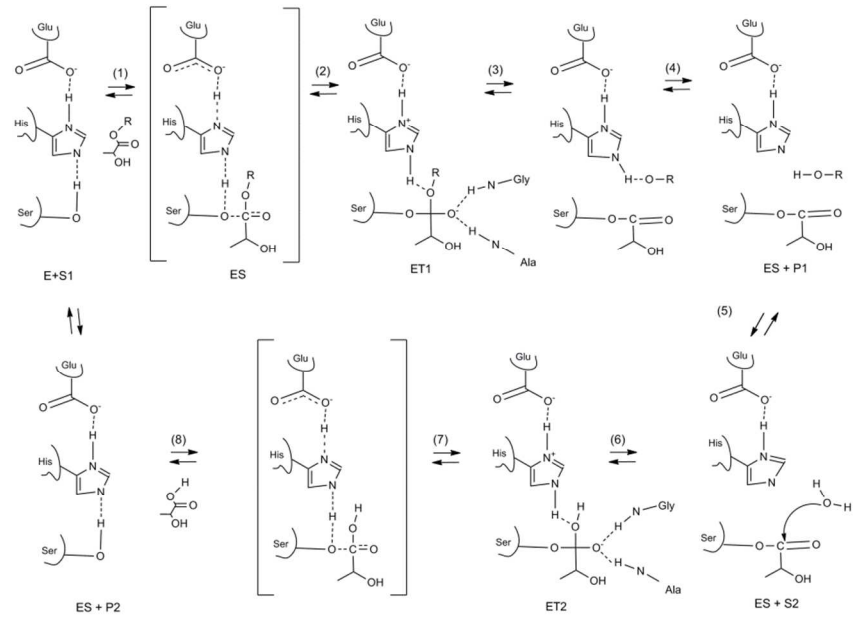

Fig.2 Propose extended mechanism of the hydrolysis of α-hydroxy esters with CRL, based on reports of Hirohara et al., Nishiziwa et al., Buchwald *et al*. and Satoh *et al.*

The alcohol addition will thus be faster with electron withdrawing R groups.[100, 101] As our kinetic data show the opposite reactivity, step (2) is certainly not the rate-determining step in the hydrolysis of lactates by CRL. Some literature suggests that the formation rate of hydrogen bonds in the oxyanion hole is defined sterically,[116] but also according to this hypothesis our results show the opposite trend. Next, the tetrahedral intermediate collapses, with the release of ROH. This collapse is often regarded as a one elementary step, in which the best leaving alcohol determines the reactivity.[87, 112] However, our kinetic results agree with a 2-step interpretation of the collapse, here presented by step (3) and (4). In step (3), the alcoholate ion leaves the acylated serine, we propose that RO^- binds the histidine proton in accordance with other reports.[110, 116] Step (4) requires a deprotonation of the histidine with release of ROH, permitting the introduction of a water molecule to initiate the hydrolysis sequence in step (5-8), ultimately resulting in the acid production. Our reactivity pattern is in accord with a rate determining histidine deprotonation (step (4)): the more electron donating the alcoholate, the better it accepts the histidine proton. Following this theory, a clear explanation for the reactivity differences of *n*PrLA, ETLA and MLA is provided.

To verify our hypothesis for other α-hydroxy esters, we additionally investigated the hydrolysis of glycolates, the shortest α-hydroxy esters, with CRL. The reaction kinetics follow the same rate order (compare **entries 3a-c** in Table 3) as for the lactates. The observation of a rate determining histidine deprotonation in a lipase catalyzed hydrolysis of esters is unique as the leaving ability of the alcohol is generally accepted to be rate determining.[87, 112]

Conclusions

In conclusion, we succeeded in performing a productive enantioseparation of chemically formed, racemic α-hydroxy compounds such as lactate esters with commercial *Candida rugosa* lipase in mild hydrolytic conditions. The envisioned route comprises a unique synergy between chemo- and biocatalysis: the Sn-catalyzed formation of racemic alkyl lactates from common sugars like sucrose in a green alcoholic solvent, followed by the enantioselective hydrolysis with CRL. Clear advantages compared to the current lactic acid production process are: i) no gypsum waste, ii) a high volume productivity, *viz*. up to 18.1 $g.L^{-1}h^{-1}$, iii) less demanding workup, and iv) co-generation of enantiopure L- and D-lactic acid with molar enantiomeric purity, sufficiently high to foresee various PLA polymers ranging from more hydrolysable forms to strong stereocomplexes with melting points between 200°C and 265 °C (see supporting information).[117] In meanwhile, a fully novel reactivity trend was encountered, pointing the ester with the longer leaving alcohol as the most reactive one. An unencountered rate determining deprotonation step of the histidine residu by the alcoholate ion proved to be the explanation for this unexpected pattern, while intelligently modifying the histidine basicity might result in an increased intrinsic activity. An economic assessment based on the obtained productivity, industrial product market prices and reported enzyme stability, in similar reaction conditions, suggests a profitable route towards PLA for specialty and medical applications (see supporting information).[118-123] As enzyme stability and productivity were key in the process economics evaluation, the study of immobilization strategies and protein engineering will be crucial in subsequent research. A realistic prospect based on recent achievements for analogue cases (see supporting information) renders the proposed kinetic resolution strategy challenging, but likely also for commodity applications.

Notes and references

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