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Enantioselective formation of mandelonitrile acetate: investigation of a dynamic kinetic resolution II

Lars Veum and Ulf Hanefeld*

Gebouw voor Scheikunde, Technische Universiteit Delft, Julianalaan 136, 2628 BL Delft, The Netherlands

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Abstract—The base- and lipase-catalysed enantioselective synthesis of a cyanohydrin ester was investigated. This dynamic kinetic resolution proved to be prone to residual water. However, when the lipase was immobilised on Celite R-633 as a carrier, the Celite adsorbed the water and suppressed the water induced side reactions. Both, the enantioselectivity and the reaction times for this dynamic kinetic resolution were improved. It thus enabled a nearly enantiospecific and high yielding synthesis of mandelonitrile acetate (yield = 97% and ee = 98%).

1. Introduction

Cyanohydrins are versatile building blocks in organic synthesis. Consequently their enantioselective synthesis has attracted considerable attention. Chemical and enzymatic approaches have been investigated, both having great potential.[1–3] A particularly elegant approach is the lipase- and base-catalysed synthesis of cyanohydrin esters, a synthetic dynamic kinetic resolution (Scheme 1).[4]

This is a combination of two reaction systems: (a) the dynamic, base-catalysed equilibria between acetone cyanohydrin **2**, acetone, HCN, aldehyde **1** and racemic cyanohydrin **4** and **5** and (b) the lipase-catalysed enantioselective and irreversible acylation of **4**. This combination yields the stable cyanohydrin ester **6**. This methodology was first published in 1991[5–7] and has been quoted frequently. However, only a few reports of its successful application are currently available.[8–10] A significant drawback of this synthetic dynamic kinetic resolution is the long reaction time (3–10 days). Moreover, it was reported that the reaction does not always proceed with satisfactory results.[11,12] We investigated potential bottle-necks and found that residual water hampered the reaction, since it caused the hydrolysis of isopropenyl acetate **7** and of product **6**. The addition of larger amounts of base to neutralise the released acetic acid led to the polymerisation of HCN and subsequent deactivation of the lipase.[13]

2. Results and discussion

Several different approaches can be utilised to circumvent the difficulties described above. Acyl donors that release less acidic acids upon hydrolysis might be used instead of **7**. Other bases or solid buffers,[14] instead of the alkaline amberlite, may prevent the HCN polymerisation. Equally other HCN sources than **2**, which release the HCN more slowly could serve for the same purpose. Alternatively the amount of water in the reaction mixture could be reduced to avoid the hydrolysis of **6** and **7**. When comparing the different reaction conditions described in the literature, two facts are noteworthy. For one, the extent of hydrolysis of both **6** and **7** is much higher than the amount of water present in the solvent used.[13] This indicates that there is another source of water present. Most likely this will be the dried enzyme or the support on which it is adsorbed. Secondly, in all the successful, albeit slow, experiments, the lipases were immobilised on Celite. Celite, as a natural silicate, adsorbs large amounts of water. It binds this water tightly via hydrogen bridges, indeed it can be used to control low water activities in organic solvents.[15] In comparison the *Candida antarctica* lipase B (CAL-B; Novozyme 435 or Chirazyme L-2, c.-f., C2, Lyo; both enzymes are identical), which we used in our earlier experiments, was adsorbed on a divinylbenzene cross-linked, hydrophobic

* Corresponding author. Tel.: +31 (0)15 278 9304; fax: +31 (0)15 278 4289; e-mail: u.hanefeld@tnw.tudelft.nl

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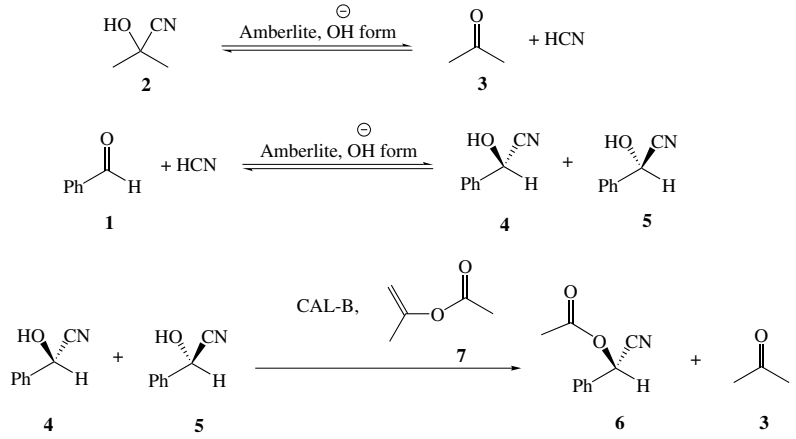

Scheme 1. Enantioselective synthesis of cyanohydrins by a dynamic kinetic resolution. All reactions proceed simultaneously in one pot.

macroporous polymer based on methyl and butyl methacrylic esters.[16] This lipophilic material will readily release any water that is attached to it into the dry reaction mixture, thereby enabling the hydrolysis of both the product **6** and the acyl donor **7**.

In order to verify this hypothesis lyophilised CAL-B was immobilised on Celite R-633 following the procedure[17] used in Refs. 8–10. This Celite immobilised CAL-B (CAL-Bcel) was compared with the polymethacrylate immobilised enzyme (CAL-Bpma, Novozyme 435 or Chirazyme L-2, c.-f., C2, Lyo) in the dynamic kinetic resolution. As described earlier, the ratio of **1**, **2** and **7** was 1:2:3, respectively.[5–10,13] 370 units CAL-B/mmol **1**, an amount that was shown to rapidly catalyse the kinetic resolution of mandelonitrile via esterification, was applied.[13,18] However, no complete conversion was observed and even after 3 days, the conversion was still below 50% (Fig. 1). This is less than the theoretical maximum yield that can be obtained in kinetic resolutions. This normal kinetic resolution was achieved after 6 h when 740 U/mmol CAL-Bpma were used.[13]

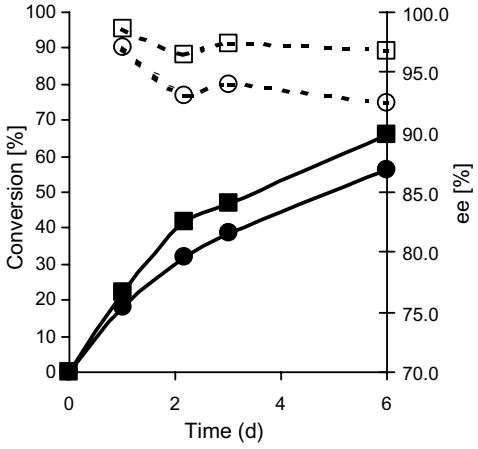

Figure 1. Dynamic kinetic resolution according to Scheme 1 utilising 370 U/mmol CAL-Bcel (■ % **6** formed; □ ee of **6**) or CAL-Bpma (● % **6** formed; ○ ee of **6**).

Although the desired result was not obtained in the dynamic kinetic resolution catalysed with 370 U/mmol, it was evident that CAL-Bcel performed better than CAL-Bpma. Moreover, its enantioselectivity was higher, indicating that Celite as a carrier material is overall advantageous. When comparing these results with the successful dynamic kinetic resolution,[5–10] the amount of enzyme used was relatively low. Therefore, the reactions were repeated with larger amounts of enzyme. Indeed the reaction proceeded considerably faster with higher conversions being observed (Fig. 2). When 1350 U/mmol CAL-Bcel were introduced into the reaction mixture, close to quantitative conversions were obtained within 3 days. (*S*)-Mandelonitrile acetate **6** was formed almost enantioselectively (ee = 98%). This is a significant improvement of the enantioselectivities described up to now. When the large amounts of enzyme activity were applied even with CAL-Bpma, excellent conversions approaching 100% could be obtained, albeit after 6 days. The enantioselectivity for CAL-Bpma, although still good (ee >92%), was in the range of earlier reports.

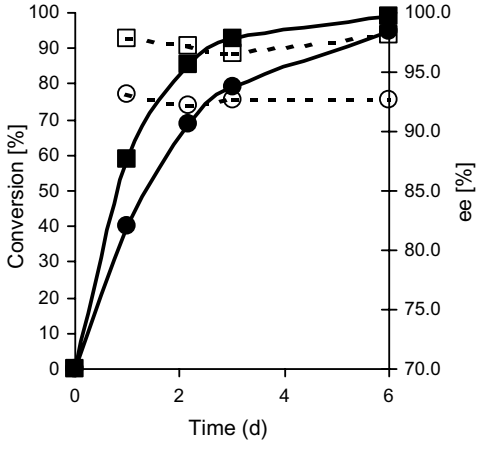

Figure 2. Dynamic kinetic resolution according to Scheme 1 utilising 1350 U/mmol CAL-Bcel (■ % **6** formed; □ ee of **6**) or CAL-Bpma (● % **6** formed; ○ ee of **6**).

When the reaction was performed with CAL-Bcel on a preparative scale (4.7 mmol **1**, 9.4 mmol **2**, 14.1 mmol **7**,

1350 U/mmol, toluene, 40 °C) (*S*)-mandelonitrile acetate **6** was obtained in excellent yield (97%) and enantiomeric excess (ee = 98%). The preparative reaction proceeded within 4 days, which is faster than described earlier (4 d rather than 6 d for **6**). More importantly the enantioselectivity was significantly improved. Instead of an enantioselective reaction (ee = 84%)[6] this is now almost an enantiospecific reaction. When comparing it to the vanadium-Salen catalysed formation of **6** from benzaldehyde **1**, KCN and acetic anhydride, it is a significant step forward. Although the vanadium-catalysed reaction proceeds faster (10 h), the yield (88%) and the enantioselectivity (ee = 90%) are lower.[19]

3. Conclusion

In conclusion, it was demonstrated that the synthesis of cyanohydrin esters via a synthetic dynamic kinetic resolution is highly dependant on the carrier of the enzyme. The carrier influences the amount of water available in the reaction mixture, suppressing or enhancing the undesired hydrolysis of the acyl donor **7** and the product **6**. By immobilising CAL-B on Celite and establishing well-defined reaction conditions, the reaction times could be shortened while the reaction became almost enantiospecific. These improvements make this lipase-catalysed cyanohydrin synthesis truly competitive to other cyanohydrin syntheses.

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