Highly Enantioselective Cleavage of α-Amino Acid *p*-Nitrophenyl Esters by Chiral Metallomicelles

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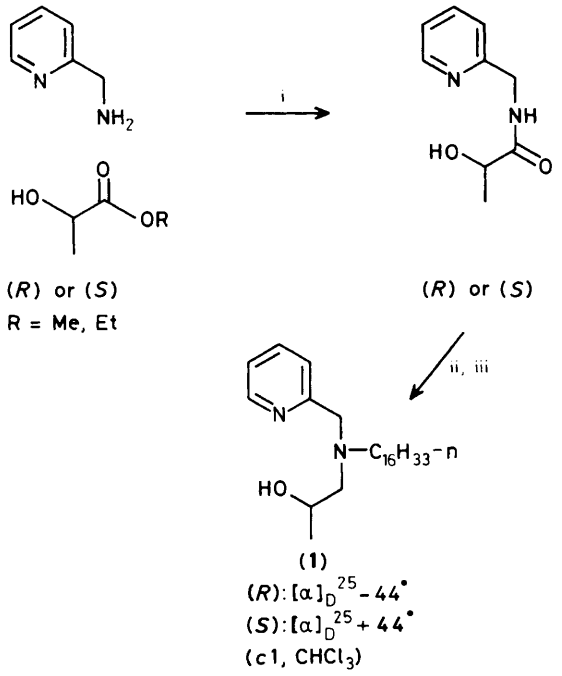
Chiral Cu^{II}-chelating micelles of 2-[hexadecyl-*N,N*-(2-hydroxypropyl)aminomethyl]pyridine are effective and remarkably enantioselective catalysts for the hydrolytic cleavage of *p*-nitrophenyl esters of α-amino acids.

In previous studies[1] aimed at designing micellar models of hydrolytic metalloenzymes[2] we observed that micelles of surfactants whose structure contains the 2-hydroxymethylpyridine moiety as a chelating subunit, in the presence of Zn^{II} or Cu^{II}, effectively catalyse the cleavage of the *p*-nitrophenyl ester of picolinic acid and also of other α-amino acids. The catalytic process was shown to involve the formation of a ternary complex (ligand–metal ion–substrate) in which, owing to the template effect of the metal ion, the hydroxy function of the ligand acts as a nucleophile and cleaves the ester in a transesterification process.

We thought that a chiral surfactant ligand, structurally similar to those already investigated, could be a good candidate for enantioselective hydrolysis of enantiomeric α-amino acid esters. In such a system, the template effect within the micellar aggregate could lead to remarkable enantioselectivity effects.[3—5]

Accordingly we synthesized both enantiomers of the lipophilic ligand (**1**). The main features of the ligand structure are the pyridine moiety, a chiral centre bearing an alcoholic function which may act as a nucleophile for the transacylation process, and the hydrophobic hydrocarbon chain. Compound (**1**) was synthesized by the reactions in Scheme 1 using as chiral starting materials ethyl or methyl lactate. The oily, pure enantiomers could be isolated as the HCl salts (m.p. 136—139 °C) and showed correct elemental analyses (C, H, N) and the expected n.m.r. spectra.

While ligand (**1**) enantiomers are, as free bases, insoluble in



Scheme 1. *Reagents and conditions:* i, $CHCl_3$, room temp., 7 days, 90%; ii, $LiAlH_4$, tetrahydrofuran (THF), reflux, or BH_3·THF, reflux; iii, n-$C_{16}H_{33}Br$, $NEtPr^i_2$, EtOH, reflux, 1 day, 30% yield overall.

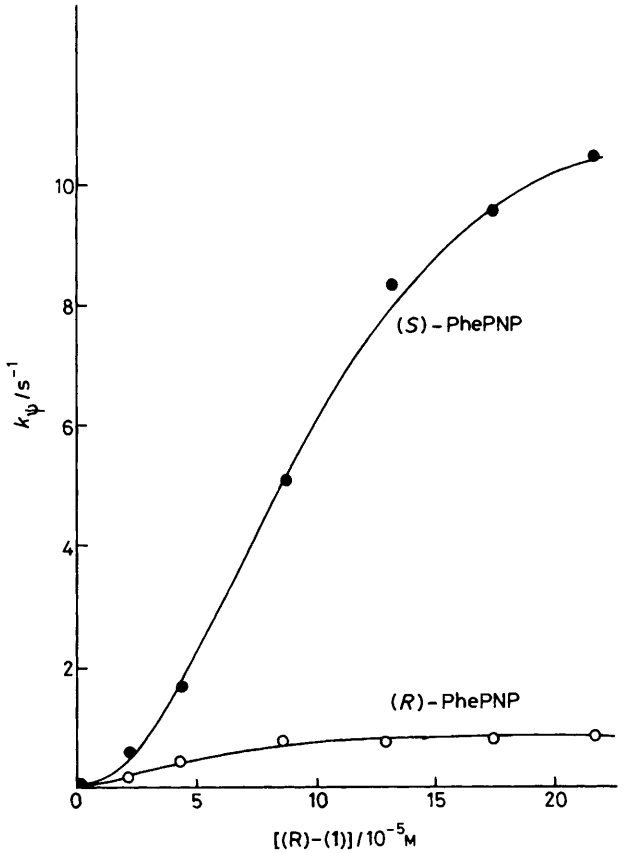


Figure 1. Rate *vs.* concentration profiles for the cleavage of (*S*)- and (*R*)-PhePNP by (*R*)-(**1**) in MES buffer, pH 5.5, [Cu^{II}] = 8.3 × 10^{-5} M.†

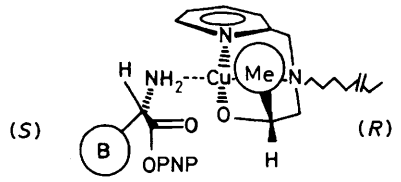


Figure 2. Proposed geometry for the ternary, productive complex (*S*)-amino acid PNP–Cu^{II}–(*R*)-(**1**).

water, on protonation, or in the presence of Cu^{II}, they form aggregates of the micellar type [critical micelle concentration (c.m.c.) = 2—3 × 10^{-5} M] and are soluble up to a concentration of 5 × 10^{-4} M in water solution [pH 5.5, 2-(*N*-morpholino)ethanesulphonate (MES) buffer]. In this buffer, Cu^{II}·(**1**) micelles were tested with the enantiomers of the *p*-nitrophenyl esters of phenylalanine (PhePNP) and leucine (LeuPNP).[6] Figure 1 shows a rate–concentration profile for the cleavage of (*R*)- and (*S*)-PhePNP by (*R*)-(**1**) in the presence of a fixed concentration of $Cu(NO_3)_2$ (8.3 × 10^{-5} M). Under these conditions {[substrate] = 8 × 10^{-6} M and [(*R*)-(**1**)] = 2.2 × 10^{-4} M} the following pseudo-first-order rate constants were measured (k_ψ/s^{-1}): 10.5 [(*S*)-PhePNP], 0.75 [(*R*)-PhePNP]; 2.5 [(*S*)-LeuPNP], 0.25 [(*R*)-LeuPNP]. The enantioselectivity factors, in terms of the ratio $k_\psi^{(S)}/k_\psi^{(R)}$ are therefore 14 (PhePNP) and 10 (LeuPNP). The rate and selectivity data (as indicated in Figure 1) were obtained for concentrations of the surfactant still rather far from those which may give rise to maximum rate enhancements (see Figure 1) which were not experimentally accessible. These data can be taken as the lower limits of the accelerations and of the enantioselectivities of the system under the conditions described. Optimization of the results by changing either the concentrations of the surfactant or those of the metal ion is under way. Similar rate profiles and enantioselectivity ratios (mostly within experimental error) were obtained in the case of the (*S*) enantiomer of the surfactant and the two enantiomers of LeuPNP.

The present enantioselectivities are by far the largest observed for purely micellar chiral systems.[3,7] Normal micelles have a loose, mobile structure which is not very effective at inducing stereoselectivity. However, as in the present system, the strong catalyst–metal–substrate interaction adds a further and effective degree of order. Stereoselectivity may be due not only to transition state but also to initial state interactions. In the cases so far considered the (*R*)-catalyst–(*S*)-substrate or (*S*)-catalyst–(*R*)-substrate interactions lead to higher kinetic effects than the opposite diastereoisomeric complexes. Inspection of molecular models suggests that in the productive ternary complex in which the ester function is located in close proximity to the hydroxy group (this is, of course, not necessarily the preferential binding mode), the methyl group of the catalyst and the bulky substituent at the chiral carbon of the amino acid are on opposite sides with respect to the Cu^{II} co-ordination plane (see Figure 2): a more favourable geometry than that of the corresponding (*R*)–(*R*) complex.

† *Note added in proof.* The curves shown in Figure 1 were not analysed, as is usual for functional micelles, to give plateau rates since [Cu^{II}] < [(**1**)] plateauing (and perhaps at higher (**1**) concentration, inhibition) could be due to the formation of a non-productive, ternary 2(**1**)·Cu^{II} complex.

Analogous substrates and appropriate conditions for the kinetic resolution of amino acids are being studied.

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