

Enantioselective cleavage of activated amino acid esters promoted by chiral palladacycles

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Dedicated to a bright memory of Professor M.E. Vol'pin (1923–1996)

Abstract

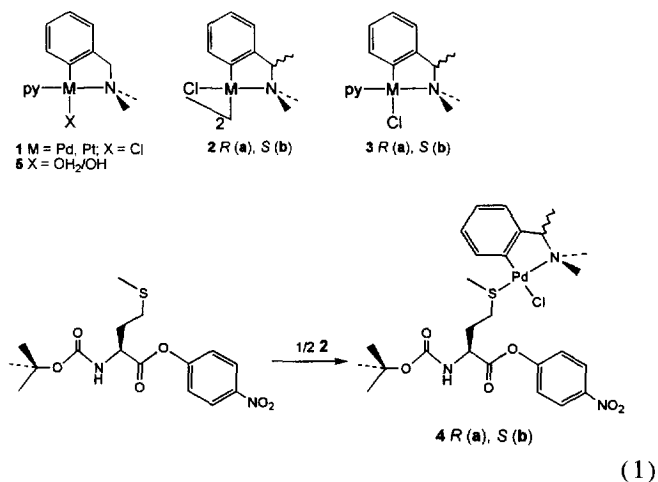
The ester cleavage of *R*- and *S*-isomers *N*-CBZ-leucine *p*-nitrophenyl ester intermolecularly catalyzed by *R*- (**a**) and *S*-stereoisomers (**b**) of the Pd(II) metallacycle [Pd(C₆H₄C*HMeNMe₂)Cl(py)] (**3**) follows the rate expression $k_{\text{obs}} = k_o + k_{\text{cat}}[\mathbf{3}]$, where the rate constants k_{cat} equal 25.8 ± 0.4 and $7.6 \pm 0.5 \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$ for the *S*- and *R*-ester, respectively, in the case of **3a**, but are 5.7 ± 0.6 and $26.7 \pm 0.5 \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$ for the *S*- and *R*-ester, respectively, in the case of **3b** (pH 6.23 and 25°C). Thus, the best catalysis occurs when the asymmetric carbons of the leucine ester and Pd(II) complex are *R* and *S*, or *S* and *R* configured, respectively. Molecular modeling suggests that the stereoselection results from the spatial interaction between the CH₂CHMe₂ radical of the ester and the α -methyl group of **3**. A hydrophobic/stacking contact between the leaving 4-nitrophenolate and the coordinated pyridine also seems to play a role. Less efficient intramolecular enantioselection was observed for the hydrolysis of *N*-t-BOC-*S*-methionine *p*-nitrophenyl ester with *R*- and *S*-enantiomers of [Pd(C₆H₄C*HMeNMe₂)Cl] coordinated to sulfur. © 1998 Elsevier Science S.A. All rights reserved.

Keywords: Kinetics and mechanism; Enantioselectivity; Palladacycles; Amino acid esters

1. Introduction

Previously, we reported on using of pallada- and platina-cycles of type **1** as mimetics of metalloesterases [1–4]. In aqueous media, these complexes undergo ready halide hydrolysis to afford a metal-coordinated aqua/hydroxo nucleophile and imitate several fundamental features of enzymes in terms of reaction rates [1] and regiospecificity with respect to the methionine residues [3]. In this paper, we demonstrate that metallacycles are also capable of mimicking such a key attribute of enzymatic catalysis as stereospecificity. To achieve this, it is sufficient to introduce a stereogenic center into the cyclometallated organic ligand, i.e. to use enantiomerically pure α, N, N -trimethylbenzylamine [5] instead of achiral *N, N*-dimethylbenzylamine. It will be demonstrated that palladium complexes **3** derived from *R*- and *S*-enantiomers of α, N, N -trimethylbenzylamine display different catalytic activity in the intermolecular hydrolysis of *R*-

and *S*-enantiomers of *N*-CBZ-leucine *p*-nitrophenyl ester. Less pronounced enantioselectivity will be shown to occur when the stereogenic palladacyclic fragment is coordinated to the sulfur of *N*-t-BOC-*S*-methionine *p*-nitrophenyl ester in complex **4** (Eq. (1)).



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2. Experimental

2.1. Reagents

Ortho-palladated chloro-bridged dimers **2a,b** were synthesized from *R*- and *S*-enantiomers of α,N,N -trimethylbenzylamine (Aldrich) and Li_2PdCl_4 in aqueous dioxane in the presence of NaOAc [6]. The dimers were converted into pyridine adducts **3a,b** as described previously [7]. $^1\text{H NMR}$ (Bruker CXP-200, δ) **2** (CDCl_3): 1.59 (d, CCH_3), 2.65 and 2.92 (s, $\text{N}(\text{CH}_3)_2$), 3.87 (m, CH), 6.74–7.24 (m, H3–H6); **2** ($\text{CDCl}_3 + \text{py-d}_5$): 1.64 (d, CCH_3), 2.75 and 2.97 (s, $\text{N}(\text{CH}_3)_2$), 3.85 (m, CH), 5.97 (dd, H6), 6.73–6.96 (m, H3–H5). **3a**: $[\alpha]_{\text{D}}^{20} = -82^\circ$ ($c = 11.7$, CHCl_3). **3b**: $[\alpha]_{\text{D}}^{20} = +86^\circ$ ($c = 39.3$, CHCl_3). It is interesting to note that the monomerization of **2** into **3** changes the sign of optical rotation of the corresponding palladium(II) complex as follows. **2a**: $[\alpha]_{\text{D}}^{20} = +57.3^\circ$ ($c = 1.85$, CHCl_3). **2b**: $[\alpha]_{\text{D}}^{20} = -42.8^\circ$ ($c = 0.71$, CHCl_3). *R*- and *S*-isomers of *N*-CBZ-leucine *p*-nitrophenyl ester were kindly provided by Dr A.N. Semenov.

Complexes **4** derived from *N*-t-BOC-*S*-methionine *p*-nitrophenyl ester (Sigma) were synthesized by treating the ester with **2** according to the recently adopted procedure [3]. **4a**: $[\alpha]_{\text{D}}^{20} = +39^\circ$ ($c = 11.9$, CHCl_3). **4b**: $[\alpha]_{\text{D}}^{20} = -62^\circ$ ($c = 13.5$, CHCl_3). UV-Vis (acetonitrile): $\lambda(\text{max}) = 242$ nm, $\epsilon(\text{max.}) = (1.87 \pm 0.12) \times 10^4 \text{ M}^{-1} \text{ cm}^{-1}$, $\lambda(\text{sh}) = 265$ nm. $^1\text{H NMR}$ (δ , CDCl_3): 1.46 (s, $\text{C}(\text{CH}_3)_3$), 1.59 (d, CCH_3), 2.50 (m, $\beta\text{-CH}_2$), 2.64 (s, SCH_3), 2.74 and 2.89 ($\text{N}(\text{CH}_3)_2$), 3.19 (m, $\gamma\text{-CH}_2$), 3.76 (m, CH), 4.73 (m, $\alpha\text{-CH}$), 5.60 (NH), 6.90–7.40 (m H3'–H6'), 7.28 (d, H2,6), 8.24 (d, H3,5).

2.2. Kinetic measurements

Reaction rates at 25°C were measured spectrophotometrically using Hitachi 150-20 and Shimadzu UV-160A spectrophotometers. Stock solutions of **3a** and **3b** (7.7×10^{-3} and $8.3 \times 10^{-3} \text{ mol dm}^{-3}$, respectively), as well as of *N*-CBZ-leucine *p*-nitrophenyl esters (ca. $9.5 \times 10^{-3} \text{ mol dm}^{-3}$) were prepared using acetonitrile as solvent. The stock solutions of **3a,b** were added to a 0.01 M NaClO_4 aqueous solution (pH 6.23) to achieve final concentrations of **3a,b** in the range $(4\text{--}18) \times 10^{-5} \text{ mol dm}^{-3}$. The reactions were initiated by addition of the stock solutions of *N*-CBZ-leucine *p*-nitrophenyl esters to the aqueous solution of **3a,b** to achieve the final concentration of the esters of $1 \times 10^{-4} \text{ mol dm}^{-3}$. The reaction progress was monitored by following the absorbance build-up at 395 nm. The pseudo-first-order rate constants k_{obs} were calculated from the absorbance (A) versus time (t) graphs by plotting $\ln\{A_\infty/[A_\infty - A(t)]\}$ against t . The linearity was observed in a matter of 4–6 half-lives. Every k_{obs} constant is a mean value of at least three determinations.

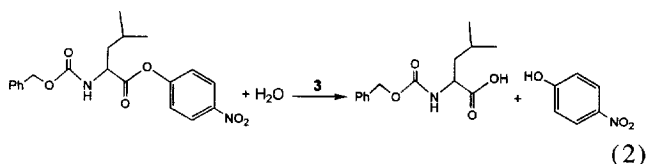
The kinetics of a slower *p*-nitrophenolate departure in complexes **4a,b** was studied spectrophotometrically at 400 nm after addition of 0.1 cm^3 of a $4.0 \times 10^{-3} \text{ mol dm}^{-3}$ solution

of **4** in acetonitrile to 3.0 cm^3 of a phosphate buffer ($0.002 \text{ mol dm}^{-3}$), pH 8.0. The total amount of MeCN in solutions was 3.3%. The pseudo-first-order rate constants k_{obs} were evaluated from the absorbance versus time plots by fitting the data to the expression $A(t) = A_\infty + (A_0 - A_\infty)e^{-kt}$. In this case a satisfactory first-order dependence was usually observed only in a matter of 1.0–1.5 half-lives excluding a short initial period of the reaction.

3. Results

3.1. *3a*- and *3b*-catalyzed hydrolysis of *R*- and *S*-enantiomers of *N*-CBZ-leucine *p*-nitrophenyl ester

The leucine ester undergoes slow spontaneous first-order hydrolysis at pH 6.2 to release *p*-nitrophenol/phenolate (Eq. (2)).



Cyclopalladated complexes **3a,b** increase the rate of hydrolysis (Fig. 1), the catalytic effect being strongly dependent on the absolute configuration of the stereogenic centers in both **3** and the leucine ester. If any stereoisomer of **3** displayed the highest catalytic activity with respect to a given stereoisomer of the ester, it was less reactive toward the mirror image of the latter. The catalyzed reactions were run when $[\mathbf{3}] \leq [\text{ester}]$ and the first-order kinetics was observed in the presence of **3** as well. From the data in Fig. 1, in the case of

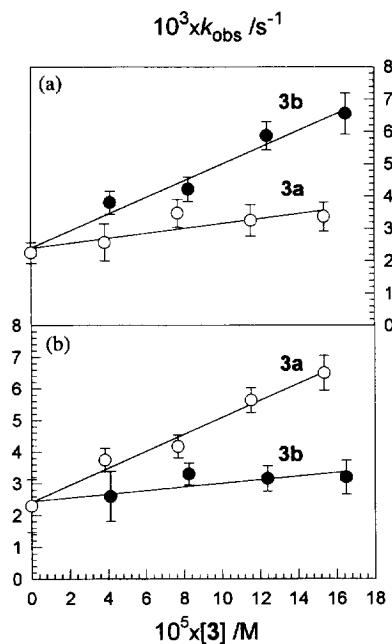


Fig. 1. Dependence of observed rate constants for hydrolysis of (a) *R*- and (b) *S*-stereoisomers of the *N*-CBZ-leucine *p*-nitrophenyl ester catalyzed by **3a** and **3b**; pH 6.23, 25°C .

all four pairs of reagents, the pseudo-first-order rate constant k_{obs} is given by

$$k_{\text{obs}} = k_0 + k_{\text{cat}}[3] \quad (3)$$

where the rate constants k_0 and k_{cat} correspond to the spontaneous and catalyzed hydrolysis, respectively. The calculated values of k_0 and k_{cat} are summarized in Table 1. As seen, there is a pronounced stereoselectivity and the enantioselectivity factor, defined as a ratio of the rate constants k_{cat} for *R* and *S* enantiomers of the ester, equals 4.5 (**3a/3b**) and 3.5 (**3b/3a**), respectively.

3.2. Acceleration of hydrolysis of *N*-*t*-BOC-*S*-methionine *p*-nitrophenyl ester by chiral Pd(II) species

The first-order rate constant for spontaneous hydrolysis of *N*-*t*-BOC-*S*-methionine *p*-nitrophenyl ester equals $1.1 \times 10^{-4} \text{ s}^{-1}$ at pH 8 [3]. The reaction in the case of complexes **4a,b** occurs faster, but the formation of *p*-nitrophenolate anion followed acceptable first-order kinetics over a period of 1.0–1.5 half-lives only. These portions of kinetic curves were used for evaluation of k_{obs} , which appeared to be dependent on the total concentration of either **4a** or **4b** (Fig. 2). Formally, Eq. (3) holds for hydrolysis of **4** as well, suggesting both intra- and intermolecular pathways in the hydrolysis of **4**. Thus, as a first, rather rough approximation we suggest the following reaction sequence to account for the kinetic data shown in Fig. 2.



The second-order step (5), in the course of which only one substrate molecule is converted into the products, is presumably the reason why the first-order kinetics is observed for a limited period of time. The enantioselectivity factors (k^{4b}/k^{4a}) calculated from the rate constants summarized in Table 2 equal 1.69 and 1.68 for the k_0 and k_{cat} pathways, respectively. It should be noted that the rate constant k for the spontaneous hydrolysis of *N*-*t*-BOC-*S*-methionine *p*-nitrophenyl ester was extracted from k_0 and the enantioselectivity factor in this case equals $(k_0^{4b} - k)/(k_0^{4a} - k)$.

Table 1
Catalytic rate constants k_{cat} ($\text{dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$) and k_0 (s^{-1}) for the hydrolysis of *R*- and *S*-enantiomers of *N*-CBZ-leucine *p*-nitrophenyl ester in the presence of **3a** and **3b**, pH 6.23, 25°C

Complex	<i>S</i> -ester		<i>R</i> -ester	
	$10^3 \times k_0$	k_{cat}	$10^3 \times k_0$	k_{cat}
3a (<i>R</i>)	2.4 ± 0.1	25.8 ± 0.4	2.4 ± 0.1	7.6 ± 0.5
3b (<i>S</i>)	2.4 ± 0.1	5.7 ± 0.6	2.4 ± 0.1	26.7 ± 0.5

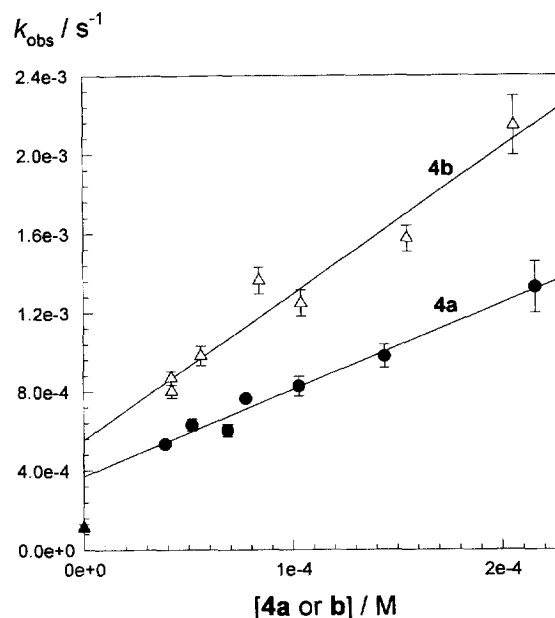


Fig. 2. Dependence of observed pseudo-first-order rate constants for hydrolysis of **4a** and **4b** on their total concentrations at pH 8.0 (0.002 M phosphate), 25°C. The closed triangle indicates the rate constant for spontaneous hydrolysis of free *N*-*t*-BOC-*S*-methionine *p*-nitrophenyl ester.

Table 2
Catalytic rate constants k_{cat} and k_0 for the hydrolysis of **4a** and **4b** at pH 8.0 (0.002 M phosphate), 25°C

Complex	<i>S</i> -ester	
	$10^4 \times k_0$ (s^{-1})	k_{cat} ($\text{dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$)
4a (<i>R</i>)	3.7 ± 0.3	4.4 ± 0.3
4b (<i>S</i>)	5.5 ± 0.8	7.4 ± 0.7

4. Discussion

4.1. Intermolecular catalysis

As mentioned in Section 1, the complexes **3** and **4** display the catalytic esterase type activity in aqueous media because of the fast and complete hydrolysis of the chloro ligand, which is strongly labilized by the *trans* phenyl carbon, to afford species of type **5** [7–9]. The existence of this hydrolytic process has much experimental evidence [7–9]. The $\text{p}K_{\text{a}}$ of the aqua ligand in the Pd(II) complexes derived from **3** or **4** is usually in the range 4–5 [7], implying that the catalytic species generated in water most likely contain the coordinated hydroxo ligand. Therefore, the molecular reason for the catalytic effect is, as before, the presence of the coordinated nucleophilic center.

The observed stereospecificity in intermolecular reaction (2) provides additional evidence that the palladacycles are the true catalysts. The significant enantioselectivity factors suggest that it is the *coordinated* hydroxo ligand that carries out the nucleophilic attack at the carbonyl carbon of the ester moiety. The observation that the highest catalytic activity is observed when the absolute configuration of complex **3** is *R*

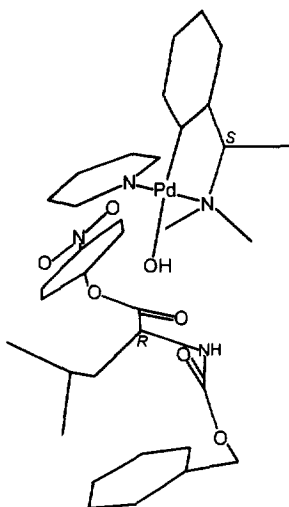


Fig. 3. Possible mode of interaction between complex **3b** and *N*-CBZ-*R*-leucine *p*-nitrophenyl ester accounting for the origin of the enantioselectivity in the ester hydrolysis. For details, see text.

and that of the ester is *S*, or vice versa, whereas the rate constants k_{cat} are much lower for the *R*-*R* or *S*-*S* pairs, allows us to suggest a possible transition state for the catalytic process. The modeling has been performed using the conventional molecular models and supported by calculations using the *Alchemy III* package. The results shown in Fig. 3 demonstrate a possible approach of the *S* isomer of **3** (**3b**) to the *R* isomer of the leucine ester. The conformation of the latter was optimized using an *Alchemy III* procedure; the dihedral angle between the palladium(II) and pyridine planes of 52° was taken from the relevant X-ray data [7]. The reason for the chiral recognition seems to be a mutual orientation of alkyl radicals at asymmetric carbons of the complex and the ester, i.e. of the methyl and isopropyl groups, respectively. If the approach of the catalyst to the carbonyl carbon of the ester is such as shown in Fig. 3, less steric repulsion is to be expected between the two above-mentioned alkyl groups in the case when the reagent and the catalyst have absolute configurations of either *S* and *R*, as in Fig. 3, or *R* and *S* respectively.

The transition state geometry suggested is also advantageous from the point of view of a possible hydrophobic or stacking interaction between the leaving 4-nitrophenolate ring and the coordinated pyridine ligand. This could favor the mutual orientation between the interacting species such as to minimize the repulsion between the alkyl groups. Thus, there are three key interactions responsible for the stereoselective catalysis, namely (i) between the coordinated hydroxide and the carbonyl carbon, (ii) between the nitro-substituted aromatic ring of the ester and coordinated pyridine, and (iii) between the alkyl groups at the ligand and catalyst stereogenic centers. The three bring about a significant kinetic enantioselectivity [10,11].

The disadvantage of the system reported is that the enantioselectivity is observed together with a pronounced spontaneous, catalyst-independent, hydrolysis of the activated

ester. Naturally, this minimizes the applicability of the system for kinetic resolution of racemic esters. Nevertheless, the fact of enantioselective hydrolysis gives an easy entry for construction of stereoselective catalysts.

4.2. 'Intramolecular' promotion coupled with intermolecular catalysis

The hydrolysis within complexes **4** revealed a curious combination of intra- and intermolecular pathways. The former is not a true catalytic process. Rather, it is a promotion of the 4-nitrophenolate dissociation by an extra pseudo-catalytic center present in the molecule. The promoted hydrolysis (Eq. (4)) driven by the rate constant k_o is faster by a factor of 3.4 and 5.0 than hydrolysis of the free ester in the case of **4a** and **4b**, respectively. Interestingly, the intra- (k_o) and intermolecular (k_{cat}) processes have almost the same enantioselectivity factors, namely 1.69 and 1.68, respectively, which are substantially lower than that in the case discussed in Section 4.1.

In general, the effect must be treated as a 'secondary' one. The manipulations with molecular models did not reveal any clear source for the kinetic discrimination. The stereogenic centers at the amino acid derivative and the palladium(II) fragment of **4** do not practically affect each other in the transition state in which the coordinated hydroxide is involved in the nucleophilic attack at the ester carbonyl carbon. As a result, the enantioselectivity factors did not exceed 1.7.

5. Conclusions

Chiral palladacycles have frequently been used for resolution of racemic phosphines and related ligands [5,12–14]. They have also been employed in synthetically relevant organic reactions [15]. To our knowledge, this report is the first example in which the compounds were shown to promote the enantioselective hydrolysis of activated esters. Taking in to account that other Pd(II) complexes display high reactivity toward nonactivated amide and ester bonds [16–20], there is a hope that artificial 'palladazymes' may gain an ability to carry out stereoselective hydrolysis.

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