ISSN 0027-1314, Moscow University Chemistry Bulletin, 2008, Vol. 63, No. 5, pp. 255–259. © Allerton Press, Inc., 2008.
Original Russian Text © A.V. Medved'ko, S.A. Kurzeev, S.Z. Vatsadze, G.M. Kazankov, 2008, published in Vestnik Moskovskogo Universiteta. Khimiya, 2008, No. 5, pp. 306–312.

Biomimetical Catalysis of α-Amino Acid Hydrolysis over Chiral Palladacycles

A. V. Medved'ko, S. A. Kurzeev, S. Z. Vatsadze, and G. M. Kazankov

Organic Chemistry Department and Chemical Enzymology Department

e-mail: gkazankov@hotmail.com

Received January 24, 2008

Abstract—A 4.5-fold difference in catalytic hydrolysis rate constants between stereomer pairs was achieved as a result of the incorporation of bulky substituents into chiral cyclopalladated arylamines used as catalysts for hydrolysis of esters of optically active amino acids. An unexpected inversion of catalyst stereoselectivity depending on the bulkiness of substituents at the palladacycle a-carbon atom was discovered.

DOI: 10.3103/S0027131408050040

The design of simple hydrolytic systems capable of separating racemates into optical isomers via kinetic optical induction is promising for separating enantiomers of optically active carboxylic acids and amino acids [1–4]. This strategy is efficient in fine organic synthesis, including large-scale production of drugs.

One possible strategy to solve this problem is to use cyclopalladated arylamines with one or several chiral centers as hydrolysis catalysts. It is well known that such complexes can enhance hydrolysis of ester bonds [5–7]; in some cases [8, 9], there is a considerable difference between the rate constants of the reaction depending on the optical configuration of the reagents.

The chemistry of catalytic hydrolysis in the presence of palladacycles is as follows [10–12]: in aqueous solutions, a strong nucleophilic center is generated in such complexes with the hydroxo ligand coordinated in the *trans*-position to the aromatic carbon atom, which performs the nucleophilic attack at the carbonyl atom of the ester. The mechanism of this reaction resembles the hydrolysis of peptide bonds catalyzed by carboxypeptidase A [13] or hydrolysis of ester bonds catalyzed by carboanhydrase [14]. Therefore, a situation appears in palladacycles where biomimetics is targeted not only at modeling active sites of enzymes but also at imitating the main features of enzymes, namely, high activity and stereoselectivity.

Ortho-palladated arylamines are convenient substrates for accommodating optically active centers; there are two sites for their accommodation: (a) in the side chain and (b) at the chiral nitrogen atom (Fig. 1).

Hydrolysis rates for esters of optically active α-amino acids catalyzed by chiral cyclopalladated arylamines are affected by the configurations of the chiral centers of the substrate and catalyst [8, 9]. Complexes of phenylethylamine (I), *N*,*N*-dimethylphenylethylamine (II), and *N*-methylphenylethylamine (III) were used as catalysts (Fig. 2).

In catalytic hydrolysis of sulfur-containing amino acid derivatives, which occurs by an intramolecular mechanism, the difference between the reaction rates of stereomers increases from *ortho*-palladated primary arylamines (k_S/k_R = 1.1) to tertiary ones (k_S/k_R = 1.5); the catalytic effect is highest when the reacting ester and complex have the same absolute configurations of their chiral centers. The efficiency of intramolecular catalysis is higher when the reacting complex and ester have opposite absolute configurations of their chiral centers; catalytic hydrolysis rate constants for two stereomer pairs coincide within the error. The maximal difference between the rates is observed in the catalysis by cyclopalladated secondary arylamines, being 2.3 times for the phenylalanine derivative [8, 9]. In view of the aforesaid, we can infer that the hydrolysis selectivity for chiral substrates is affected by both chiral centers, the chiral nitrogen atom having a stronger effect than the chiral center at the benzyl carbon atom.

To improve the hydrolysis selectivity, we decided to design catalysts with bulkier substituents at both the nitrogen and carbon atoms (Fig. 3).

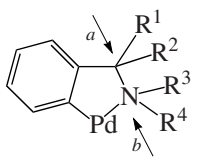
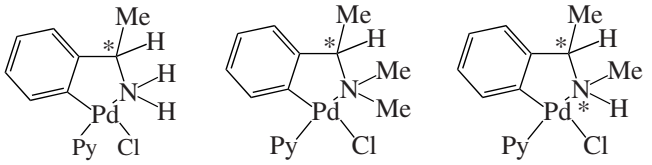
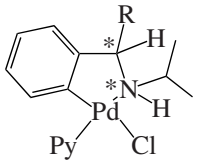


Fig. 1. Chiral centers in palladated benzylamine.



I **II** **III**

Fig. 2. Cyclopalladated amines used as catalysts for hydrolysis of α-amino acid esters.



IVa: R = (*S*)–Me **IVc**: R = (*S*)–Et
IVb: R = (*R*)–Me **IVd**: R = (*R*)–Et

Fig. 3. *Ortho*-palladated *N*-isopropylalkylbenzylamines with the absolute configuration of the benzyl carbon atom indicated. The configuration of the chiral center associated with the nitrogen atom is opposite to the configuration of the chiral center associated with the carbon atom.

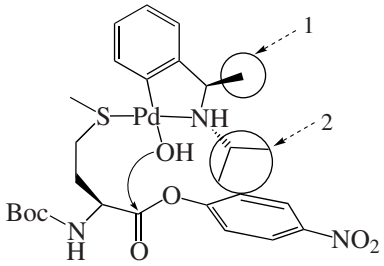


Fig. 4. Groups potentially affecting the nucleophilic substitution selectivity in amino acid esters.

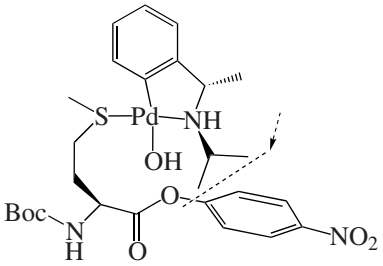


Fig. 5. Spatial hindrance to the attack of a palladacycle of identical configuration on *L*-methionine.

RESULTS

Hydrolysis of 4-Nitrophenyl Ester of N-BOC-L-Methionine Catalyzed by Chiral Palladacycles

Figure 4 schematizes the interaction of a palladium-coordinated hydroxide ion with a carboxy carbon atom.

For the attack of a hydroxy group to occur at the carbonyl carbon atom, they must closely approach each other; group **1** and group **2** can both affect this approach, but the effect of group **1** on the spatial arrangement of parts of the transition state is weak. Bulky group **2** can decrease the absolute value of the hydrolysis constant in view of strong steric hindrances to the approach of the carbonyl carbon atom and hydroxy group. At the same time, the hydrolysis selectivity should increase: for the palladacycle with the chiral center of the opposite configuration, the approach of the hydroxy group will be hindered by the interaction between isopropyl group **2** and the phenyl ring (Fig. 5).

The catalytic hydrolysis rate constants (Table 1) in part support the above-assumed effect of substituents in the catalyst molecule on the reaction rate. Compounds **IVc** and **IVd** obey the above model. For compounds **IVa** and **IVb**, however, the diametrically opposite effect is observed, possibly because of the different conformations of the transition state for ethyl and methyl substituents.

Hydrolysis of 4-Nitrophenyl Esters of N-BOC-L-Isoleucine and N-CBZ-L-Phenylalanine Catalyzed by Chiral Palladacycles

Esters of amino acids lacking donor atoms in the side chain (these atoms are capable of binding to palladium) are hydrolyzed by an intermolecular mechanism [8]. In this work, we studied the hydrolysis of *N*-BOC-

Table 1. Catalytic hydrolysis rate constants for *N*-BOC-*L*-methionine 4-nitrophenyl ester catalyzed by various substituted chiral palladacycles

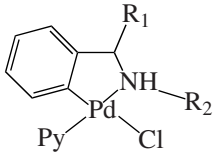
Compound	Compound no.	R_1	R_2	k_{cat}, L/(mol s)	$k_{cat}(R)/k_{cat}(S)$	*T*, °C
	**IVa**	(*S*)-Me	(*R*)-i-Pr	3.72	1.8	25
	IVb	(*R*)-Me	(*S*)-i-Pr	6.71		25
	IVc	(*S*)-Et	(*R*)-i-Pr	8.28	0.6	25
	IVd	(*R*)-Et	(*S*)-i-Pr	5.20		25

Table 2. Catalytic hydrolysis rate constants for *N*-carbobenzoxy-*L*-phenylalanine 4-nitrophenyl ester and *N*-*tert*-butoxycarbonyl-*L*-isoleucine 4-nitrophenyl ester catalyzed by various substituted chiral palladacycles

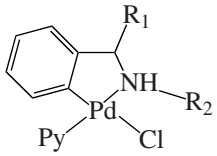
Compound	Amino acid	Compound no.	R_1	R_2	$k_{cat} \times 10^2$, L/(mol s)	$k_{cat}(R)/k_{cat}(S)$	*T*, °C
	*N*-CBZ-*L*-Phe	**IVa**	(*S*)-Me	(*R*)-i-Pr	1.06	4.5	30
		IVb	(*R*)-Me	(*S*)-i-Pr	5.06		30
		IVc	(*S*)-Et	(*R*)-i-Pr	0.56	2.7	30
		IVd	(*R*)-Et	(*S*)-i-Pr	1.51		30
	N-BOC-*L*-Ile	**IVa**	(*S*)-Me	(*R*)-i-Pr	3.14	0.5	45
		IVb	(*R*)-Me	(*S*)-i-Pr	1.48		45
		IVc	(*S*)-Et	(*R*)-i-Pr	0.88	2.2	45
		IVd	(*R*)-Et	(*S*)-i-Pr	1.95		45

Table 3. Chiral secondary α-alkylbenzylamines

Compound	Compound no.	Boiling temperature, °C	$[\alpha]_D^{20}$	Yield, %
(–)-*N*-isopropyl-(1*S*)-1-phenylethylamine	**Va**	53–55 (3 mmHg)	–59.9°	76
(+)-*N*-isopropyl-(1*R*)-1-phenylethylamine	**Vb**	67–69 (6 mmHg)	+59.7°	76
(–)-*N*-isopropyl-(1*S*)-1-phenylpropylamine	**Vc**	73–74 (3 mmHg)	–45.3°	86
(+)-*N*-isopropyl-(1*R*)-1-phenylpropylamine	**Vd**	72–73 (3 mmHg)	+47.6°	83

L-isoleucine and *N*-CBZ-*L*-phenylalanine 4-nitrophenyl esters catalyzed by chiral cyclopalladated complexes (Fig. 4); the rate constants of the relevant reactions are listed in Table 2.

Comparing the ratio of the rate constants obtained for *N*-CBZ-*L*-phenylalanine hydrolysis in the presence of compounds **IVa** and **IVb** with the ratio of the hydrolysis constants for the same substrate but in the presence of cyclopalladated secondary benzylamines having a methyl substituent at the nitrogen atom [9], we see that the bulkier isopropyl radical enhances the kinetic optical induction effect considerably, from 2.3 [9] to 4.5 times. The hydrolysis rate constant is greater when the ester and palladacycles have different absolute configurations, in agreement with our suggested kinetic optical induction mechanism [9].

For isoleucine ester with the use of compounds **IVa** and **IVb**, we observe the same phenomenon as for methionine ester (Table 1), namely, the inversion of catalyst selectivity. Methionine and isoleucine esters are similar in that the transition state in their reaction with the palladacycle will have one more chiral center than for phenylalanine. For example, isoleucine itself has an extra chiral center in the side chain; in methionine, a chiral center is associated with the sulfur atom that bears four different substituents (assuming that inversion at the sulfur atom is sterically hindered). Therefore, the effect observed for methionine and isoleucine esters, presumably, arises from the existence of an extra (third) chiral center in the transition state, this extra chiral center affecting the difference between the catalytic activities of palladacycles with different optical configurations.

Thus, this work demonstrates the possibility of increasing the selectivity of α-amino acid ester hydrolysis via increasing the bulkiness of the substituent at the nitrogen atom. An unexpected effect was discovered: inversion of the catalyst activity occurred in response to variations in radical length in the side chain of cyclopalladated arylamine.

EXPERIMENTAL

NMR spectra were recorded on a Bruker Avance 400 instrument. Spectrophotometric experiments were carried out on Hitachi 150-20 and Shimadzu UV-160A spectrophotometers equipped with thermostated cells. Specific rotation at the sodium *D*-line frequency was measured on a VNIIEKIprodmash A1-EPO automated polarimeter.

Synthesis of Cyclopalladated Complexes

Chiral secondary α-alkylbenzylamines were synthesized as described in [15] (Table 3); dimeric palladacycles were synthesized as described in [15] (Table 4), and monomeric palladacycles were also synthesized as described in [15] (Table 5). All compounds were char-

Table 4. Dimeric palladacycles

Compound	Compound no.	Boiling temperature, °C	$[\alpha]_D^{20}$	Yield, %
Di-μ-chlorobis(*N*-isopropyl)-(1*S*)-1-phenylethylamine-2*C*,*N*)dipalladium(II)	**IVa**	200–203 (dec.)	+127.7°	76
Di-μ-chlorobis(*N*-isopropyl)-(1*R*)-1-phenylethylamine-2*C*,*N*)dipalladium(II)	**IVb**	203–205 (dec.)	–130.6°	72
Di-μ-chlorobis(*N*-isopropyl)-(1*S*)-1-phenylpropylamine-2*C*,*N*)dipalladium(II)	**IVc**	170–173 (dec.)	+126.8°	82
Di-μ-chlorobis(*N*-isopropyl)-(1*R*)-1-phenylpropylamine-2*C*,*N*)dipalladium(II)	**IVd**	175–178 (dec.)	–118.0°	85

Table 5. Monomeric palladacycles

Compound	Compound no.	Boiling temperature, °C	$[\alpha]_D^{20}$	Yield, %
Chloro-(*N*-isopropyl)-(1*S*)-1-phenylethylamine-2*C*,*N*)(pyridine)palladium(II)	**IVa**	117–122 (dec.)	+230.2°	76
Chloro-(*N*-isopropyl)-(1*R*)-1-phenylethylamine-2*C*,*N*)(pyridine)palladium(II)	**IVb**	117–120 (dec.)	–231.0°	78
Chloro-(*N*-isopropyl)-(1*S*)-1-phenylpropylamine-2*C*,*N*)(pyridine)palladium(II)	**IVc**	123–128 (dec.)	+212.5°	83
Chloro-(*N*-isopropyl)-(1*R*)-1-phenylpropylamine-2*C*,*N*)(pyridine)palladium(II)	**IVd**	125–129 (dec.)	–213.3°	90

Table 6. Elemental analysis data for monomeric palladacycles

Compound	C, %		H, %		N, %	
	found	calcd	found	calcd	found	calcd
IVa	50.06	50.20	5.58	5.49	7.18	7.32
IVb	50.24		5.46		7.23	
IVc	51.29	51.45	5.70	5.80	7.05	7.06
IVd	51.27		5.90		7.03	

acterized by ^{1}H NMR spectra; for monomeric palladacycles, elemental analysis was done (Table 6).

Kinetic Experiments

Hydrolysis of 4-nitrophenyl amino acid esters catalyzed by *ortho*-palladated complexes was studied in 0.01 M phosphate buffered solution (pH 8). The hydrolysis kinetics was monitored spectrophotometrically by accumulation of 4-nitrophenolate ion at 395 nm. Hydrolysis was initiated by consecutive addition of stock solutions of the palladium complex and ester in acetonitrile to the spectrophotometer cell. The final reagent concentration in the cell was 1×10^{-5} to 9×10^{-5} mol/L for ester and 2×10^{-5} to 6×10^{-4} mol/L for the metal complex. The acetonitrile concentration in the reaction mixture was 10%.

Kinetic parameters were found by nonlinear regression analysis using the SigmaPlot software. Observed pseudo-first-order rate constants k_{obs} were derived from the rate curve using

$$D(t) = D_{in} + (D_{in} - D_{fin})\exp(-k_{obs}t),$$

where $D(t)$, D_{fin}, and D_{in} are, respectively, optical densities at moment t, at the finish of the reaction, and in the initial moment. The rate curves were described by a first-order equation over at least five half-reaction times. From the relationship between the pseudo-first-order observed rate constants and palladium complex concentration, catalytic hydrolysis constants k_{cat} were found from $k_{obs} = k_0 + k_{cat}[Pd(II)]$, where k_0 is the rate constant of background hydrolysis of the ester and [Pd(II)] is initial palladium complex concentration based on monomer.

REFERENCES

1. Calmes, M., Glot, C., Michel, T., Rolland, M., and Martinez, J., *Tetrahedron: Asymmetry*, 2000, vol. 11, p. 737.
2. Scrimin, P., Tecilla, P., and Tonellato, U., *J. Org. Chem.*, 1994, vol. 59, p. 4194.
3. Cleija, M.C., Mancina, F., Sriminb, P., Tecillaa, P., and Tonelato, U., *Tetrahedron*, 1997, vol. 53, no. 1, p. 357.
4. Pellissier, H., *Tetrahedron*, 2003, vol. 59, p. 8291.
5. Kazankov, G.M., Poselenov, P.V., Ryabov, A.D., and Yatsimirskii, A.K., *Metalloorg. Khim.*, 1991, vol. 4, p. 45.
6. Kurzeev, S.A., Kazankov, G.M., and Ryabov, A.D., *Inorg. Chim. Acta*, 2000, vol. 305, p. 304.
7. Kurzeev, S.A., Kazankov, G.M., and Ryabov, A.D., *J. Inorg. Biochem.*, 2001, vol. 86, p. 304.
8. Ryabov, A.D., Kazankov, G.M., Kurzeev, S.A., Samuleev, P.V., and Polyakov, V.A., *Inorg. Chim. Acta*, 1998, vol. 280, p. 57.
9. Ageeva, Yu.V., Kurzeev, S.A., and Kazankov, G.M., *Zh. Org. Khim.*, 2007, vol. 43, p. 49.
10. Dehand, J., Pfeffer, M., and Zinsius, M., *Inorg. Chim. Acta*, 1975, vol. 13, p. 229.
11. Girling, I.R. and Widdowson, D.A., *Tetrahedron Lett.*, 1982, vol. 23, p. 1957.
12. Constable, E.C., Thompson, A.M., Leese, T.A., Reese, G.F., and Tocher, D.A., *Inorg. Chim. Acta*, 1991, vol. 182, p. 93.
13. *Inorganic Biochemistry*, Eichhorn, G., Ed., Amsterdam: Elsevier, 1975.
14. *Inorganic Biochemistry*, Eichhorn, G., Ed., Amsterdam: Elsevier, 1975.
15. Dunina, V.V., Zalevskaya, O.A., and Potapov, V.M., *Zh. Org. Khim.*, 1984, vol. 54, p. 389.