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Stereoselective Properties of Nickel(II) Complexes of Optically Active Tetraamines Including Pyrrolidinyl Groups toward α-Amino Acids and Their Esters

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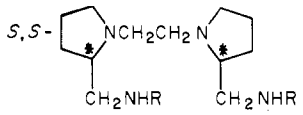
The equilibrium for the coordination of optically active amino acids to nickel(II) complexes of 1,2-bis[2(*S*)-aminomethyl-1-pyrrolidinyl]ethane (AMPE) and 1,2-bis[2(*S*)-*N*-methylaminomethyl-1-pyrrolidinyl]ethane (MMPE) has been investigated together with the hydrolysis of amino acid esters. Some α-amino acidate ions coordinate stereoselectively; to the AMPE complex D enantiomers of amino acidate ions coordinate in preference to their L enantiomers, while the reverse selective tendency is observed for the MMPE complex. These tetraamine complexes promote the hydrolysis of amino acid methyl esters, and moreover the hydrolysis proceeds stereoselectively. The selectivity agrees fairly with that in the coordination of amino acidate ions.

In general, nickel(II) complexes have labile character for ligand-exchange reactions, and therefore it is difficult to isolate each of their optical and/or geometrical isomers. However, the ligand having a type of steric restriction within itself may coordinate stereospecifically to the labile nickel(II) ion. In previous papers,[2,3] we reported that the optically active tetraamines containing pyrrolidinyl groups formed stereospecific nickel(II) complexes. To the two remaining coordination sites in the tetraamine complexes, if it is the case, other ligands such as amino acids are expected to coordinate stereoselectively.

On the stereoselectivity of metal complexes toward the two optical isomers of α-amino acids or hydroxy acids and their esters, some investigations have been reported.[4-9] This type of study could be thought as a significant approach to the enzymic specific reaction,[10,11] and the selectivity is applicable to the resolution of racemic substrates.[12-14]

In this paper, we wish to report on the stereoselectivity of nickel(II) complexes with 1,2-bis[2(*S*)-aminomethyl-1-pyrrolidinyl]ethane (AMPE) and 1,2-bis[2(*S*)-*N*-methylaminomethyl-1-pyrrolidinyl]ethane (MMPE) both in the formation of the mixed complexes with α-amino acidate ions and in the hydrolysis of α-amino acid esters promoted by these tetraamine complexes.



AMPE: R = H
MMPE: R = CH_3

Experimental Section

Materials. AMPE and MMPE and their nickel(II) complexes were prepared according to the procedure reported previously.[3] D-, L-, and DL-amino acids were all of commercial grade and used without further purification. The hydrochlorides of D- and L-amino acid methyl esters were prepared according to the literature[15] and identified by their elementary analyses.

Spectral Measurements. Samples for the spectral measurements were prepared as follows. To an aliquot of aqueous solutions of the AMPE and MMPE complexes was added a definite amount of an amino acid, and the mixture was diluted to a desired concentration (about 0.05 M) and then adjusted to pH 8–10 with 10 N sodium hydroxide. The amount of the sodium hydroxide solution added was very small, so that the concentration of the solution is little affected. Visible and ultraviolet absorption spectra were recorded on a Hitachi EPS-3T spectrophotometer. Circular dichroism (CD) spectra were measured with a Jasco J-20A automatic spectropolarimeter at 25.0 °C.

Kinetic Measurements. Rates of ester hydrolysis were measured with a Hiranuma RAT-101S recording titrator by using a pH stat technique.[11] The reaction vessel used was a jacketed beaker of about 20-ml capacity which was held at a desired temperature by means of water from a constant-temperature bath. The mixed solution (10 ml) containing equimolar amounts (0.01 M) of the ester hydrochloride and the tetraamine complex was stirred with a magnetic stirrer at 35.0 °C under a nitrogen atmosphere. Standard sodium hydroxide of 0.1 N concentration was added to maintain constant pH (9.0) and also to provide a means of following the rate of hydrolysis. The ionic strength of the reaction mixture was previously adjusted to 0.1 M with potassium nitrate.

Results and Discussion

Stereoselective Coordination of α-Amino Acidate Ions to the Nickel(II) Complexes of AMPE and MMPE.[16] When racemic amino acid is mixed with the tetraamine complexes in aqueous solutions, equilibria 1 and 2 may coexist, where Tet is the

$$Ni(Tet)^{2+} + L\text{-}am^- \overset{K_L}{\rightleftharpoons} Ni(Tet)(L\text{-}am)^+ \quad (1)$$

$$Ni(Tet)^{2+} + D\text{-}am^- \overset{K_D}{\rightleftharpoons} Ni(Tet)(D\text{-}am)^+ \quad (2)$$

tetraamine (AMPE and MMPE) and am^- is an amino acidate ion. On the basis of the CD spectra, the molar ratio (α_L) of the coordinated L isomer is given by

$$\alpha_L = (\Delta\epsilon_D - \Delta\epsilon_{DL})/(\Delta\epsilon_D - \Delta\epsilon_L) \quad (3)$$

where $\Delta\epsilon_D$, $\Delta\epsilon_L$, and $\Delta\epsilon_{DL}$ are molar circular dichroism values at the same wavenumber of the mixture of the tetraamine complex with D-, L-, and DL-amino acids, respectively.

Figure 1 shows the CD spectra (800–1000 nm) of the mixtures of L-, D-, and DL-alanine with the AMPE complex in aqueous solutions at pH 8.09. The CD curve of the DL-alanine system does not lie on the midline between the two curves given by the L- and D-alanine systems but, to some extent, lies closer to the curve for the D-alanine system. At 880 nm, for example, the values of $\Delta\epsilon_D$, $\Delta\epsilon_L$, and $\Delta\epsilon_{DL}$ are 0.39, 0.52, and 0.44, respectively. This shows that a stereoselective coordination of D-alanine does occur, because, if the selective coordination did not occur, the value of $\Delta\epsilon_{DL}$ should be the average value of $\Delta\epsilon_D$ and $\Delta\epsilon_L$, i.e., 0.46. Thus, the molar ratio, α_L, in the DL-alanine system is evaluated from these CD curves by using eq 3. From the value of α_L, the ratio of the two stability constants of equilibria 1 and 2 can be determined according to

$$\frac{K_L}{K_D} = \frac{\alpha_L}{1-\alpha_L}\,\frac{(n/2-1)+\alpha_L}{n/2-\alpha_L} \quad (4)$$

where n is the value of the molar ratio of racemic amino acid to the tetraamine complex.[17,18] Equation 4 is derived under the assumption that the tetraamine complex completely forms the mixed complex with the added amino acid.[17]

In Table I are summarized the values of α_L and K_L/K_D. From the wavelengths of the absorption maxima in the three spin-allowed d–d bands, it was found that almost all of the

Table I. Values of α_L and K_L/K_D[a]

Tetraamine	Amino acid		Wavelength, nm 840	860	880	900	920	940	$\bar{\alpha}_L$	K_L/K_D
AMPE	Alanine	$\Delta\epsilon_D - \Delta\epsilon_{DL}$	0.049	0.052	0.050	0.044	0.037			
		$\Delta\epsilon_D - \Delta\epsilon_L$	0.123	0.122	0.129	0.123	0.111		0.38	0.59
		α_L	0.40	0.43	0.39	0.36	0.33			
	Valine	$\Delta\epsilon_D - \Delta\epsilon_{DL}$		0.072	0.076	0.082	0.091	0.085		
		$\Delta\epsilon_D - \Delta\epsilon_L$		0.163	0.182	0.197	0.205	0.206	0.43	0.73
		α_L		0.44	0.42	0.42	0.44	0.41		
MMPE	Alanine	$\Delta\epsilon_D - \Delta\epsilon_{DL}$		0.059	0.063	0.063	0.057	0.049		
		$\Delta\epsilon_D - \Delta\epsilon_L$		0.117	0.128	0.127	0.114	0.096	0.50	1.0
		α_L		0.50	0.49	0.50	0.50	0.51		
	Valine	$\Delta\epsilon_D - \Delta\epsilon_{DL}$			0.059	0.064	0.065	0.065		
		$\Delta\epsilon_D - \Delta\epsilon_L$			0.114	0.122	0.124	0.124	0.52	1.1
		α_L			0.52	0.52	0.52	0.52		
	Proline	$\Delta\epsilon_D - \Delta\epsilon_{DL}$		0.022	0.030	0.035	0.032	0.030		
		$\Delta\epsilon_D - \Delta\epsilon_L$		0.047	0.057	0.064	0.059	0.052	0.54	1.3
		α_L		0.47	0.53	0.55	0.54	0.58		

[a] Conditions: [alanine or valine]/[Ni] = 25, [Ni] = 2.5×10^{-3} M; [proline]/[Ni] = 2.5, [Ni] = 2.5×10^{-2} M; temperature 25 °C. Errors for $\Delta\epsilon$ values are within 2%.

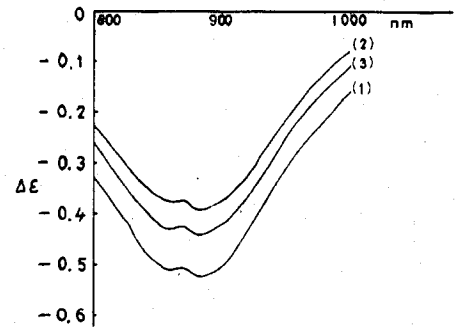


Figure 1. CD spectra (800–1000 nm) of the mixtures of (1) L-, (2) D-, and (3) DL-alanine with the AMPE complex in aqueous solutions. The ratio of the added alanine to $Ni(AMPE)^{2+}$ is 25 (pH 8.09, 25 °C).

AMPE complex formed the mixed complexes of the type $[Ni(N_5O)]$ with α-amino acids.[3,17] Therefore, the assumption above is satisfied. From Table I, it can be said that D enantiomers of alanine and valine are more favorable to coordinate to the AMPE complex 1.7 and 1.4 times as strongly as L enantiomers, respectively.

In the case of the MMPE complex, the formation of the mixed complexes was incomplete in valine and proline systems.[3,17] Nevertheless, attempts to evaluate the selectivity were made according to the procedure mentioned above. The values of α_L and K_L/K_D obtained indicate that the selectivity is very low for alanine and valine, while L-proline is more favorable to coordinate than D-proline.

Thus, the AMPE and MMPE complexes exhibit the reverse tendency in the stereoselective coordination of α-amino acidate ions. This reverse selectivity may be attributed not to the different chiralities of the two tetraamine complexes but to the steric effect of the terminal *N*-methyl groups in the MMPE complex, since the CD spectra of the two tetraamine complexes and their mixed complexes with α-amino acidate ions were similar.[17]

Stereoselective Hydrolysis of α-Amino Acid Esters by the AMPE and MMPE Complexes. When an α-amino acid ester is mixed with a metal complex in an aqueous solution, hydrolysis of the ester depends upon the coordination of the ester to the metal ion; this is followed by hydrolysis of the coordinated ester. And when the reaction mixture is kept alkaline (in the present study, pH 9.0), hydroxide ion should attack the coordinated ester. Therefore, it can be assumed that the mechanism in the present systems is represented by eq 5–7,[5] where E is the methyl ester of the amino acid. Equation 5 is the path independent of the nickel(II) complex.

Table II. Rate Constants for Hydrolysis of Optically Active Amino Acid Esters (pH 9.0, 35 °C, μ = 0.1)

Ester	Without promotor[a]	With promotor[b] $Ni(AMPE)^{2+}$	$Ni(MMPE)^{2+}$
$(ala)OCH_3$ L	7.4×10^{-4}	2.0	2.9
$(ala)OCH_3$ D		2.8	2.4
$Ph(ala)OCH_3$ L	7.4×10^{-4}	1.7	2.6
$Ph(ala)OCH_3$ D		2.8	2.5

[a] In min^{-1}. [b] In M^{-1} min^{-1}.

$$E + OH^- \xrightarrow{k_f} am^- + CH_3OH \quad (5)$$

$$Ni(Tet)^{2+} + E \overset{K}{\rightleftharpoons} Ni(Tet)(E)^{2+} \quad (6)$$

$$Ni(Tet)(E)^{2+} + OH^- \xrightarrow{k_c} Ni(Tet)(am)^+ + CH_3OH \quad (7)$$

The rate law for the overall rate of the ester hydrolysis is written as

$$\text{rate} = k_f[E][OH^-] + k_c[Ni(Tet)(E)^{2+}][OH^-]$$
$$= k_f[E][OH^-] + k_cK[Ni(Tet)^{2+}][E][OH^-] \quad (8)$$

Since the metal-free path was very slow compared with the path involving the tetraamine complex (see Table II), eq 8 becomes

$$\text{rate} = k_cK[Ni(Tet)^{2+}][E][OH^-]$$
$$= k_{obsd}[Ni(Tet)^{2+}][E] \quad (9)$$

where $k_{obsd} = k_CK[OH^-]$. When equimolar amounts of the ester and the tetraamine complex are used, the rate is given by

$$\text{rate} = k_{obsd}[E]^2 \quad (10)$$

Thus, on integrating eq 10, eq 11 is obtained, where $[E]_0$ is

$$1/[E] - 1/[E]_0 = k_{obsd}t \quad (11)$$

an initial concentration of the ester and the tetraamine complex.

Figure 2 shows plots of $1/[E]$ vs. t, which can be regarded as linear in the initial stage of the hydrolysis. Therefore, the assumption used in order to introduce the above rate law may be pertinent in the initial stage at least.

In Table II are summarized the values of k_{obsd} ($=k_CK\cdot[OH^-]$) for methyl esters of D- and L-alanine and phenylalanine, together with the values of k_{OH^-} ($=k_f[OH^-]$) in the metal-free path. The path involving the nickel(II) complexes is much faster than the metal-free path. This is apparent from

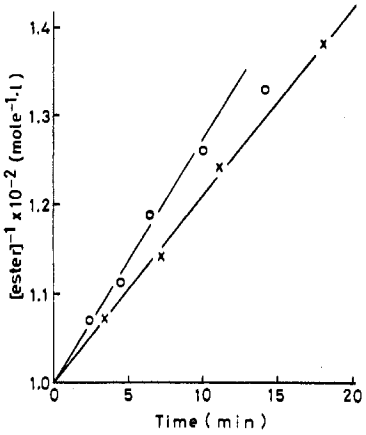


Figure 2. Rates of hydrolysis of the L (−×−) and D (−○−) isomers of methyl alaninate in the presence of Ni(AMPE)$^{2+}$.

the comparison of the half-life periods for the two paths. This remarkable acceleration suggests the coordination of the ester group to the tetraamine complex.[19,20] Whether the ester group coordinates through the carbonyl or the ether oxygen is not known,[21] but the first step in the hydrolysis is probably chelation through the ester and amino groups to the tetraamine complex.

From the values of k_{obsd} in Table II, it can be said that the hydrolysis promoted by the tetraamine complexes is stereoselective; in the AMPE complex system D esters of alanine and phenylalanine are hydrolyzed 1.4 and 1.7 times as fast as their L isomers, respectively, while the selectivity in the MMPE complex system is opposite to that in the AMPE complex system. These selectivities in the ester hydrolysis are in fair agreement with those in the coordination of α-amino acidate ions. This will be significant when discussing the selectivity-determining step of the hydrolysis. The agreement in the selective tendency suggests that the ester is sterically selected at the time of the coordination to the tetraamine complex, as well as the coordination of α-amino acidate ions. Leach and Angelici have obtained the opposite results: L enantiomers of α-amino acids and esters coordinate to (L-valine-*N*-monoacetato)copper(II) several times as strongly as their D enantiomers, while the rate of hydrolysis of the esters in the presence of the copper(II) complex is higher for the D esters than for the L esters.[5] This suggests that the stereoselectivity at the hydroxide attack on the coordinated ester is opposite to that at the coordination step and that the former is larger than the latter. This difference between the selectivities of the nickel(II) and copper(II) complexes may result from the nature of the two metal ions; the ligand-substitution reaction of nickel(II) complexes is much slower than that of copper(II) complexes.[22]

Registry No. Ni(AMPE)$^{2+}$, 58801-77-7; Ni(MMPE)$^{2+}$, 58801-78-8; Ni(AMPE)(D-alanine)$^{+}$, 55219-73-3; Ni(AMPE)(L-alanine)$^{+}$, 55331-58-3; Ni(AMPE)(D-valine)$^{+}$, 58846-33-6; Ni(AMPE)(L-valine)$^{+}$, 55186-39-5; Ni(MMPE)(D-alanine)$^{+}$, 55272-41-8; Ni(MMPE)(L-alanine)$^{+}$, 55331-59-4; Ni(MMPE)(D-valine)$^{+}$, 58846-34-7; Ni(MMPE)(L-valine)$^{+}$, 55272-40-7; Ni(MMPE)(D-proline)$^{+}$, 58846-35-8; Ni(MMPE)(L-proline)$^{+}$, 55290-20-5; Ni(AMPE)(L-(ala)OCH_3)$^{2+}$, 58801-79-9; Ni(AMPE)(D-(ala)OCH_3)$^{2+}$, 58846-36-9; Ni(AMPE)(L-Ph(ala)-OCH_3)$^{2+}$, 58801-80-2; Ni(AMPE)(D-Ph(ala)OCH_3)$^{2+}$, 58846-37-0; Ni(MMPE)(L-(ala)OCH_3)$^{2+}$, 58801-81-3; Ni(MMPE)(D-(ala)-OCH_3)$^{2+}$, 58846-38-1; Ni(MMPE)(L-Ph(ala)OCH_3)$^{2+}$, 58801-82-4; Ni(MMPE)(D-Ph(ala)OCH_3)$^{2+}$, 58846-39-2.

References and Notes

(1) To whom correspondence should be addressed.
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