Table VI. Intramolecular Angles and Distances for $(C_6H_5)_3Sb(OCH_3)_2$

Intramolecular angle, deg						Intramolecular distance, A			
O1-Sb-O2	175.3 (3)	Sb-C3-C4	121.5 (1.1)	C10-C11-C12	120.9 (8)	Sb-O1	2.039 (8)	C9-C10	1.388 (14)
C3-Sb-C9	124.0 (5)	Sb-C3-C8	119.7 (9)	C11-C12-C13	120.1 (1.3)	Sb-O2	2.027 (8)	C10-C11	1.390 (18)
C3-Sb-C15	121.4 (5)	C4-C3-C8	118.8 (1.0)	C12-C13-C14	121.8 (1.2)	O1-O1	1.429 (12)	C11-C12	1.344 (16)
C9-Sb-C15	114.6 (4)	C3-C4-C5	118.9 (1.2)	C13-C14-C9	120.1 (1.1)	O2-C2	1.411 (13)	C12-C13	1.327 (16)
O1-Sb-C3	85.5 (4)	C4-C5-C6	122.0 (1.1)	Sb-C15-C16	119.4 (9)	Sb-C3	2.119 (10)	C13-C14	1.355 (16)
O1-Sb-C9	93.4 (4)	C5-C6-C7	119.4 (1.2)	Sb-C15-C20	121.4 (9)	Sb-C9	2.121 (11)	C14-C9	1.380 (14)
O1-Sb-C15	92.2 (4)	C6-C7-C8	119.1 (1.1)	C16-C15-C20	119.2 (1.0)	Sb-C15	2.119 (12)	C15-C16	1.395 (14)
O2-Sb-C3	91.5 (4)	C7-C8-C3	121.7 (1.0)	C15-C16-C17	120.6 (1.0)	C3-C4	1.366 (14)	C16-C17	1.376 (15)
O2-Sb-C9	85.6 (4)	Sb-C9-C10	119.8 (1.0)	C16-C17-C18	121.8 (1.1)	C4-C5	1.371 (16)	C17-C18	1.356 (16)
O2-Sb-C15	92.1 (4)	Sb-C9-C14	121.6 (1.0)	C17-C18-C19	117.3 (1.2)	C5-C6	1.363 (17)	C18-C19	1.399 (17)
Sb-O1-C1	122.5 (6)	C10-C9-C14	118.5 (1.0)	C18-C19-C20	122.1 (1.1)	C6-C7	1.335 (16)	C19-C20	1.394 (17)
Sb-O2-C2	120.7 (6)	C9-C10-C11	118.7 (1.1)	C19-C20-C15	119.1 (1.1)	C7-C8	1.395 (15)	C20-C15	1.366 (14)
						C8-C3	1.353 (14)		

Table VII. Phenyl Group Least-Squares Planes[a]

Carbon atom nos. in plane	A	B	C	D
		Compound I		
2-7	7.514	14.437	1.527	3.873
8-13	2.837	3.158	16.132	1.750
14-19	10.760	−4.643	−10.538	−0.250
20-25	6.256	−6.683	13.647	0.250
		Compound II		
3-8	8.408	−6.145	−5.919	−4.382
9-14	5.448	7.478	−8.078	−1.382
15-20	7.204	−0.924	−15.312	−4.982

[a] Of the form $Ax + By + Cz - D = 0$ where x, y, and z are the fractional coordinates of the atoms.

Sb, C_3, C_9, and C_{15} atoms are coplanar; the best least-squares plane through these four atoms has the equation $11.251X + 1.731Y - 1.701Z + 2.709 = 0$, and the atomic displacements from this plane are 0.0001 (7) Å for Sb and −0.01 (1) Å for C_3, C_9, and C_{15}. The slight distortion of the O_1-Sb-O_2 angle to 175.3 (3)° may plausibly be the result of packing requirements; *i.e.*, the six oxygen nearest *o*-phenyl hydrogen contacts are at distances which range from 2.45 to 2.67 Å. The coefficients of the least-squares plane through the carbon atoms for each phenyl ring of both compounds are listed in Table VII. The maximum displacement from these planes is 0.018 (18) Å, with the average being about half this value. The nmr spectrum[2] of this compound is in agreement with the molecular structure determined here.

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Stereoselectivity in the Metal-Complex-Catalyzed Hydrolysis of Amino Acid Esters[1a]

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Abstract: The hydrolysis of (*R*)-(−)- and (*S*)-(+)-histidine methyl esters in the presence of the catalytically active complexes Ni((*R*)-(−)-histidinate)$^+$ and Ni((*S*)-(+)-histidinate)$^+$ has been examined in detail. The rate of hydrolysis of the (*R*)-(−) ester is greater in the presence of the Ni((*S*)-(+)-histidinate)$^+$ ion than in the presence of Ni((*R*)-(+)-histidinate)$^+$, and these rate differences are mirrored in the behavior of the (*S*)-(+) ester. The system with opposite ester-histidine configurations has an observed rate constant approximately 40% greater than that found with identical ester-histidine configurations. A more detailed evaluation of the experimental data indicates that the stereoselectivity results from differences in the specific rates of hydrolysis for the coordinated ligands, arising from differences in the degree of interaction between the ester carbonyl group and the coordination center. Differences in the stability constants of the species involved are not believed to play an important role in the stereoselectivity.

It has previously been shown in various studies that several metal ions and their complexes are effective catalysts for the hydrolysis of amino acid esters.[2-6] In these instances, coordination of the ester to a metal ion makes it more susceptible to attack by the nucleo-

(1) (a) Abstracted from the thesis submitted by J. E. Hix, Jr., to Vanderbilt University in partial fulfillment of the requirements for the degree of Doctor of Philosophy. (b) This investigation was supported by National Institutes of Health Predoctoral Fellowship No. 5-F1-GM-20,537 for which J. E. Hix, Jr., wishes to express sincere thanks.

philes, water and hydroxide ion. The present study was undertaken to delineate the occurrence of stereoselectivity in such reactions when the catalyst is a metal complex with an optically active ligand.

Two previous studies have indicated the presence of such stereoselectivity in related processes involving inert complexes. Murakami and his coworkers[7] found stereoselective effects in the hydrolysis of L(−)-phenylalanine ethyl ester when it was hydrolyzed in the presence of *cis* or *trans* isomers of dichlorobis(propylenediamine)cobalt(III) which contained only one of the isomeric forms of propylenediamine as a ligand. Thus the rate was found to be greater in the presence of *trans*-$[Co(D(-)pn)_2Cl_2]Cl$ than when *trans*-$[Co(L(+)pn)_2Cl_2]Cl$ was present. In this case, however, the over-all reaction was a composite one which involved hydrolysis of the Co–Cl linkage, the formation of intermediate complexes with the buffer, and subsequent coordination of the ester followed by its hydrolysis. The separation of these steps was not clear-cut in all cases.

A second example of a stereoselective ligand reaction with a cobalt(III) complex is the recently reported synthesis of alanine by Asperger and Liu.[8] In this case the decarboxylation of α-amino-α-methylmalonato-L,L′-α,α′-dimethyltriethylenetetraminecobalt(III) in aqueous solution leads to the production of more of the L enantiomer of alanine than of the D enantiomer.

The present study was undertaken to provide information on more labile systems in which the slowest net reaction in the system would always be the reaction of the reactive ligand with a reagent other than the coordination center. In this way stereoselectivity of the coordination processes could be sorted out from stereoselectivity in the reaction of the coordinated ligand. The reactions chosen were the hydrolyses of (*R*)-(−)- and (*S*)-(+)-histidine methyl esters, catalyzed by the 1:1 nickel(II) complexes of (*R*)-(−)- and (*S*)-(+)-histidine. This allowed data to be obtained on the following four closely related reactions

$$RE + Ni(RA)^+ + OH^- \longrightarrow Ni(RA)_2 + CH_3OH \quad (1)$$

$$RE + Ni(SA)^+ + OH^- \longrightarrow Ni(SA)(RA) + CH_3OH \quad (2)$$

$$SE + Ni(RA)^+ - OH^- \longrightarrow Ni(RA)(SA) + CH_3OH \quad (3)$$

$$SE + Ni(SA)^+ + OH^- \longrightarrow Ni(SA)_2 + CH_3OH \quad (4)$$

where A and E refer to histidine and its ester, respectively, and the prefixes R and S refer to the absolute configurations of the ligands. (In the case of histidine and its methyl ester, (*R*)-(−) is the preferred method of designating the absolute configuration of the enantiomer formerly called D(−), while (*S*)-(+) corresponds to the old L(+).[9])

Experimental Section

Reagents. (*S*)-(+)-Histidine hydrochloride monohydrate (CP), (*R*)-(−)-histidine hydrochloride monohydrate (CP), and (*S*)-(+)-histidine methyl ester dihydrochloride were obtained from Nutritional Biochemicals Corp. (*R*)-(−)-Histidine methyl ester dihydrochloride was prepared in the usual manner[10] from (*R*)-(−)-histidine and methanol using hydrogen chloride gas as the catalyst. Chemical analysis and melting points, as well as infrared spectra and optical rotatory dispersion curves, were obtained for both the isomers of histidine and ester in order to check the qualitative and optical purities. In all cases the enantiomers gave equivalent results within experimental error.[1a]

All other chemicals used were of reagent grade and the solutions prepared from them standardized by analysis.

Procedures. The rate of hydrolysis of histidine methyl ester in the presence of nickel(II) and histidine was followed by the pH-stat technique described in an earlier investigation.[11] As the ester was hydrolyzed, histidine and methanol were produced. The acid proton of the histidine was titrated by the instrument to maintain constant pH. Solution conditions were chosen such that the histidinate ion formed was completely complexed to the nickel ion, none remaining free in solution to form the zwitterion. Thus a 1:1 correspondence between the ester hydrolyzed and the base consumed is valid.

A predetermined amount of the 1.00 *M* standard sodium perchlorate solution was added to the thermostated beaker (this was to maintain the ionic strength at 0.75 in all the runs) which was equipped with a magnetic stirrer. Then a known amount of standard nickel(II) perchlorate solution was pipetted into the solution. This was followed by a weighed amount of histidine equivalent to the amount of nickel(II) and then the histidine methyl ester. A solution pH of about 3.5 resulted. Hydrolysis was then initiated by adjusting the pH to the desired value with standard sodium hydroxide, the pH profile *vs.* base added being recorded to verify instrument standardization and to furnish data for the determination of various stability constants.

The hydrolysis was then followed manually by recording the amount of base added by the pH-stat *vs.* time. The reaction was usually followed to more than 80% completion. The data were observed to approximate first-order kinetics, with the total base consumption being equal to the amount of ester or metal–histidine complex, whichever was present in the smaller amount.

Experimental data were gathered on solutions containing varying amounts of total ester with the initial amounts of nickel(II) and histidine remaining constant. Data were also obtained on the systems in which the initial amounts of ester were held constant, but varying amounts of nickel(II) and histidine were used. In all cases, the amount of histidine used was equivalent to the amount of nickel(II) present. These restrictions were placed on the system to keep the interpretation of the data as simple as possible. Since the rate constants were obtained during the first half of the reaction, the amino acid generated by the hydrolysis was never present in amounts sufficient to displace that present originally, to a significant extent.

Configurational Stability of Ligands. The configurational stability of the various optically active ligands under the conditions of this investigation was determined by observing the optical rotations of solutions of the ligands both in the presence and absence of nickel(II) for a period of several days. The solutions were observed to maintain their optical activities with the only changes being due to the hydrolysis of the ester producing the corresponding histidinate species. Therefore racemization of the ligands was not significant during rate studies. The temperature used in our studies was much lower than that used in previous studies of metal-catalyzed amino acid racemizations.[12]

Computer Program for Determining the Solution Composition. A FORTRAN computer program was written to calculate the analytical concentrations of all the species present in the reaction media. In this program, equations were set up to calculate the total concentrations of the metal and each ligand as functions of the free metal and free ligand concentrations. These simultaneous equations were then solved by the Newton–Raphson method to obtain the concentrations of free nickel(II), histidine, and histidine methyl ester

(2) M. L. Bender, Advances in Chemistry Series, No. 37, American Chemical Society, Washington, D. C., 1963, p 22.
(3) H. L. Conley and R. B. Martin, Jr., *J. Phys. Chem.*, **69**, 2923 (1965).
(4) M. D. Alexander and D. H. Busch, *J. Am. Chem. Soc.*, **88**, 1130 (1966).
(5) J. E. Hix, Jr., and M. M. Jones, *Inorg. Chem.*, **5**, 1863 (1966).
(6) R. J. Angelici and B. E. Leach, *J. Am. Chem. Soc.*, **89**, 4605 (1967).
(7) M. Murakami, H. Itatani, K. Takahashi, J. Kang, and K. Suzuki, *Mem. Inst. Sci. Ind. Res., Osaka Univ.*, 20, 95 (1963); see also M. Murakami and K. Takahashi, *Bull. Chem. Soc. Japan*, **32**, 308 (1959), for an asymmetric synthesis of threonine.
(8) R. G. Asperger and C. F. Liu, *Inorg. Chem.*, **6**, 796 (1967).
(9) E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p 92 ff.
(10) A. C. Andrews and D. M. Zebolsky, *J. Chem. Soc.*, 742 (1965).
(11) W. A. Connor, M. M. Jones, and D. L. Tuleen, *Inorg. Chem.*, **4**, 1129 (1965).
(12) J. Olivard, D. E. Metzler, and E. E. Snell, *J. Biol. Chem.*, **199**, 669 (1952).

from which the concentration of all complexes could be calculated. Further details of this program are available.[13]

Results and Discussion

Stability Constant for the Histidinato(methyl histidinate)nickel(II) Complexes. The kinetic results can be interpreted only after the equilibria involved between the various ligands and nickel(II) are evaluated. When a metal ion and two different ligands are present in solution, the ligands may segregate themselves by the following equilibrium.

$$2\text{NiAE} \overset{K}{\rightleftharpoons} \text{NiA}_2 + \text{NiE}_2 \qquad (5)$$

For a stereoselective effect to be observed, this equilibrium must partly favor the left-hand side of the equation. If most of the ester is coordinated as the 1:2 nickel(II)–ester complex, then the catalyzed rate observed should be independent of the nature of the other complex present (NiA_2). In addition, this rate of hydrolysis should be identical with the rate of hydrolysis observed when no histidine is present at all, where the ester is present in a 2:1 ratio with the metal.

The equilibrium constant K for the above reaction is not required to be the same value when different isomers of histidine are used with the ester of only one isomer. It was observed *experimentally* that all combinations of isomers gave the same titration curve within experimental error, prior to the hydrolytic reaction. These titration curves (Figure 1) yield a value for the mixed stability constant, β_{NiAE}, of 2.5×10^{13}, by comparison of the observed points with the curves predicted when various estimated values for this constant are used with the other known stability constants.[14]

From this value of β_{NiAE} and the other stability constants for the 1:2 nickel–ligand complexes, β_{NiA_2} and β_{NiE_2}, one can solve for the value of K using the following equation.

$$K = \frac{[\text{NiA}_2][\text{NiE}_2]}{[\text{NiAE}]^2} = \frac{\beta_{\text{NiA}_2}\beta_{\text{NiE}_2}}{(\beta_{\text{NiAE}})^2} \qquad (6)$$

The value of K so obtained is 0.051. Therefore the equilibrium represented by eq 5 is far to the left, with most of the ester being present as the 1:1:1 complex NiAE when the components are present in equimolar amounts.

Hydrolysis of Histidine Methyl Ester in the Presence of Nickel(II) and Histidine. In the reduction of the kinetic data to observed rate constants, it is necessary to utilize some special information or assumptions on the systems: (1) so long as two or more coordination positions are available on the nickel(II), all of the histidine and its ester are coordinated under the conditions of this investigation; (2) nickel(II) is coordinated to the histidine in preference to the ester when they are in competition; (3) the major contribution to the hydrolysis reaction is the hydrolysis of the *coordinated* ester.

The first statement is supported by calculations of the solution composition when the metal and each ligand

(13) J. E. Hix, Jr., Ph.D. Thesis, Vanderbilt University, Nashville, Tenn. Available from University Microfilm, Inc., Ann Arbor, Mich.

(14) Titration curves of the ligands, both in the presence and absence of nickel(II), agreed with the curves predicted when the stability and dissociation constants given in ref 10 were used; therefore, no attempt was made to obtain new values for these constants in this study.

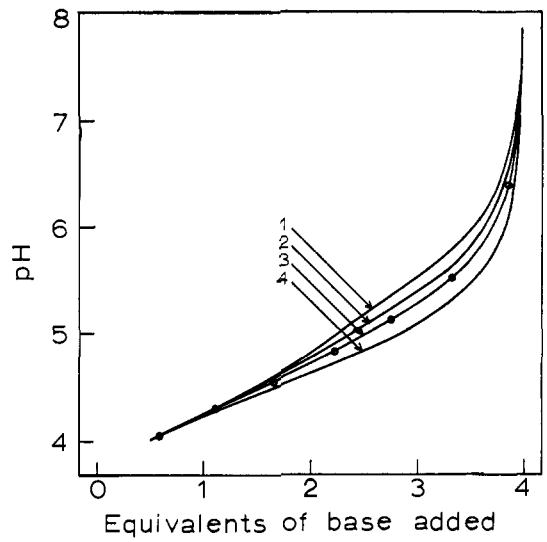

Figure 1. Calculated and observed titration curves for (*R*)-(−)- and (*S*)-(+)-histidine methyl ester in the presence of nickel(II) and (*R*)-(−)- and (*S*)-(+)-histidine using various estimated values for β_{NiAE}. The values used for curves 1, 2, 3, and 4 respectively are 0, 1.0×10^{13}, 2.5×10^{13}, and 1.0×10^{14}. The circles indicate the observed curves.

are present initially in equivalent amounts. This is shown in Table I. It is found that throughout the pH region used in this study the major species present in solution are the 1:2 metal–ligand complexes NiAE, NiA_2, and NiE_2. The observed titration curves of the

Table I. Per Cent Composition of a Solution Containing 10^{-2} *M* Ni(II) (M), Histidine (A), and Histidine Methyl Ester (E) as a Function of pH

pH	$E_{\text{uncoordntd.}}$ %	ME, %	ME_2, %	ME_3, %	MAE, %	MA, %	MA_2, %
7.00	6.0	3.4	12.6	1.1	63.0	4.3	15.7
7.25	5.2	2.8	12.7	1.4	63.7	3.5	16.0
7.50	4.9	2.2	12.7	1.8	64.1	2.8	16.3
7.75	5.1	1.7	12.4	2.3	64.1	2.2	16.6
8.00	5.9	1.2	11.9	2.8	63.6	1.6	17.2
8.25	7.5	0.8	11.0	3.6	62.7	1.2	17.9
8.50	10.0	0.5	9.9	4.8	61.0	0.8	19.0

reaction mixture to hydrolysis conditions (Figure 1) likewise shows that a sharp break in the curves is reached well before a pH of 7 is approached, whereas any free ligand would show its characteristic acid–base titration curve in this region. As mentioned previously in the Experimental Section, the stoichiometric amount of base was required to reach this pH break.

The second statement is also supported by solution composition calculations. Therefore, when nickel(II) and histidine are present in equivalent amounts, the histidinatonickel(II) complex is considered to be the species to which the ester coordinates. (The possibility of disproportionation has been discussed in an earlier section.) Since histidine is tridentate,[15] only three binding sites remain on the histidinatonickel(II) complex for ester coordination. Thus, there is room for only one ester ligand to chelate to the histidinatonickel(II) complex. As histidine is generated by hydrolysis,

(15) R. H. Carlson and T. L. Brown, *Inorg. Chem.*, 5, 268 (1966).

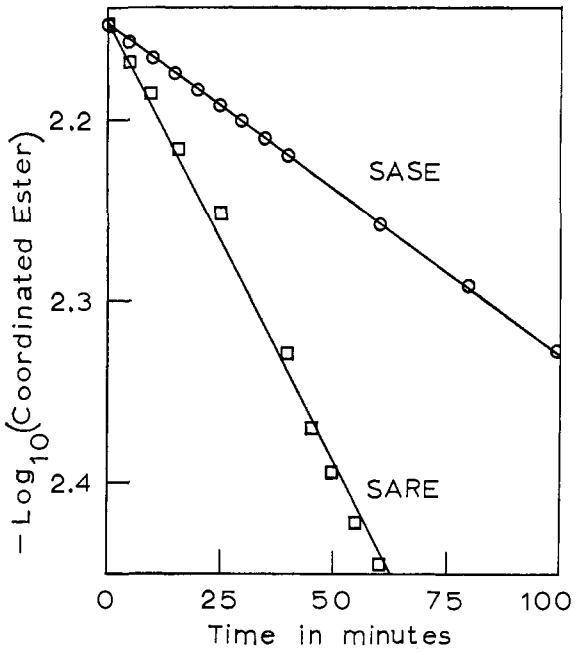

Figure 2. Pseudo-first-order rate plots for (*R*)-(−)- and (*S*)-(+)-histidine methyl ester (RE and SE) in the presence of nickel(II) and (*S*)-(+)-histidine (SA) at a pH of 8.25. Initial concentrations of all species are 7.14×10^{-3} *M*.

again due to its stronger coordinating characteristics, it remains coordinated to the metal as histidinate ion, preventing another ester ligand from replacing the one consumed by hydrolysis.

These lead to the following approximations. The initial concentration of coordinated ester is equal to the initial concentration of total ester up to the limiting value equal to the amount of histidinatonickel(II) present initially. For initial ester concentrations greater than this limiting value, the initial concentration of coordinated ester is equal to the amount of histidinatonickel(II) present initially. As hydrolysis occurs, the concentration of coordinated ester remaining decreases directly with the amount of ester consumed by hydrolysis (which is equivalent to the amount of base consumed by the generated acid). Therefore the rate expression used was

$$\text{rate} = \frac{-\text{d[ester]}}{\text{d}t} = k_{\text{obsd}}[\text{coordinated ester}] \quad (7)$$

which, with the above assumptions, integrates to

$$2.303 \log [\text{coordinated ester}] = 2.303 \log [\text{coordinated ester}]_{\text{initial}} - k_{\text{obsd}}t \quad (8)$$

The plots based on this equation were observed to be linear to well beyond 50% completion of the reaction (Figure 2). The rate constants obtained by this manner are given in Table II. When histidine ester is present in excess, the rate drops off after all of the coordinated ester has reacted. Unfortunately, one cannot directly determine the exact nature of the active species from the kinetic data since the other ligand present, namely histidine, also complexes with the metal. However, as has been shown, since the ligands are to a close approximation completely coordinated, the major complexes must be of the form 1:1:1 nickel(II)–histidine–ester, and/or 1:2 nickel(II)–ester.

Table II. Observed Pseudo-First-Order Rate Constants for the Hydrolysis of (*S*)-(+)- and (*R*)-(−)-Histidine Methyl Ester (SE and RE) in the Presence of Nickel(II) and (*S*)-(+)- and (*R*)-(−)-Histidine (SA and RA)

pH	k_{obsd}, sec^{-1}	k_{obsd}, sec^{-1}
A.	$\text{Ni(II)}_{\text{total}} = \text{A}_{\text{total}} = \text{E}_{\text{total}} = 0.714 \times 10^{-2}$ *M*	
	Ni(II) + SA + SE	Ni(II) + RA + RE
7.00	0.35×10^{-5}	0.38×10^{-4}
7.25	0.74	0.71
7.50	1.26	1.18
7.75	2.00	2.7
8.00	3.8	3.8
8.25	7.1	8.0
8.50	15.1	12.3
	Ni(II) + RA + SE	Ni(II) + SA + RE
7.00	0.54×10^{-5}	0.66×10^{-5}
7.25	1.00	0.85
7.50	1.95	1.82
7.75	2.8	3.6
8.00	5.5	5.5
8.25	11.2	11.0
8.50	13.2	17.8
X	k_{obsd}, sec^{-1}	k_{obsd}, sec^{-1}
B.	$\text{Ni(II)}_{\text{total}} = \text{A}_{\text{total}} = 0.714 \times 10^{-2}$ *M*; (pH 8)	$\text{E}_{\text{total}} = X \times 10^{-2}$ *M*
	Ni(II) + SA + SE	Ni(II) + RA + SE
0.357	4.3×10^{-5}	5.8×10^{-5}
0.536	4.4	5.7
0.714	3.8	5.5
0.893	3.0	4.5
1.07	3.6	4.3
C.	$\text{Ni(II)}_{\text{total}} = \text{A}_{\text{total}} = X \times 10^{-2}$ *M*;	$\text{E}_{\text{total}} = 0.714 \times 10^{-2}$ *M*
0.357	3.6×10^{-5}	5.5×10^{-5}
0.714	3.8	5.5
1.43	4.4	6.9
3.57	4.7	7.5

In addition, the nature of the attacking nucleophiles must be determined. Plots of the catalyzed rates as a function of pH are linear and of slope very close to unity, so that it may be assumed that, in the system under study in this investigation, the primary nucleophile is the hydroxide ion, at least in the pH range studied here. One may then solve for the composite rate constants by dividing the observed first-order rate constants by the hydroxide ion concentration. The average values obtained in this manner are given in Table III.

Table III. Composite Rate Constants for the Base Hydrolysis of (*R*)-(−)- and (*S*)-(+)-Histidine Methyl Ester in the Presence of Nickel(II) and (*R*)-(−)- and (*S*)-(+)-Histidine

$k_{\text{SS}}{}^{a} = 40 \pm 1\ M^{-1}\ \text{sec}^{-1}$	$k_{\text{RR}}{}^{a} = 40 \pm 1\ M^{-1}\ \text{sec}^{-1}$
$k_{\text{RS}}{}^{a} = 58 \pm 2\ M^{-1}\ \text{sec}^{-1}$	$k_{\text{SR}}{}^{a} = 56 \pm 2\ M^{-1}\ \text{sec}^{-1}$

[a] The first subscript refers to the configuration of the histidinate ion, and the second subscript refers to that of the ester.

An obvious feature of these results is that the *observed* rates of hydrolysis for the different combinations of isomers differ in a regular fashion. The rate of hydrolysis of the (*R*) ester is greater in the complex with (*S*)-histidine than that with (*R*)-histidine and equal (within experimental error) to the rate of hydrolysis of the (*S*) ester in the presence of (*R*)-histidine. The two slower rates are also equivalent. This pattern of rates indicates that the observed effect is not a result of trace

contaminants or experimental error but is a property of the system itself. The effect must therefore be due to a difference in specific rate constants for the two combinations of isomers, since it has already been shown that there is no significant difference in the equilibrium constants for the different diastereoisomeric complexes.

It is assumed that the observed rates are a summation of terms due to each form of the ester present in solution. The total rate expressions are then of the form

$$\text{rate} = k_{xy}[\text{total complex}][\text{OH}] = k_{\text{E}}[\text{E}][\text{OH}] + k_{\text{HE}}[\text{HE}][\text{OH}] + k_{\text{ME}}[\text{ME}][\text{OH}] + k_{\text{ME}_2}[\text{ME}_2][\text{OH}] + k_{\text{ME}_3}[\text{ME}_3][\text{OH}] + k_{\text{MAE}}[\text{MAE}][\text{OH}] \quad (9)$$

which may be reduced by dividing through by [total complex][OH] and combining the terms due to uncoordinated ester to the following form

$$k_{xy} = \frac{k_{\text{E}}'[\text{uncoordinated ester}]}{[\text{total complex}]} + \frac{k_{\text{ME}}[\text{ME}]}{[\text{total complex}]} + \frac{k_{\text{ME}_2}[\text{ME}_2]}{[\text{total complex}]} + \frac{k_{\text{ME}_3}[\text{ME}_3]}{[\text{total complex}]} + \frac{k_{\text{MAE}}[\text{MAE}]}{[\text{total complex}]} \quad (10)$$

in which each component is expressed in terms of its fractional concentration, previously given in Table II. In eq 10, the constant k_{E}' is equal to

$$k_{\text{E}}' = \frac{k_{\text{E}} + \frac{k_{\text{HE}}[\text{H}]}{K_{a2}}}{1 + \frac{[\text{H}]}{K_{a2}}} \quad (11)$$

The side reactions have previously been studied,[3,14,16,17] and the values for the rate constants used in this analysis are given in Table IV.

Table IV. Rate Constants for the Hydrolysis of Histidine Methyl Ester and Its Three Nickel(II) Complexes

$k_{\text{E}} = 0.65^a\ M^{-1}\ \text{sec}^{-1}$	$k_{\text{HE}} = 56^a\ M^{-1}\ \text{sec}^{-1}$
$k_{\text{ME}} = 125^b\ M^{-1}\ \text{sec}^{-1}$	$k_{\text{ME}_2} = 175^b\ M^{-1}\ \text{sec}^{-1}$
$k_{\text{ME}_3} = 300^b\ M^{-1}\ \text{sec}^{-1}$	

[a] From ref 3. These values give the following values for k_{E}' from pH 7 to 8.50 (units = $M^{-1}\ \text{sec}^{-1}$; pH values in parentheses): Reference 3: 37 (7.00), 30 (7.50), 23 (7.50), 16 (7.75), 10.4 (8.00), 6.7 (8.25), 4.2 (8.50). Reference 14: 29 (7.00), 24 (7.50), 13.9 (8.00), 7.6 (8.50). [b] From ref 14.

The partial contributions to the composite rates from the various side reactions are given in Table V. The differences between the composite rate constants and the sum of the contributions from the side reactions are equal to the final term of eq 10

$$k_{xy} - \sum(\text{side reactions}) = k_{\text{MAE}}(\text{fraction MAE}) \quad (12)$$

also given in Table V.

One may now obtain the specific rate constants for the hydrolysis of the isomeric histidinato(methyl histidinate)-nickel(II) complexes by dividing the differences discussed above by the fractions of these complexes

(16) R. W. Hay, L. J. Porter, and P. J. Morris, *Australian J. Chem.*, **19**, 1197 (1966).
(17) R. W. Hay, *J. Chem. Educ.*, **42**, 413 (1965).

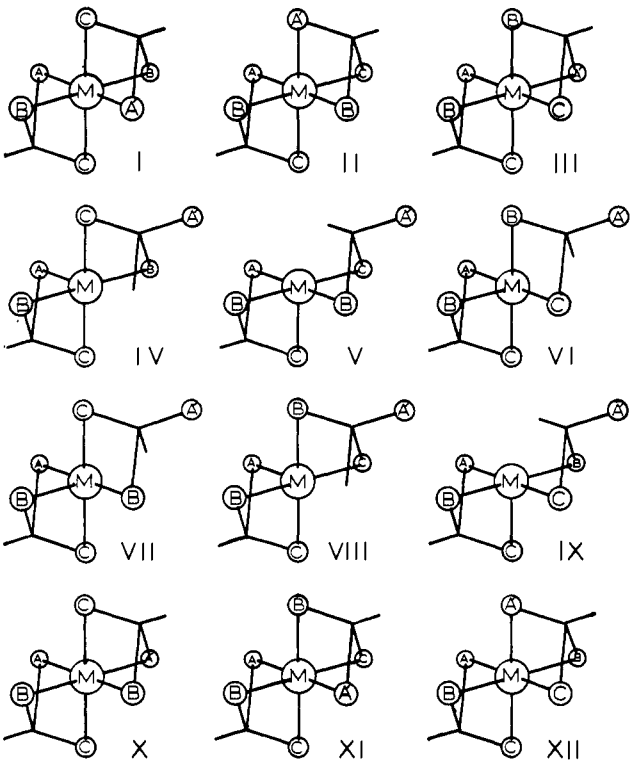

Figure 3. Possible structures for the nickel(II) complexes of (*R*)-(−)-histidine (the ligand to the lower left of the metal ion) and (*R*)-(−)- and (*S*)-(+)-histidine methyl ester (the ligand to the upper right of the metal ion). The (*R*) ester is used in structures IV, V, VI, X, XI, and XII. The corresponding complex of the (*S*) ester is used in structures I, II, III, VII, VIII, and IX. A is the histidine carboxyl group, A′ is the ester carbonyl group, B is the amino group, and C is the imidazole group.

present in solution. The average values of the specific rate constants obtained in this manner are ($M^{-1}\ \text{sec}^{-1}$) $k_{\text{NiSASE}} = 17$, $k_{\text{NiRASE}} = 43$, $k_{\text{NiRARE}} = 17$, $k_{\text{NiSARE}} = 45$. *Thus the nickel complex of histidine catalyzes the hydrolysis of histidine methyl ester more effectively if the ester and the histidine are of different configuration.*

Note that this is primarily a kinetic effect, since it is the specific rate constants which differ and not the thermodynamic stability constants.

Table V. Calculated Partial Contributions to the Composite Rate Constants from the Various Ester-Containing Species[a]

pH	Uncoordinated ester	ME	ME_2	ME_3	MSASE and MRARE	MSARE	MRASE
7.00	1.3	4.3	22.1	2.2	10	26	28
7.25	1.0	3.5	22.2	2.9	10	26	28
7.50	0.7	2.8	22.2	3.8	11	27	29
7.75	0.5	2.1	21.7	4.5	11	27	29
8.00	0.4	1.5	20.6	5.8	12	28	30
8.25	0.3	1.0	19.2	7.4	12	28	30
8.50	0.2	0.6	17.3	9.3	13	29	31

[a] The final three columns are obtained by subtracting the other terms from the composite rate constants as described in the text (units = $M^{-1}\ \text{sec}^{-1}$).

Under the conditions of this investigation, it has been shown[15] that histidine behaves as a tridentate ligand, with all three binding sites, the imidazole group, the amine group, and the carboxyl group, being co-

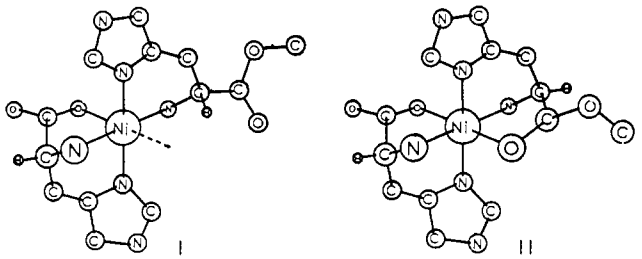

Figure 4. Possible structures for the nickel(II) complexes of (*R*)-(−)-histidine and (*R*)-(−)- and (*S*)-(+)-histidine methyl ester in which the equivalent nitrogen donors are *trans*. The (*R*) ester is used in structure I and the (*S*) ester is used in structure II.

ordinated to the nickel(II) ion. The ester must be considered primarily bidentate since complexes with a metal–ester ratio of 1:3 have been reported to be quite stable.[10] In this case, only the imidazole group and the amine group act as donors.

For most effective catalysis of the hydrolysis of the ester to be observed, a transient intermediate involving coordination of the ester carbonyl must result.[3] There are six ways in which a bidentate ligand may coordinate to the nickel(II)–histidine complex. These six ways, with both enantiomorphs of the ester being shown for each isomer, are illustrated in Figure 3. McDonald and Phillips[18] have shown that the similar coordination sites of histidine prefer a *trans* arrangement on cobalt(II), so consider structures I and IV, which have this arrangement for the nitrogen donors (Figure 4 shows these structures in more detail). Only the ester isomer differing in configuration from the coordinated amino acid has the carbonyl group in a position favorable for interaction with the metal ion. The stereoselective effect in the rate constants for the hydrolysis of histidine methyl ester in the presence of nickel(II) and the different isomers of histidine may therefore be explained as being due to a difference in interactions in the catalytically active complexes. When models of the other ways of coordinating the ester to the nickel(II)–histidine complex are also considered (Figure 3), it is observed that each way favors interaction between the ester group and the metal for only one of the two ester enantiomers. Since the 2:1 complex with different isomers of histidine on Co(II) is 0.7 kcal more stable than the complexes with the same isomers,[18] it is possible that the greater stability of the complexed product contributes somewhat to the observed stereoselectivity in this reaction. The *titration data* do not show a correspondingly enhanced stability for the nickel(II)–acid–ester complexes when the acid and ester are of enantiomeric configuration.

(18) C. C. McDonald and W. D. Phillips, *J. Am. Chem. Soc.*, **85**, 3736 (1963).

Conclusions

Conley has found[3] that, in the cases of many amino acid esters and their various complexes where carbonyl chelation does not occur, a hydrolysis rate increase of the order of 40-fold per unit charge is observed as the electrostatic charge on the ester species is increased. Therefore as the ester species is changed from a charge of zero to a charge of one, by coordination to the histidinatonickel(II) complex, a rate of hydrolysis on the order of 26 M^{-1} sec^{-1} would be predicted. The observed rate increases are somewhat greater than this in the case of coordination to the histidinatonickel(II) complex where the histidine and ester are of different configuration, while somewhat lower when coordinated to the histidinatonickel(II) complex where the histidine and ester are of the same configuration. This is further evidence that carbonyl chelation occurs at least to a small degree when the different configurations are used, though the available evidence does not establish that the mechanisms are this similar for the two enantiomers.

In all of these reactions the attacking nucleophile was found to be hydroxide ion. No evidence indicating nucleophilic attack by water was observed under the conditions of this investigation.

Since no detectable differences in the stabilities of the histidinato(methyl histidinate)nickel(II) complexes could be observed experimentally, it must be concluded that the main source of stereoselectivity results from differences in the hydrolytic activities of the isomeric complexes once formed. It has been shown that these differences in activities can result from the greater ease of interaction of the metal and the ester group in the proposed complex when the ester and histidine are opposite in configuration. This interaction, also indicated by the magnitudes of the specific rate constants, facilitates a greater polarization of the carbonyl group in the intermediate complex, therefore making nucleophilic attack on the ester more favorable.