Resolution of Racemic Amino Acids *via* Stereoselective Ligand-exchange Reactions on an Optically Pure Nickel(II) Complex‡

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Racemic amino acids (Ala, Val, Leu) co-ordinate steroselectively to the square-planar chiral matrix complex $[Ni\{(S,S)\text{-}L\}]^{2+}$ {(*S*,*S*)-L = *N*,*N*′-bis[(2*S*)-pyrrolidin-2-yl]propane-1,3-diamine}. The stereoselectivities [Ala, 60% (*S*), 40% (*R*); Val, 75% (*S*), 25% (*R*); Leu, 68% (*S*), 32% (*R*)] have been predicted by molecular mechanics calculations and determined experimentally by potentiometric titrations. The structure of the chiral matrix complex has also been determined: orthorhombic, space group $P2_12_12_1$, $a = 8.298(3)$, $b = 13.513(4)$, $c = 18.293(7)$ Å, $Z = 4$, $R' = 0.051$.

Owing to their occurrence in nature, optically pure materials are of some importance in areas related to bio-organic, -inorganic and pharmaceutical chemistry. In the many cases where asymmetric syntheses are not viable, enantiomeric separation is an important alternative. Many methods for racemate separations have been reported.[1,2] Optical resolution based on stereoselective ligand-exchange reactions has been used both for analytical and preparative separations; it involves the reversible stereoselective co-ordination of a ligand substrate to a chiral matrix complex.[1-3] We are interested in this technique and, in particular, in the accurate design of chiral matrix host complexes by molecular mechanics calculations.[2,4-9] Here, the thermodynamic stabilities of the diastereomeric product complexes are calculated *via* their strain energies. The chiral matrix complex $[Ni\{(S,S)\text{-}L\}]^{2+}$ {(*S*,*S*)-L = *N*,*N*′-bis[(2*S*)-pyrrolidin-2-ylmethyl]propane-1,3-diamine} has been evaluated for the optical resolution of racemic pn (pn = 1,3-diaminopropane) and pyrrolidin-2-ylmethylamine (pam).[2] This work is now extended to include a range of the biologically and technically more relevant chiral bidentate α-amino acids. The crystal structure of the chiral matrix complex $[Ni\{(S,S)\text{-}L\}][ClO_4]_2$ is also reported.

The methods which have been used for the experimental analysis of the stereoselectivity of ligand-exchange processes include chromatography (*e.g.* HPLC on chiral phases[2]), spectroscopy (NMR of derivatives with chiral auxiliaries,[2] CD[10]) or determination of stability constants.[11] Here we show that the determination of the stability constants of mixed-ligand complexes is, under favourable conditions, a viable and rather quick method for the experimental elucidation of the chiral recognition process.

Experimental

Materials.—The chiral matrix ligand (*S*,*S*)-L and its complex $[Ni\{(S,S)\text{-}L\}]^{2+}$ were prepared as described in the literature.[2,12] X-Ray-quality crystals of $[Ni\{(S,S)\text{-}L\}][ClO_4]_2$ were collected from an aqueous solution of the perchlorate salt of the complex.

Structure Determination of $[Ni\{(S,S)\text{-}L\}][ClO_4]_2$.—*Crystal data.* $C_{13}H_{28}Cl_2N_4NiO_8$, *M* 497.98, orthorhombic, space group $P2_12_12_1$, $a = 8.298(3)$, $b = 13.513(4)$, $c = 18.293(7)$ Å, $U = 2051(1)$ Å^3, D_c ($Z = 4$) = 1.613 g cm^{-3}, μ(Mo-Kα) = 12.10 cm^{-1}, λ(Mo-Kα) = 0.7107 Å, *F*(000) = 1040. Specimen: orange prisms. *N* 2012, N_o 1941, *h* 0–19, *k* 0–16, *l* 0–21, *R* 0.043, *R*′ 0.051, $w = 1.90/[\sigma^2(F_o) + 0.000\,36\,F_o^2]$, residual extrema +0.7 and −0.4 e Å^{-3}.

Data collection and refinement. A crystal of dimensions 0.25 × 0.32 × 0.32 mm was mounted on a glass fibre with cyanoacrylate resin. Lattice parameters at 21 °C were determined by a least-squares fit to the setting parameters of 25 independent reflections, measured and refined on an Enraf-Nonius CAD4F four-circle diffractometer, employing graphite-monochromated Mo-Kα radiation. Intensity data were collected in the range $1 < \theta < 25°$ using an ω–θ scan. The scan width and horizontal counter aperture employed were (0.90 + 0.34 tanθ)° and (2.70 + 1.05 tanθ) mm, respectively. Data reduction and application of Lorentz polarization and absorption (maximum, minimum transmissions 0.744, 0.688) corrections were carried out using the Enraf-Nonius structure determination package.[13] The structure was solved by direct methods using SHELXS 86[14] and the solution was extended by Fourier difference methods. Hydrogen atoms were included at calculated sites with group isotropic thermal parameters and all other atoms were refined anisotropically.

Scattering factors and anomalous dispersion terms used for Ni were taken from ref. 15 and all others used were those supplied in SHELX 76.[16] All calculations were carried out using SHELX 76[16] and plots were drawn using ORTEP.[17]

The atom numbering scheme is given in Fig. 1. Final atomic coordinates, bond lengths and angles are listed in Tables 1 and 2.

Additional material available from the Cambridge Crystallographic Data Centre comprises H-atom coordinates, thermal parameters, and remaining bond lengths and angles.

Molecular Mechanics Calculations.—Force-field calculations were performed with the strain-energy-minimization program MOMEC 87,[18] using a published force field.[8] Trial coordinates were generated with the graphics program SMILE.[19]

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‡ *Supplementary data available:* see Instructions for Authors, *J. Chem. Soc., Dalton Trans.*, 1993, Issue 1, pp. xxiii–xxviii.

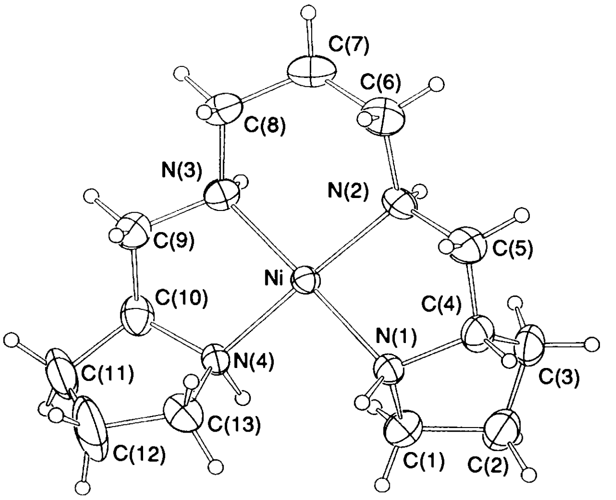

Fig. 1 An ORTEP[17] diagram of [Ni{(*S*,*S*)-L}]$^{2+}$

Table 1 Positional parameters (× 10^4) for [Ni{(*S*,*S*)-L}][ClO$_4$]$_2$

Atom	*x*	*y*	*z*
Ni	9 587(1)	9 809(1)	5 685(1)
N(1)	10 304(7)	8 568(4)	6 099(3)
N(2)	8 430(6)	10 010(5)	6 583(3)
N(3)	9 054(7)	11 080(4)	5 270(3)
N(4)	10 825(6)	9 582(4)	4 814(3)
C(1)	12 095(12)	8 460(7)	6 184(5)
C(2)	12 345(16)	8 166(6)	6 984(5)
C(3)	10 959(15)	8 630(6)	7 361(4)
C(4)	9 568(13)	8 409(5)	6 849(4)
C(5)	8 086(10)	9 031(7)	6 920(4)
C(6)	7 008(10)	10 632(7)	6 607(5)
C(7)	7 226(11)	11 629(7)	6 233(6)
C(8)	7 524(11)	11 578(5)	5 425(5)
C(9)	9 287(12)	11 020(6)	4 462(5)
C(10)	10 859(10)	10 506(7)	4 345(5)
C(11)	11 070(16)	10 091(10)	3 566(5)
C(12)	10 581(32)	9 036(12)	3 578(6)
C(13)	10 227(9)	8 736(7)	4 335(4)
Cl(1)	10 352(2)	15 894(1)	5 427(1)
O(1)	9 524(10)	5 014(6)	5 242(8)
O(2)	9 181(9)	6 679(5)	5 445(5)
O(3)	11 572(11)	6 092(9)	4 894(5)
O(4)	11 104(15)	5 811(10)	6 118(6)
Cl(2)	12 316(2)	11 714(1)	6 634(1)
O(5)	6 535(9)	7 321(6)	8 016(3)
O(6)	8 681(13)	7 343(8)	8 802(6)
O(7)	8 813(12)	6 304(7)	7 857(4)
O(8)	7 101(17)	6 029(11)	8 821(10)

Table 2 Bond lengths (Å) and angles (°) for [Ni(*S*,*S*)-L}][ClO$_4$]$_2$

N(1)–Ni	1.934(5)	N(2)–Ni	1.923(5)
N(3)–Ni	1.928(6)	N(4)–Ni	1.920(5)
C(1)–N(1)	1.502(11)	C(4)–N(1)	1.518(9)
C(5)–N(2)	1.486(10)	C(6)–N(2)	1.449(10)
C(8)–N(3)	1.465(10)	C(9)–N(3)	1.494(10)
C(10)–N(4)	1.516(9)	C(13)–N(4)	1.523(9)
C(2)–C(1)	1.531(13)	C(3)–C(2)	1.480(17)
C(4)–C(3)	1.516(14)	C(5)–C(4)	1.495(13)
C(7)–C(6)	1.521(14)	C(8)–C(7)	1.501(14)
C(10)–C(9)	1.493(13)	C(11)–C(10)	1.541(12)
C(12)–C(11)	1.483(19)	C(13)–C(12)	1.472(13)
O(1)–Cl(1)	1.413(7)	O(2)–Cl(1)	1.439(7)
O(3)–Cl(1)	1.430(9)	O(4)–Cl(1)	1.414(10)
N(2)–Ni–N(1)	86.6(3)	N(3)–Ni–N(1)	175.3(3)
N(3)–Ni–N(2)	95.5(3)	N(4)–Ni–N(1)	91.3(2)
N(4)–Ni–N(2)	177.3(2)	N(4)–Ni–N(3)	86.5(3)
C(1)–N(1)–Ni	115.4(5)	C(4)–N(1)–Ni	110.7(4)
C(4)–N(1)–C(1)	106.9(7)	C(5)–N(2)–Ni	109.0(4)
C(6)–N(2)–Ni	120.9(5)	C(6)–N(2)–C(5)	110.3(6)
C(8)–N(3)–Ni	122.2(5)	C(9)–N(3)–Ni	108.2(5)
C(9)–N(3)–C(8)	109.1(6)	C(10)–N(4)–Ni	110.4(5)
C(13)–N(4)–Ni	115.0(4)	C(13)–N(4)–C(10)	107.4(6)
C(2)–C(1)–N(1)	105.0(9)	C(3)–C(2)–C(1)	103.3(8)
C(4)–C(3)–C(2)	102.8(8)	C(3)–C(4)–N(1)	103.0(7)
C(5)–C(4)–N(1)	109.3(6)	C(5)–C(4)–C(3)	117.5(7)
C(4)–C(5)–N(2)	107.8(6)	C(7)–C(6)–N(2)	113.8(6)
C(8)–C(7)–C(6)	115.0(7)	C(7)–C(8)–N(3)	110.7(6)
C(10)–C(9)–N(3)	106.3(7)	C(9)–C(10)–N(4)	106.6(6)
C(11)–C(10)–N(4)	103.1(8)	C(11)–C(10)–C(9)	113.6(9)
C(12)–C(11)–C(10)	107.7(9)	C(13)–C(12)–C(11)	109.5(9)
C(12)–C(13)–N(4)	105.6(9)	O(2)–Cl(1)–O(1)	107.3(5)
O(3)–Cl(1)–O(1)	109.8(6)	O(3)–Cl(1)–O(2)	110.9(6)
O(4)–Cl(1)–O(1)	111.2(8)	O(4)–Cl(1)–O(2)	109.6(7)
O(4)–Cl(1)–O(3)	108.1(7)		

Table 3 Stability constants of mixed-ligand complexes *

Amino acid (Haa)	log β	
	[Ni{(*S*,*S*)-L}{(*S*)-aa}]$^+$	[Ni{(*S*,*S*)-L}{(*R*)-aa}]$^+$
Ala	18.37(1)	18.54(1)
Val	18.02(1)	18.51(1)
Leu	18.19(1)	18.52(1)
Thr	18.41(1)	18.68(1)
Ser	18.52(1)	18.62(1)

* β = [Ni{(*S*,*S*)-L}(aa)]/[Ni][(*S*,*S*)-L][aa]; for L pK_1 5.41(1), pK_2 7.06(1), pK_3 9.82(1) and pK_4 10.46(1); stability constant of [Ni{(*S*,*S*)-L}]$^{2+}$ log β 15.24(1).

Potentiometric Titrations.—The concentration of Ni^{II} was 2×10^{-3} mol dm^{-3} and the ratio Ni^{II} : L : amino acid was 1 : 1 : 1. The titration was performed in the range pH 7.5–10, where L is fully co-ordinated to Ni^{II}. For further details see ref. 20.

Results and Discussion

Structure of [Ni{(*S*,*S*)-L}]$^{2+}$.—The structure of [Ni{(*S*,*S*-L}][ClO$_4$]$_2$ consists of the resolved chiral ligand co-ordinated to Ni^{II}. As in the corresponding complex of copper(II),[21] the two pyrrolidinyl amines [N(1) and N(4)] have the same chirality (*S*) as those of the adjacent tertiary carbon atoms [C(14) and C(10)]. This is the most stable configuration, and it is generally observed in experimentally determined and calculated structures of co-ordinated proline derivatives.[2,21] The other two amines have opposite chiralities [N(2), *S*; N(3), *R*}. This enables the six-membered chelate ring to adopt a chair conformation. The geometry around Ni^{II} is close to square planar with the metal lying only slightly out (0.04 Å) of the plane defined by the four N(amine) atoms. The four Ni–N bond lengths are not significantly different and lie in the range observed for structures of macrocyclic tetraamine complexes.[22] The closest intermolecular contact to the Ni^{II} is 2.978 Å to the oxygen atom of one of the perchlorate anions.

Potentiometric Titrations.—Stability constants of the binary system Ni^{2+}–(*S*,*S*)-L and of the ternary systems containing [Ni{(*S*,*S*)-L}]$^{2+}$ and optically pure forms of various α-amino acids (Haa) were determined by potentiometric titrations and are collected in Table 3. The calculation of the ratio of the mixed-ligand complexes is based on equations (1)–(3).* From equation

$$[\mathrm{Ni}\{(S,S)\text{-L}\}]^{2+} + (S)\text{-aa}^- \xrightleftharpoons{K_S} [\mathrm{Ni}\{(S,S)\text{-L}\}\{(S)\text{-aa}\}]^+ \quad (1)$$

$$[\mathrm{Ni}\{(S,S)\text{-L}\}]^{2+} + (R)\text{-aa}^- \xrightleftharpoons{K_R} [\mathrm{Ni}\{(S,S)\text{-L}\}\{(R)\text{-aa}\}]^+ \quad (2)$$

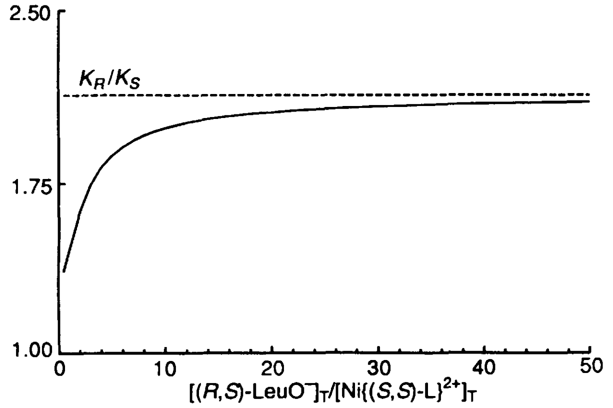

Fig. 2 Plot of the ratio (r) of $[\mathrm{Ni}\{(S,S)\text{-L}\}\{(R)\text{-LeuO}\}]^+/[\mathrm{Ni}\{(S,S)\text{-L}\}\{(S)\text{-LeuO}\}]^+$ (LeuO = leucinate) as a function of the concentration of added *rac*-LeuO⁻ [see equation (3); $[\mathrm{Ni}^{2+}] = 2.10 \times 10^{-3}$, $[(S,S)\text{-L}] = 2 \times 10^{-3}$ mol dm^{-3}}

Table 4 Calculated and experimentally determined stereoselective co-ordination of racemic bidentate ligands to $[\mathrm{Ni}\{(S,S)\text{-L}\}]^{2+}$

	Calculated (%)		Experimental (%)		
Substrate	(*S*)	(*R*)	(*S*)	(*R*)	Ref.
pn	44	56	43	57	2
pam	53	47	56	44	2
Ala	58	42	60	40	This work
Val	69	31	75	25	This work
Leu	67	33	68	32	This work

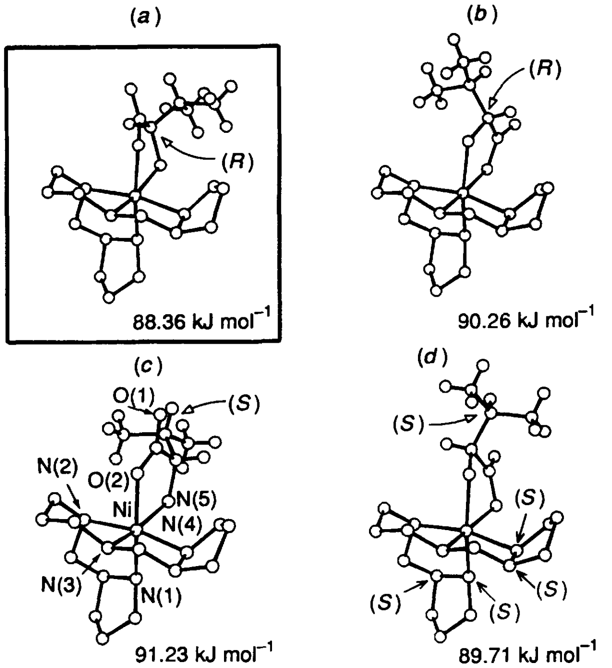

Fig. 3 The ORTEP[17] diagrams of the calculated structures of four conformers of $[\mathrm{Ni}\{(S,S)\text{-L}\}(\mathrm{Val})]^+$, including the most stable species Λ-β-*endo-endo*-$[\mathrm{Ni}\{(S,S)\text{-L}\}\{trans\text{-}\delta\text{-}(R)\text{-Val}\}]^+$ (*a*) [Λ/Δ and α/β describe the co-ordination geometry of L, *exo*/*endo* the conformation of the two pyrrolidinyl rings, *cis*/*trans* the co-ordination mode of Val and λ/δ the conformation of the amino acid chelate ring; the atom numbering scheme, given in (*c*), is general]. Selected bond lengths (Å) and angles (°) for (*a*): Ni–N(1) 2.12, Ni–N(2) 2.09, Ni–N(3) 2.09, Ni–N(4) 2.11, Ni–N(5) 2.10, Ni–O(2) 2.07, N(1)–Ni–N(2) 83, N(3)–Ni–N(4) 84, N(2)–Ni–N(3) 91, N(5)–Ni–O(2) 166, N(2)–Ni–N(4) 169, N(3)–Ni–N(5) 166

$$\frac{[\mathrm{Ni}\{(S,S)\text{-L}\}\{(S)\text{-aa}\}^+]}{[\mathrm{Ni}\{(S,S)\text{-L}\}\{(R)\text{-aa}\}^+]} = \frac{K_S(1 + K_R[\mathrm{Ni}\{(S,S)\text{-L}\}^{2+}])}{K_R(1 + K_S[\mathrm{Ni}\{(S,S)\text{-L}\}^{2+}])} \quad (3)$$

(3) it emerges that the ratio of the mixed-ligand complexes and therefore the amount of enantiomeric excess is dependent on the amount of free matrix complex present at equilibrium, and therefore on the relative concentration of the added substrate. This also emerges from Fig. 2 which is a plot of equation (3) for the $[\mathrm{Ni}\{(S,S)\text{-L}\}]^{2+}$–$(R,S)$-Leu system, showing that the enantiomeric excess of the ligand-exchange reaction increases with increasing concentration of the racemic substrate, reaching the maximum selectivity given by the thermodynamic ratio of K_R/K_S ($[\mathrm{Ni}\{(S,S)\text{-L}\}^{2+}] = 0$) at ⩾20-fold excess of the leu substrate. Good results with moderate substrate excesses obviously require relatively high stabilities of the six-co-ordinated species. However, the requirement for disappearance of the terms of the form (1 + K [chiral matrix complex]) indicates that, even in cases with a large preference for the six-co-ordinated species, some excess of the substrate is needed. This is of importance if experimentally determined stereoselectivities of a ligand-exchange reaction (independent of the method for their determination) are compared with calculated thermodynamic data, and we note that in our earlier work[2] the experimental data were generally based on reactions with a large enough excess of racemic substrate.

Stereoselectivity.—The calculated stereoselectivities are in good agreement with the experimentally determined data, and both are presented in Table 4. The minimized structures of the four possible β-Λ isomers of the $[\mathrm{Ni}\{(S,S)\text{-L}\}]^{2+}$– Val system [carboxylate of the amino acid *cis* or *trans* to the central N(amines) N(2) and N(3) of (*S*,*S*)-L, *R* and *S* configurations of the amino acid substrate; α- and β-Δ configurations are less stable[2]] are shown in Fig. 3.

The differences in enantioselectivities between the various α-amino acid substrates shown in Table 4 are not easy to interpret without molecular mechanics calculations. A thorough inspection of all interaction-energy terms for all the relevant conformers of each system indicates that the selectivity is mainly the result of the balance of small changes in non-bonded interaction, angle bending and torsional energies. It therefore is of some importance that the calculated selectivities are in good agreement with the experimental data, and this quality of the predictions seems to be general with the presently used approach and force field.[2,4–9]

The matrix complex $[\mathrm{Ni}\{(S,S)\text{-L}\}]^{2+}$ is a valuable system for racemate separations of simple bidentate chiral ligands, which are not usually easy to resolve. We have shown before that the matrix complex may be charged onto an ion-exchange resin which then may be used for efficient preparative resolutions.[2] The molecular mechanics approach used for the computation of enantioselective ligand-exchange reactions is ideal for the design of improved chiral matrix ligands, either through modifications of the present or development of new chiral matrix ligands.

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* For simplicity $[\mathrm{Ni}\{(S,S)\text{-L}\}]^{2+}$ = [NiL]. From equations (1) and (2), (2a) follows.Since $[(S)\text{-aa}]_\mathrm{T} = [(R)\text{-aa}]_\mathrm{T}$ (racemic mixture), [(*S*)-

$$\frac{[\mathrm{NiL}\{(S)\text{-aa}\}]}{[\mathrm{NiL}\{(R)\text{-aa}\}]} = \frac{K_S[\mathrm{NiL}][(S)\text{-aa}]}{K_R[\mathrm{NiL}][(R)\text{-aa}]} = \frac{K_S[(S)\text{-aa}]}{K_R[(R)\text{-aa}]} \quad (2a)$$

aa] + [NiL{(*S*)-aa}] = [(*R*)-aa] + [NiL{(*R*)-aa}] and [(*S*)-aa](1 + K_S[NiL]) = [(*R*)-aa](1 + K_R[NiL]). There we obtain expression (2b),

$$\frac{[(S)\text{-aa}]}{[(R)\text{-aa}]} = \frac{1 + K_R[\mathrm{NiL}]}{1 + K_S[\mathrm{NiL}]} \quad (2b)$$

and from (2a) and (2b), (3) follows.

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