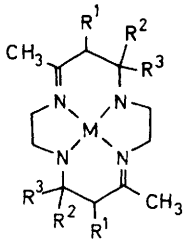
Reactions of Tris[(2S)-2-(aminomethyl)pyrrolidine]nickel(II) Ion with Alk-3-en-2-ones or 4-Hydroxyalkan-2-ones: Formation of an Optically Active Tetra-aza Macrocycle

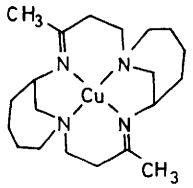
Tadashi Makino, Kazuo Miyamura, Masahiko Saburi,* and Sadao Yoshikawa*
Department of Synthetic Chemistry, Faculty of Engineering, The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113, Japan

Reactions of $[Ni(ampr)_3]^{2+}$ [ampr = (2S)-2-(aminomethyl)pyrrolidine] and several alk-3-en-2-ones or 4-hydroxyalkan-2-ones were carried out, and the resulting nickel(II) complexes separated chromatographically. Structures of the complexes are proposed based on i.r., c.d., proton n.m.r., and elemental analytical data. The products with but-3-en-2-one were a tetra-aza macrocyclic complex and an open-chain complex, where reaction at the secondary amino-group of ampr is selective. The products with 4-hydroxybutan-2-one were the same open-chain complex as above and another open-chain complex. The reactions with 4-methylpent-3-en-2-one and pent-3-en-2-one occurred specifically at the primary amino-group, due to steric repulsions involving the methyl group(s) on the β-carbon, and resulted in open-chain complexes.

It has been demonstrated that reactions of α,β-unsaturated ketones with 1,2-diaminoethane in the presence of a metal ion [1] such as Ni^{II} or Cu^{II} or of a proton acid [2–6] provide a convenient route to a variety of fourteen-membered tetra-aza macrocycles having the general structure (**1**). However, most macrocycles synthesized *via* the above-mentioned and related procedures [7] have no substituent attached to the two carbon linkages derived from the 1,2-diamine part, except for the isomers of the condensation product of $[Ni\{(R)\text{-pn}\}_3]^{2+}$ with acetone [(*R*)-pn = (*R*)-propane-1,2-diamine].[8,9]



(1)



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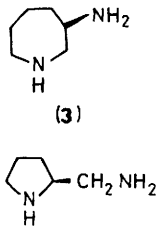
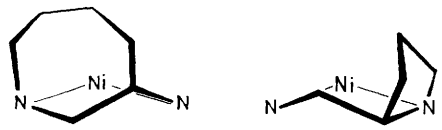


(3) (4)

In a previous communication [10] we reported the synthesis of an optically active fourteen-membered tetra-aza macrocycle (**2**) *via* a reaction of (3*S*)-3-aminohexahydroazepine (**3**) with but-3-en-2-one in the presence of Cu^{2+} as a template. The diamine (**3**) contains substituents at C and N, both of which should adopt the axial orientation with regard to the chelate plane [Figure 1(*a*)].[10] This led to an assumption that any mono-N-substituted 1,2-diamine involving an axially oriented substituent at N would similarly afford a tetra-aza macrocycle upon treatment with an α,β-unsaturated ketone.

(2*S*)-2-(Aminomethyl)pyrrolidine (**4**) (abbreviated as ampr) is a 1,2-diamine with a substituent at N which would preferably adopt the axial orientation [Figure 1(*b*)].[11] With a view to preparing new macrocyles containing ampr as the 1,2-diamine component, the reactions of $[Ni(ampr)_3]^{2+}$ with alk-3-en-2-ones have been investigated. Similar reactions with a few 4-hydroxyalkan-2-ones have also been studied. The methyl ketones employed in this study are listed in Table 1. Some of the results have been published previously.[12]



(a) (b)

Figure 1. Structures of co-ordinating ligands: (*a*) (3*S*)-3-aminohexahydroazepine; (*b*) (2*S*)-2-(aminomethyl)pyrrolidine

Table 1. List of methyl ketones used for the reactions with $[Ni(ampr)_3]^{2+}$, and the isolated products

Methyl ketone	Structure	Products[a]
But-3-en-2-one	$CH_3COCH{=}CH_2$	(**5**), (**6**)
4-Hydroxybutan-2-one	$CH_3COCH_2CH_2OH$	(**6**), (**7a**)
4-Methylpent-3-en-2-one	$CH_3COCH{=}C(CH_3)_2$	(**7b**)
4-Hydroxy-4-methylpentan-2-one	$CH_3COCH_2C(CH_3)_2OH$	(**7b**)
Pent-3-en-2-one[b]	$CH_3COCH{=}CHCH_3$	(**7c**), (**7d**)

[a] The structures of the products are given in Schemes 1—3. [b] A mixture of *E* and *Z* isomers is used.

Experimental

(2*S*)-2-(Aminomethyl)pyrrolidine was prepared by a reported method,[13] and purified by distillation, b.p. 60—62 °C (21 Torr, *ca.* 2 793 Pa), α(neat, 303 K, 589.3 nm) = +14.6°. Dihydrochloride: α (*c* = 0.031 g cm^{-3}, water, 589.3 nm) = −1.1 ± 0.05° (lit.,[13] −1.2 ± 0.12°). Pent-3-en-2-one and (*R,S*)-4-hydroxypentan-2-one were obtained by a reported method.[14] But-3-en-2-one, 4-hydroxybutan-2-one, 4-methylpent-3-en-2-one, and 4-hydroxy-4-methylpentan-2-one were of reagent grade, and used as received.

Tris[(2S)-2-(*Aminomethyl*)*pyrrolidine*]*nickel*(II) *Diperchlorate Hydrate*, $[Ni(ampr)_3][ClO_4]_2{\cdot}H_2O$.—To a solution of $Ni(ClO_4)_2{\cdot}6H_2O$ (7.3 g) in ethanol (30 cm^3) was added ampr (6.0 g). The pale violet crystals formed were collected, washed with a small volume of ethanol and diethyl ether, and air-dried (8.7 g, 76%) (Found: C, 31.65; H, 6.70; N, 14.85. Calc. for $C_{15}H_{38}Cl_2N_6NiO_9$: C, 31.65; H, 6.65; N, 14.65%).

[(7S,17S)-4,14-*Dimethyl*-1,5,11,15-*tetra-azatricyclo*-[15.3.0.0^{7,11}]*icosa*-4,14-*diene*]*nickel*(II) *Bis*(*tetraphenylborate*).—The salt $[Ni(ampr)_3][ClO_4]_2 \cdot H_2O$ (1.50 g) and but-3-en-2-one (1.75 g) were dissolved in methanol (150 cm^3), and the solution allowed to stand at room temperature for 24 h. The resultant solution was evaporated under reduced pressure. The brown oily residue was dissolved in water (500 cm^3) and undissolved materials were removed by filtration. The filtrate was poured onto a column of SP-Sephadex C-25 (40 × 4 cm; sodium form), and the adsorbed complexes were eluted with 0.2 mol dm^{-3} $NaClO_4$ aqueous solution. Two yellow bands developed, partly overlapping with a few brown bands. The fraction corresponding to the first minor yellow band was collected and excess of sodium tetraphenylborate was added. The precipitate formed was collected, washed with a large volume of water, and dried under vacuum (yield 0.36 g, 14%). The crude product was mixed with acetone (5—10 cm^3) and the mixture stirred overnight. The BPh_4 salt of (**5**) which remained was collected, washed with methanol and diethyl ether, and air-dried (0.072 g) (Found: C, 78.8; H, 7.30; N, 5.55. Calc. for $C_{66}H_{72}B_2N_4Ni$: C, 79.15; H, 7.25; N, 5.60%).

{(2S,2″S)-2-(*Aminomethyl*)-1-[3′-*methyl*-5′-(*pyrrolidin*-2″-*yl*)-4′-*azapent*-3′-*en*-1′-*yl*]*pyrrolidine*}*nickel*(II) *Bis*(*tetraphenylborate*).—The eluant for the second dominant yellow band, mentioned in the previous preparation, was collected and excess of $NaBPh_4$ was added. The resulting precipitate was collected, washed with water, and dried under vacuum (yield 1.38 g, 55%). The finely ground crude product (1.20 g) was suspended in methanol (100 cm^3), and Dowex MSA-1 ion-exchange resin (chloride form, 15 g) was added. The mixture was stirred for 10 h at room temperature, filtered, and the resin was washed with methanol. The filtrate and washings were combined and evaporated under reduced pressure. The oily residue was dissolved in water (500 cm^3), and impurities were filtered off. The filtrate was poured onto the column of SP-Sephadex C-25 described previously and eluted with 0.2 mol dm^{-3} $NaClO_4$ solution. The fraction corresponding to the yellow band was collected and excess of $NaBPh_4$ was added. The resulting BPh_4 salt of (**6**) was collected, washed with water, and dried under vacuum (0.75 g). It was recrystallized from nitromethane by adding ethanol (Found: C, 76.25; H, 7.25; N, 6.00. Calc. for $C_{62}H_{68}B_2N_4Ni$: C, 76.95; H, 7.30; N, 5.80%).

{(2S,2″S)-2-(*Aminomethyl*)-1-[3′-*methyl*-5′-(*pyrrolidin*-2″-*yl*)-4′-*azapent*-3′-*en*-1′-*yl*]*pyrrolidine*}*nickel*(II) *Tetrachlorozincate*(II).—The crude BPh_4 salt of (**6**) (0.6 g) prepared as above was treated with Dowex MSA-1 (chloride form, 6 g) as described previously, and the methanol solution of the dichloride salt was evaporated to 5 cm^3. Zinc(II) chloride (*ca.* 1 g) was added, and the resulting crystals were collected, washed with a small volume of methanol and diethyl ether, and air-dried (0.19 g). They were dissolved in water, the solution filtered, and evaporated almost to dryness. The residue was crystallized from hot methanol (0.069 g) (Found: C, 32.4; H, 5.60; N, 10.7. Calc. for $C_{14}H_{28}Cl_4N_4NiZn$: C, 32.45; H, 5.45; N, 10.8%).

Preparation of the Tetraphenylborate Salt of Complex (**5**) *from that of* (**6**).—To a suspension of the BPh_4 salt of (**6**) (0.5 g) in methanol (300 cm^3) were added but-3-en-2-one (0.15 g) and a few drops of triethylamine. The mixture was heated under reflux for 4 h, and the precipitate formed was collected, washed with methanol and diethyl ether, and then air-dried. The crude product (0.. as recrystallized from dimethyl sulphoxide and etnanol (0.0/3). The complex thus obtained was identical with that prepared previously.

{3-*Methyl*-1,7-*bis*[(2S)-*pyrrolidin*-2′-*yl*]-2,6-*diazahept*-2-*ene*}*nickel*(II) *Bis*(*tetraphenylborate*).—A solution containing $[Ni(ampr)_3][ClO_4]_2 \cdot H_2O$ (2.0 g) and 4-hydroxybutan-2-one (1.48 g) in methanol (100 cm^3) was refluxed for 6 h, and the resultant solution treated in a manner similar to that for obtaining the crude BPh_4 salt of complex (**5**). To the fraction corresponding to the broad brownish yellow band was added excess of $NaBPh_4$, and the precipitate was collected, washed with water, and dried under vacuum (yield 1.57 g, 47%). It was treated with Dowex MSA-1 (chloride form, 20 g), concentrated, and dissolved in water according to the procedures described above. The aqueous solution was poured onto a column of SP-Sephadex C-25 (40 × 4 cm, sodium form), and eluted with 0.1 mol dm^{-3} sodium oxalate solution. A band, initially brown, was separated into two, first a violet one and then a red-brown one. The reddish violet fraction corresponding to the latter band was collected, and calcium chloride, equimolar to oxalate in the eluant, was added. The calcium oxalate precipitate was removed by filtration, and excess of $NaBPh_4$ was added to the yellow filtrate. The precipitate of the BPh_4 salt of (**7a**) was collected, washed with water, and dried under vacuum (yield 0.40 g). It was recrystallized from acetone by adding ethanol (Found: C, 78.3; H, 7.45; N, 5.75. Calc. for $C_{62}H_{68}B_2N_4Ni$: C, 78.4; H, 7.20; N, 5.90%).

From the fraction corresponding to the earlier eluted violet band, the BPh_4 salt of complex (**6**) (0.48 g) was obtained.

{3-*Methyl*-1,7-*bis*[(2S)-*pyrrolidin*-2′-*yl*]-2,6-*diazahept*-2-*ene*}*nickel*(II) *Tetrachlorozincate*(II).—The above tetraphenylborate salt of (**7a**) was converted into the tetrachlorozincate by the same procedures as for complex (**6**) (Found: C, 32.65; H, 5.35; N, 10.50. Calc. for $C_{14}H_{28}Cl_4N_4NiZn$: C, 32.45; H, 5.45; N, 10.8%).

{3,5,5-*Trimethyl*-1,7-*bis*[(2S)-*pyrrolidin*-2′-*yl*]-2,6-*diazahept*-2-*ene*}*nickel*(II) *Bis*(*tetraphenylborate*).—A solution of $[Ni(ampr)_3][ClO_4]_2 \cdot H_2O$ (1.0 g) and 4-methylpent-3-en-2-one (0.82 g) [or 4-hydroxy-4-methylpentan-2-one (0.97 g)] in methanol (80 cm^3) was heated in a pressure bottle at 105 °C for 7 h. The reaction mixture was treated according to the same procedures as those for isolating the BPh_4 salt of complex (**7a**). The yield of the crude product was 0.87 g (51%) from 4-methylpent-3-en-2-one, 1.30 g (77%) from 4-hydroxy-4-methylpentan-2-one. The BPh_4 salt of (**7b**) was recrystallized from acetone–ethanol (Found: C, 78.1; H, 7.60; N, 5.70. Calc. for $C_{64}H_{72}B_2N_4Ni$: C, 78.65; H, 7.40; N, 5.75%).

{3,5,5-*Trimethyl*-1,7-*bis*[(2S)-*pyrrolidin*-2′-*yl*]-2,6-*diazahept*-2-*ene*}*nickel*(II) *Tetrachlorozincate*(II).—The BPh_4 salt of (**7b**) (0.4 g) was treated according to the same method applied to complex (**6**). The crude product (0.092 g) was recrystallized from aqueous ethanol (yield 0.041 g) (Found: C, 35.0; H, 5.95; N, 10.45. Calc. for $C_{16}H_{32}Cl_4N_4NiZn$: C, 35.15; H, 5.90; N, 10.25%).

{(5S)- *and* {(5R)-3,5-*Dimethyl*-1,7-*bis*[(2S)-*pyrrolidin*-2′-*yl*]-2,6-*diazahept*-2-*ene*}*nickel*(II) *Bis*(*tetraphenylborate*).—A methanol solution of $[Ni(ampr)_3][ClO_4]_2 \cdot H_2O$ (1.94 g) and pent-3-en-2-one (1.48 g, a mixture of *E* and *Z* isomers) was heated under reflux for 4 h. The reaction mixture was treated according to the same procedures applied for obtaining the BPh_4 salt of the complex (**7a**). The chromatographic separation of the crude product (2.23 g, 69%) on SP-Sephadex, employing 0.1 mol dm^{-3} sodium oxalate as eluant, yielded two complexes. The earlier eluted complex, giving a blue fraction, was isolated as its BPh_4 salt (0.69 g) and recrystallized from nitromethane by adding ethanol (Found: C, 78.0; H, 7.25; N, 5.80. Calc. for $C_{63}H_{70}B_2N_4Ni$: C, 78.55; H, 7.30; N, 5.80%). This complex was assigned as the (5*S*) isomer, the BPh_4^- salt of (**7c**) (see text).

From the red-violet fraction corresponding to the second

component, the crude (5*R*) isomer of the BPh_4^- salt of (**7d**) was obtained (0.64 g). It was recrystallized from nitromethane and ethanol (Found: C, 78.7; H, 7.45; N, 5.95%).

Similarly, $[Ni(ampr)_3][ClO_4]_2 \cdot H_2O$ and (*R,S*)-4-hydroxypentan-2-one when heated in methanol under reflux for 6 h gave the same two isomers.

{(5*R*)-3,5-Dimethyl-1,7-bis[(2*S*)-pyrrolidin-2-yl]-2,6-diazahept-2-ene}nickel(II) tetrachlorozincate(II) was obtained from the above BPh_4 salt of the (5*R*) isomer (Found: C, 33.8; H, 5.70; N, 10.5. Calc. for $C_{15}H_{30}Cl_4N_4NiZn$: C, 33.85; H, 5.70; N, 10.55%).

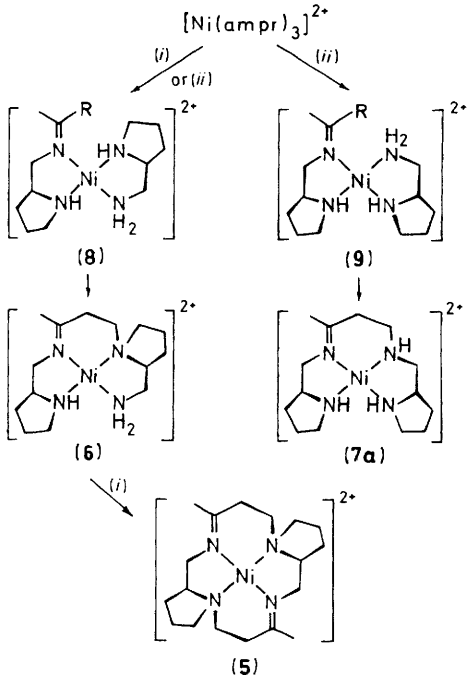
Measurements.—Infrared spectra were recorded with a Shimadzu IR-400 spectrophotometer, visible absorption spectra with a Shimadzu UV-210 spectrophotometer, and circular dichroism (c.d.) spectra with a JASCO J-20 recording spectropolarimeter. Nitromethane was used as a solvent for visible absorption and c.d. spectral measurements. 90-MHz Proton n.m.r. spectra were obtained with a Hitachi R-40 spectrometer, using $SiMe_4$ as an internal reference.

Results and Discussion

Products of Reaction of $[Ni(ampr)_3]^{2+}$ *with But-3-en-2-one or 4-Hydroxybutan-2-one.*—It has been shown that a ketimine bond (>C=N–) is rapidly formed from 1,2-diaminoethane co-ordinated to Ni^{II} and acetone[15] or 4-hydroxy-4-methylpentan-2-one.[16] We expected, therefore, that such a bond would form between the carbonyl group of but-3-en-2-one or 4-hydroxybutan-2-one and the primary amino-group of ampr in the first stage of the reaction of $[Ni(ampr)_3]^{2+}$ and the ketones. Although the exact structures of the intermediates are uncertain, for simplicity we will consider them to assume a square-planar co-ordination geometry (see Scheme 1). As ampr is a non-symmetric diamine, two intermediates, (**8**) and (**9**), are distinguishable, depending on the relative location of the primary and secondary amino-groups around the Ni^{II}. If the C–N bond formation takes place between the β-carbon of the ketone and the closest amino-nitrogen, complexes (**6**) and (**7a**) will be produced from the respective precursors (**8**) and (**9**) as shown in Scheme 1.

Complex (**6**) still has the primary and secondary amino-groups in adjacent positions, and can react with another ketone to give rise to the tetra-aza macrocycle complex (**5**). On the other hand, complex (**7a**) has no primary amino-group so that further reaction with ketone is impossible. Thus, it is possible that complexes (**6**), (**5**) and/or (**7a**) will be found in the reaction mixtures of $[Ni(ampr)_3]^{2+}$ with but-3-en-2-one or 4-hydroxybutan-2-one. In order to separate these complexes, ion-exchange chromatography on SP-Sephadex was employed in the present study. The products of the reactions with the two ketones were found to be slightly different, as outlined in Scheme 1. The detailed results are as follows.

Two yellow nickel(II) complexes were isolated from the reaction mixture of $[Ni(ampr)_3]^{2+}$ and but-3-en-2-one by elution with 0.2 mol dm^{-3} $NaClO_4$. The analytical data for the earlier eluted minor component were in agreement with that expected for the condensation product of 2 mol each of ampr and ketone. The i.r. spectrum of this complex exhibited no band assignable to $-NH_2$ and >NH groups. These results suggest that the complex is assignable to the macrocyclic complex (**5**). The later eluted dominant complex showed analytical data consistent with a condensation product of two ampr and one ketone molecules. The same 2:1 complex and a second 2:1 complex could be obtained from the reaction mixture of $[Ni(ampr)_3]^{2+}$ with 4-hydroxybutan-2-one by elution with 0.1 mol dm^{-3} sodium oxalate. These 2:1 complexes exhibited



Scheme 1. Reactions of $[Ni(ampr)_3]^{2+}$ with (*i*) but-3-en-2-one (R = $CH{=}CH_2$) or (*ii*) 4-hydroxybutan-2-one (R = CH_2CH_2OH)

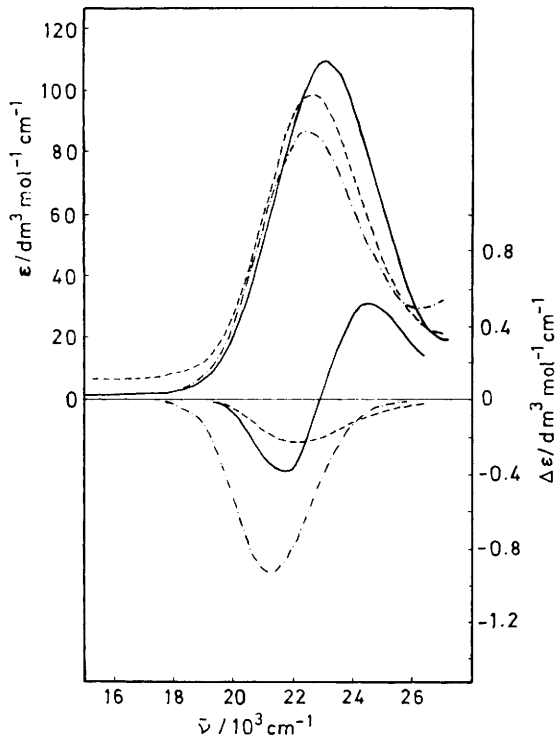


Figure 2. Visible absorption and c.d. spectra of the BPh_4 salt of complexes (**5**) (——), (**6**), the first 2:1 complex (— — —), and (**7a**), the second 2:1 complex (— · — · —)

apparently different c.d. spectra as shown in Figure 2. The spectral data are collected in Table 2.

The tetraphenylborate salts of the 2:1 complexes were converted into the tetrachlorozincate(II) salts for the purpose of

Table 2. Spectral data for the nickel(II) complexes

Parameter	Complex (5)	(6)	(7a)	(7b)	(7c)	(7d)
Visible absorption[a]						
$\tilde{\nu}_{max.}/10^3$ cm^{-1}	23.1	22.6	22.6	22.5	22.6	22.2
ε/dm^3 mol^{-1} cm^{-1}	109	99	86	95	91	75
C.d.[a]						
$\tilde{\nu}_{ext.}/10^3$cm^{-1}	21.6 24.6	22.1	21.3	21.6	21.6	21.3
$\Delta\varepsilon$/dm^3 mol^{-1} cm^{-1}	−0.38 +0.52	−0.23	−0.93	−1.05	−0.88	−1.17
I.r.[b] (cm^{-1})						
ν(–NH_2)		3 240				
		3 120				
ν(–NH)		3 170	3 170	3 170	3 170	3 160
$\delta(NH_2)$	*c*	1 580			*c*	
ν(C=N)	1 645	1 658	1 650	1 650	1 645	1 650
N.m.r. (at 90 MHz)[d]						
CH_3–C=N	1.99	2.01	1.97	2.00	1.94	1.94
CH_3–C–N				1.14	1.74	1.13
				1.92		

[a] For nitromethane solutions of the tetraphenylborate salts. [b] For tetrachlorozincate(II) salt, except for (5) and (7c). [c] Obscured by the absorption of tetraphenylborate anion. [d] Solvents: CD_3NO_2 for (6), (7a), (7c), and (7d); $(CD_3)_2SO$ for (5), and $(CD_3)_2CO$ for (7b).

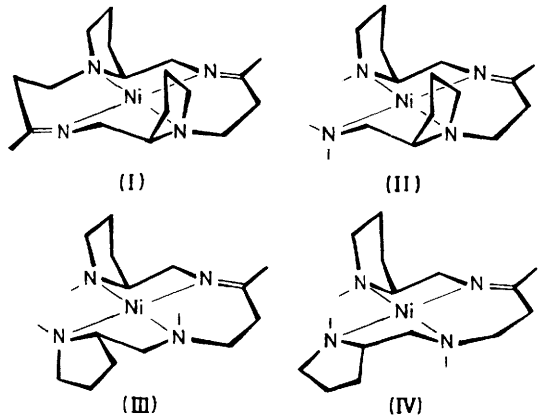


Figure 3. Proposed stereochemistries of the complexes: (I) for (5), (II) for (6), and (III) and (IV) for (7a)

obtaining i.r. spectra not obscured by the absorption of BPh_4^-. The first 2:1 complex (found in both reaction mixtures) showed bands assignable to ν(–NH_2), ν(>NH), and $\delta(NH_2)$, as summarized in Table 2. The i.r. characteristics strongly indicate that this complex is of structure (6), which involves both –NH_2 and >NH groups. On the other hand, the second 2:1 complex, which is expected to be of structure (7a), shows only the band due to ν(>NH). The observation that a base-catalysed reaction of the first 2:1 complex and but-3-en-2-one produces complex (5) supports the above assignments.

The stereochemistries of complexes (5) and (6) are unequivocally presumed to be (I) and (II) (Figure 3), respectively, because the chiral tertiary amine centres, which are incorporated in the pyrrolidine ring, are restricted to the (*S*)* configuration upon co-ordination. On the other hand, two stereoisomers, (III) and (IV), are possible for (7a), arising, as shown in Figure 3, from the difference in the configurations of the co-ordinated secondary amino-group. The proton n.m.r. spectrum of complex (7a) exhibited one sharp singlet for the

* *S* and *R* refer to the configuration of the secondary and tertiary amino-nitrogen centres co-ordinated to Ni^{II}, *cf.* refs. 3—5.

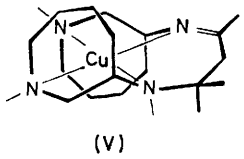
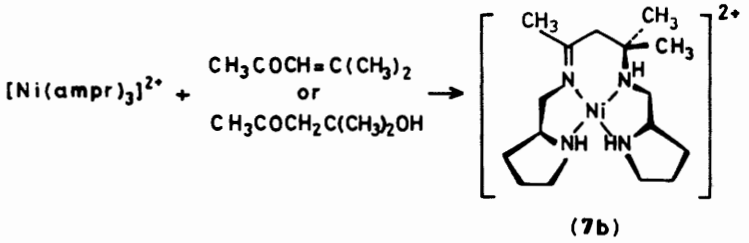


Figure 4. Possible structure (V) for the product of reaction of bis[(3*S*)-3-aminohexahydroazepine]copper(II) with 4-methylpent-3-en-2-one [12]

imine-methyl signal (Table 2). This indicates, therefore, that the product consists of a single species, either (III) or (IV).

Although no unambiguous crystallographic evidence for the structure of complex (7a) has yet been obtained, we considered (III) to be the most likely structure. A reason for this is that this structure has stereochemical characteristics antipodal to those of the copper(II) complex obtained *via* the reaction of bis[(3*S*)-3-aminohexahydroazepine]copper(II) with 4-methylpent-3-en-2-one.[12] This complex should adopt the structure (V) in Figure 4, due to the rigid conformation of the ligand. In (V) the 1,2-diamine chelates have the λ conformation, and the secondary nitrogen centre takes the (*R*) configuration as shown. On the other hand, in structure (III), the diamine chelates have the δ conformation, and the secondary nitrogen centre takes the (*R*) configuration. Although the secondary nitrogen centres in (III) and (V) are equally represented by the (*R*) configuration, their absolute configurations are evidently in a mirror-image relationship. Thus, the stereochemical features of (III) and (V), *i.e.* the conformation of the 1,2-diamine chelate and the configuration of the secondary nitrogen centre, are antipodal to each other. We conclude, therefore, that structure (III) is more probable for complex (7a) than is (IV), which has no such stereochemical similarity to (V).

It is noteworthy that the C–N bond formation takes place selectively at the secondary amino-group in the reaction with but-3-en-2-one to give complexes (5) and (6), while with 4-hydroxybutan-2-one the reaction occurs not only on the secondary but also on the primary amino-group to form (6) and (7a). The former reaction, which is regarded as a Michael reaction between the α,β-unsaturated ketone and the co-ordinated deprotonated amino-group, proceeded even at room temperature. On the other hand, the latter is considered to be an



Scheme 2. Reactions of $[Ni(ampr)_3]^{2+}$ with 4-methylpent-3-en-2-one or 4-hydroxy-4-methylpentan-2-one

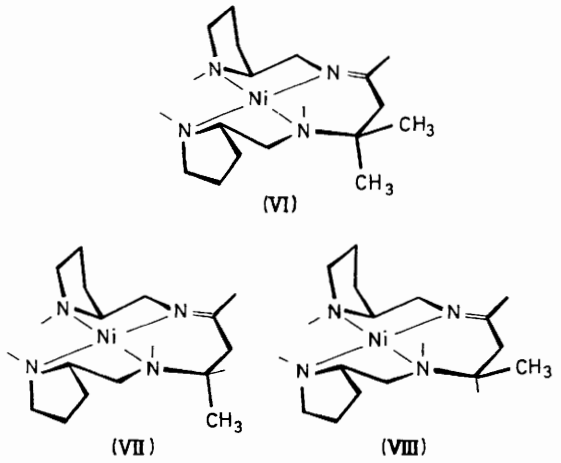
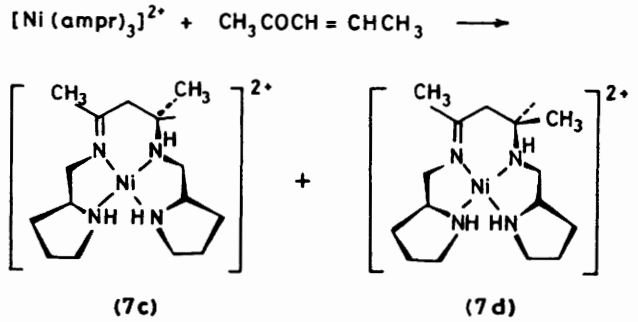


Figure 5. Proposed stereochemistries of the complexes: (**VI**) for (**7b**), (**VII**) for (**7c**), and (**VIII**) for (**7d**)



Scheme 3. Reaction of $[Ni(ampr)_3]^{2+}$ with pent-3-en-2-one (a mixture of *E* and *Z* isomers)

S_N2 type reaction, which means the replacement of the hydroxy-group with an amino-nitrogen, and so requires higher temperatures. This difference in reaction type may be responsible for the observed difference in selectivity of C–N bond formation. The reaction temperature will also contribute to the selectivity, which often decreases at higher temperatures.

Products of Reaction of $[Ni(ampr)_3]^{2+}$ *with* 4-*Methylpent*-3-*en*-2-*one or* 4-*Hydroxy*-4-*methylpentan*-2-*one*.—It has been reported[1] that 4-methylpent-3-en-2-one reacts with $[Ni(en)_3]^{2+}$ (en = 1,2-diaminoethane) to form the macrocyclic complex (**1**; R^1 = H, R^2 and R^3 = CH_3). Thus, the reaction of $[Ni(ampr)_3]^{2+}$ with this ketone was examined with a view to preparing a new macrocycle analogous to (**5**). The reaction was carried out at elevated temperature (105 °C), since the present ketone was found to be less reactive than but-3-en-2-one. However, the reaction mixture gave only one nickel(II) complex, obtained upon elution with 0.1 mol dm^{-3} sodium oxalate.

The analytical data for this complex were in good agreement with the condensation product of 2 mol of ampr and 1 mol of the ketone. The product showed no absorption in the i.r. spectrum due to a $-NH_2$ group, in a similar manner to (**7a**). Its c.d. spectral pattern also resembled that of (**7a**), and not that of (**6**). These findings suggest that the reaction proceeds selectively on the primary amino-groups to yield complex (**7b**) (Scheme 2).

The proton n.m.r. spectrum of complex (**7b**) showed three singlets at δ = 1.14, 1.92, and 2.00, ascribed to the methyl groups of the six-membered ring. A similar spectral pattern has been found for the nickel(II) complex of the chiral macrocycle (3*R*,10*R*)-3,5,7,7,10,12,14,14-octamethyl-1,4,8,11-tetra-aza-cyclotetradeca-4,11-diene, and analysed by taking into consideration magnetic anisotropy of the d^8 transition-metal ion.[17] According to the proposed assignments,[17] the singlets at 1.14 and 2.00 p.p.m. are assignable to the geminal methyls oriented, respectively, in the equatorial and axial directions, while the signal at 1.92 p.p.m. can be assigned to the imine-methyl protons. Thus, it was ascertained that complex (**7b**) involves a single isomer, the structure of which is expected to be (**VI**) in Figure 5.

Products of Reaction of $[Ni(ampr)_3]^{2+}$ *with Pent*-3-*en*-2-*one*.—It is interesting that the primary amino-group of ampr specifically participates in the reaction of $[Ni(ampr)_3]^{2+}$ with 4-methylpent-3-en-2-one to form complex (**7b**). This is clearly in contrast to the selective participation of the secondary amino-group in the C–N bond-formation reaction with but-3-en-2-one, yielding (**6**) and (**5**). It can be supposed that considerable steric repulsions arise between the methyl groups attached to the β-carbon (β-methyl group) and the pyrrolidinyl moiety of ampr. We consider that such steric factors are responsible for the opposing results described above. Pent-3-en-2-one is an α,β-unsaturated ketone having one β-methyl group, and is presumed to bring about steric repulsions which are more intense than those of but-3-en-2-one, but less intense than those of 4-methylpent-3-en-2-one. It is expected that the reaction with this ketone occurs both at the primary and the secondary amine of ampr.

The reaction of $[Ni(ampr)_3]^{2+}$ with a mixture of *E*- and *Z*-pent-3-en-2-one was carried out, and two nickel(II) complexes were isolated as BPh_4 salts from the reaction mixture and separated by elution with 0.1 mol dm^{-3} sodium oxalate. Based on the elemental analytical data and i.r. and c.d. spectral features (Table 2), these complexes were thought to adopt structures analogous to those of (**7a**) and (**7b**). Although there are two possibilities for the isomerism of the products, *i.e.* diastereomers due to the different configurations of the newly developed asymmetric carbon centre (at C^5) and those at the co-ordinated secondary nitrogen centre similar to structures (**III**) and (**IV**) for complex (**7a**), the latter seems unlikely since no interconversion of these complexes was observed. Hence, it was concluded that the complexes are either of the C^5 isomers, *i.e.* (**7c**) and (**7d**) in Scheme 3.

Provided that the stereochemistries of the above complexes

are the same as those of (**7a**) and (**7b**) with respect to the secondary nitrogen centre, structures (**VII**) and (**VIII**) are probable, respectively, for the (5*S*) and (5*R*) isomers, or (**7c**) and (**7d**) (see Figure 5). It is suggested, therefore, that the β-methyl group is directed axially for the (5*S*) isomer, and equatorially for the (5*R*) isomer.

The n.m.r. spectra of the complexes showed a singlet for the imine methyl and a doublet for the β-methyl group. It was noticed, further, that the doublet of the earlier eluted fraction appeared at 1.74 p.p.m., obviously to lower field than that of the second fraction at 1.13 p.p.m. Taking into account the effect of the magnetic anisotropy of the d^8 transition-metal ion,[17] we conclude that the β-methyl of the former fraction is directed axially, and that of the latter equatorially. Thus, the former and latter fractions, are assigned to the (5*S*) and (5*R*) isomers, respectively.

It has been shown that the C–N bond-formation reaction is sensitive to the steric repulsions between the substituent(s) around the reaction centre. The presence of one methyl group on the β-carbon of ketones prevents completely the reaction with the secondary amino-group of ampr. Therefore, the preparation of the macrocycle containing ampr as the 1,2-diamine component proceeded only for but-3-en-2-one, which is free from the repulsions around the β-carbon.

As mentioned previously, the reaction with pent-3-en-2-one generates a new chiral centre at C^5. It is expected that the product ratio (**7c**):(**7d**) will be dependent on the structure of the ketone (*E* or *Z*). An examination of those employing the pure *E* and *Z* isomers of pent-3-en-2-one is in progress.

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