Reactions of Copper(II) Complexes of Optically Active *N*-Substituted Diamines with Alk-3-en-2-ones or 4-Hydroxyalkan-2-ones: Formation of Optically Active Macrocycles

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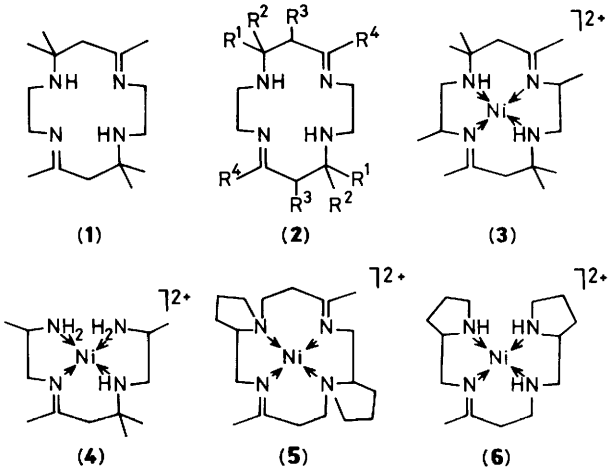
The reaction of bis[(3*S*)-3-aminopiperidine]copper(II) with but-3-en-2-one in methanol in the presence of ammonia gives an optically active tetra-azamacrocyclic complex in *ca.* 80% yield. Analogous optically active complexes are also obtained from bis[(3*S*)-3-aminohexahydroazepine]copper(II) or bis[(2*S*)-2-(aminomethyl)pyrrolidine]copper(II) by the same procedure. The introduction of methyl and/or a hydroxyl group at the C^4 position of but-3-en-2-one leads to a decrease in the reactivity of the ketones, and changes the species and distribution of the reaction products. In particular, when the C^4 position is fully substituted with methyl groups, C–N bond formation with the secondary amino group no longer proceeds. The change in the reaction mode due to the substituents at C^4 is discussed.

Curtis[1] first reported the formation of the amine–imine linkage by condensing two molecules of 1,2-diaminoethane with four molecules of acetone in the presence of Ni^{II} or Cu^{II} ions to give 5,7,7,12,14,14-hexamethyl-1,4,8,11-tetra-azacyclotetradeca-4,11-diene (**1**). Further, alk-3-en-2-ones and 4-hydroxyalkan-2-ones instead of acetone were found to give analogous macrocycles of the general formula (**2**).[2] Since then, a wide variety of diamino–di-imine macrocycles has been prepared and studied from various aspects.[3–5]

Attempts to obtain optically active macrocycles were also performed, and with optically active 1,2-diaminopropane, the macrocyclic complex (**3**) was obtained together with an open-chain complex (**4**).[6] The condensation reactions of alk-3-en-2-ones or 4-hydroxyalkan-2-ones with $[Ni(ampr)_3]^{2+}$ [ampr = (2*S*)-2-(aminomethyl)pyrrolidine] were also examined in our laboratory.[7] Reaction with but-3-en-2-one gave the macrocyclic complex (**5**) and reaction with 4-hydroxybutan-2-one gave the open-chain complex (**6**).

In a previous communication,[8] we reported the synthesis of the optically active tetra-azamacrocyclic complex (**7**) by reacting but-3-en-2-one with (3*S*)-3-aminohexahydroazepine (ahaz) in the presence of Cu^{II} ion as a template. A similar reaction of but-3-en-2-one with an analogous diamine (3*S*)-3-aminopiperidine (apip) was carried out, and the macrocyclic complex (**8**) obtained in high yield (*ca.* 80%). The high selectivity observed in the formation of complexes (**7**) and (**8**) is an interesting example of a highly selective reaction in the co-ordination sphere of a metal ion. In order to inspect the reason for this selectivity, we have carried out analogous reactions of but-3-en-2-one and related methyl-ketones with copper(II) complexes of heterocyclic diamines.



Experimental

(2*S*)-2-(Aminomethyl)pyrrolidine (ampr) and (3*S*)-3-aminohexahydroazepine (ahaz) were prepared by reported methods from L-proline[9] and (3*S*)-3-aminohexahydroazepin-2-one[10] respectively. (3*S*)-3-Aminopiperidine (apip) was prepared from L-ornithine methyl ester dihydrochloride as given below. But-3-en-2-one ($CH_3COCH{=}CH_2$), 4-methylpent-3-en-2-one [$CH_3COCH{=}C(CH_3)_2$], and 4-methyl-4-hydroxypentan-2-one [$CH_3COCH_2C(CH_3)_2OH$] were of reagent grade, and used as received. 4-Hydroxybutan-2-one ($CH_3COCH_2CH_2OH$), pent-3-en-2-one ($CH_3COCH{=}CHCH_3$), and 4-hydroxypentan-2-one [$CH_3COCH_2CH(CH_3)OH$] were obtained by a reported method.[11] The resulting 4-hydroxypentan-2-one is the racemic mixture, and pent-3-en-2-one is a mixture of *trans* and *cis* isomers. All other materials used were of reagent grade.

(3S)-3-*Aminopiperidin-2-one Hydrochloride*.—A methanol solution (420 cm^3) of sodium methoxide (22.8 g, 0.42 mol) was added dropwise to a suspension of L-ornithine methyl ester dihydrochloride (46.2 g, 0.21 mol) in methanol (210 cm^3). The reaction mixture was diluted with diethyl ether (630 cm^3) and allowed to stand for 36 h at room temperature. Sodium chloride was removed by filtration, and the resulting solution concentrated to *ca.* 300 cm^3 below 40 °C under reduced pressure, and then acidified by careful addition of methanolic hydrogen chloride (pH 3). Further evaporation of the solvent followed by seeding gave white crystals of (3*S*)-3-aminopiperidin-2-one hydrochloride, which were collected and washed with ethanol and diethyl ether repeatedly (19.1 g, yield *ca.* 60%).

(3S)-3-*Aminopiperidine*.—To a suspension of lithium tetrahydroaluminate (23.1 g) in dry tetrahydrofuran (thf) (500 cm^3) was added (3*S*)-3-aminopiperidin-2-one hydrochloride (35.2 g, 0.23 mol) in small portions with stirring. The mixture was heated under reflux for 24 h with continuous stirring. After being cooled to room temperature, the reaction mixture was

hydrolyzed by adding dropwise a mixture of thf (50 cm^3) and water (50 cm^3). The resulting slurry was heated under reflux for 30 min. The white slurry was filtered off, and the white precipitate stirred with hot thf (*ca.* 300 cm^3) for 1 h. The mixture was filtered and washed with thf. The precipitate was extracted with hot thf once more, and the extracts and filtrates were combined and acidified with hydrochloric acid. The thf was removed under reduced pressure, and the residue diluted with water and made strongly alkaline by adding an excess of solid sodium hydroxide until the product separated out of the aqueous layer, which was extracted with diethyl ether. The ether extracts were dried over potassium hydroxide pellets, and distilled under reduced pressure. (3*S*)-3-Aminopiperidine was obtained as colourless crystals (9.8 g, 42%), b.p. 71 °C/17 Torr (1 Torr = 133.3 Pa).

$[Cu(apip)_2][ClO_4]_2$, $[Cu(ahaz)_2][ClO_4]_2$, *and* $[Cu(ampr)_2][ClO_4]_2$.—These copper(II) complexes were prepared by mixing ethanolic solutions of copper(II) perchlorate hexahydrate and the appropriate diamine in a 1:2.2 molar ratio. When apip or ahaz was used, the copper(II) complex formed immediately. In the case of ampr, however, it took 1 d for the complex to crystallize. The complexes were collected by filtration, washed with ethanol and diethyl ether, and air dried (yields >90%) {Found for $[Cu(apip)_2][ClO_4]_2$: C, 26.35; H, 5.35; N, 12.25. Calc. for $C_{10}H_{24}Cl_2CuN_4O_8$: C, 25.95; H, 5.25; N, 12.10%. Found for $[Cu(ahaz)_2][ClO_4]_2$: C, 29.50; H, 5.55; N, 11.30. Calc. for $C_{12}H_{28}Cl_2CuN_4O_8$: C, 29.35; H, 5.75; N, 11.40%. Found for $[Cu(ampr)_2][ClO_4]_2$: C, 25.95; H, 5.50; N, 12.10. Calc. for $C_{10}H_{24}Cl_2CuN_4O_8$: C, 25.95; H, 5.25; N, 12.10%}.

Reactions of $[Cu(apip)_2][ClO_4]_2$.—(*a*) *With* $CH_3COCH{=}CH_2$. To a suspension of $[Cu(apip)_2][ClO_4]_2$ (1.0 g, 2 mmol) in methanol (50 cm^3) containing $CH_3COCH{=}CH_2$ (0.57 g, 8 mmol), ammonia gas was introduced for 20 min. At this stage the suspension turned into a clear blue solution. The solution was refluxed for 2 h with stirring until it turned violet. When the reaction mixture was allowed to cool to room temperature, a red precipitate of the diperchlorate salt of complex (**8**) formed. The precipitate was collected and the filtrate evaporated to dryness. The residue was extracted with water (300 cm^3) and the extract poured onto a column of SP-Sephadex C-25 (100 × 4 cm, sodium form). The adsorbed complexes were eluted with 0.2 mol dm^{-3} NaCl aqueous solution and two bands [(**8**), (**9**)] developed. Complex (**8**) was eluted first and (**9**) second, and both were crystallized as $[ZnCl_4]^{2-}$ salts by adding anhydrous zinc chloride to the desalted ethanolic solution of the complexes. Yields: $[(\mathbf{8})][ClO_4]_2$, 0.88 g (72%); $[(\mathbf{8})][ZnCl_4]$, 0.08 g (6%); and $[(\mathbf{9})][ZnCl_4]$, 0.01 g (1%) {Found for $[(\mathbf{8})][ClO_4]_2$: C, 36.45; H, 5.85; N, 9.65. Calc. for $C_{18}H_{32}Cl_2CuN_4O_8$: C, 36.95; H, 5.85; N, 9.60%. Found for $[(\mathbf{9})][ZnCl_4]$: C, 32.15; H, 5.35; N, 10.50. Calc. for $C_{14}H_{28}Cl_4CuN_4Zn$: C, 32.15; H, 5.40; N, 10.70%}.

(*b*) *With* $CH_3COCH_2CH_2OH$. The reaction between $CH_3COCH_2CH_2OH$ (0.76 g, 8 mmol) and $[Cu(apip)_2][ClO_4]_2$ (1.0 g, 2 mmol) was carried out for 6 h in a way similar to (*a*). The products separated into two components [(**8**), (**9**)] on an SP-Sephadex column. Both $[(\mathbf{8})][ZnCl_4]$ and $[(\mathbf{9})][ZnCl_4]$ obtained here gave the same i.r. spectra as those obtained from the reaction with $CH_3COCH{=}CH_2$. Yields: $[(\mathbf{8})][ZnCl_4]$, 0.21 g (20%) and $[(\mathbf{9})][ZnCl_4]$, 0.66 g (58%).

(*c*) *With* $CH_3COCH{=}CHCH_3$. The reaction between $CH_3COCH{=}CHCH_3$ (0.73 g, 8 mmol) and $[Cu(apip)_2][ClO_4]_2$ (1.0 g, 2 mmol) was carried out for 2 h in a way similar to (*a*). The products separated into three bands {(**10**), (**11**), and $[Cu(apip)_2]^{2+}$} on an SP-Sephadex column. Complex (**10**) was eluted first, (**11**) second, and finally $[Cu(apip)_2]^{2+}$. Yields: $[(\mathbf{10})][ZnCl_4]$, 0.02 g (3%) and $[(\mathbf{11})][ZnCl_4]$, 0.50 g (43%) {Found for $[(\mathbf{11})][ZnCl_4]$: C, 33.65; H, 5.60; N, 10.30. Calc. for $C_{15}H_{30}Cl_4CuN_4Zn$: C, 33.55; H, 5.65; N, 10.45%}. The amount of $[(\mathbf{10})][ZnCl_4]$ obtained after recrystallization was too small to perform an elemental analysis.

(*d*) *With* $CH_3COCH_2CH(CH_3)OH$. The reaction between $CH_3COCH_2CH(CH_3)OH$ (0.88 g, 8 mmol) and $[Cu(apip)_2][ClO_4]_2$ (1.0 g, 2 mmol) was carried out for 6 h in a way similar to (*b*). The products separated into three bands {a brown band, (**11**), and $[Cu(apip)_2]^{2+}$}. The brown band which eluted first was not identical with (**10**) and could not be crystallized by adding $ZnCl_2$. Complex (**11**), eluted second, was crystallized as its $[ZnCl_4]^{2-}$ salt. Yield: 0.54 g (47%).

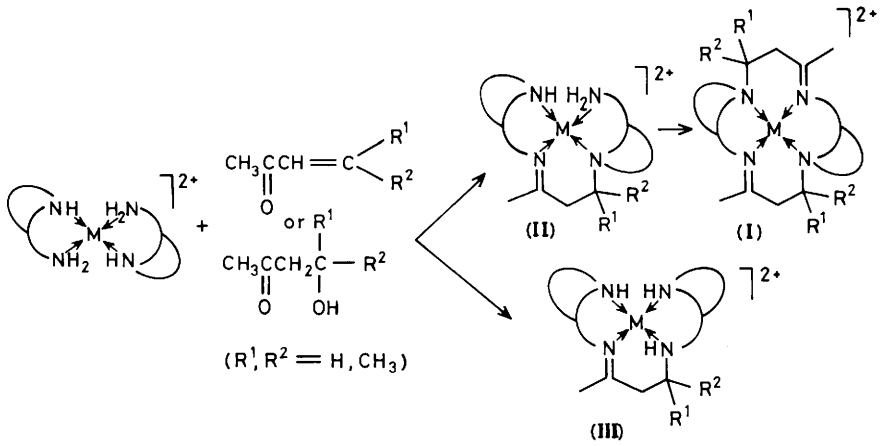
(*e*) *With* $CH_3COCH{=}C(CH_3)_2$. The reaction between $CH_3COCH{=}C(CH_3)_2$ (0.85 g, 8 mmol) and $[Cu(apip)_2][ClO_4]_2$ (1.0 g, 2 mmol) was carried out for 2 h in a way similar to (*a*). The products separated into five bands {a blue band, (**12**), (**13**), a red band, and $[Cu(apip)_2]^{2+}$}. The blue complex, (**Y**), obtained from the blue band was concluded to be the reaction product of ammonia, apip, and $CH_3COCH{=}C(CH_3)_2$ from visible absorption and c.d. spectra and elemental analysis (see Results and Discussion section). $[Cu(apip)_2]^{2+}$ was recovered in a substantial amount indicating the poor reactivity of $CH_3COCH{=}C(CH_3)_2$. Yields: perchlorate of (**Y**), 0.10 g (11% based on copper); $[(\mathbf{12})][ZnCl_4]$, 0.02 g (2%); and $[(\mathbf{13})][ZnCl_4]$, 0.03 g, (3%) {Found for $[(\mathbf{12})][ZnCl_4]$: C, 35.15; H, 6.10; N, 10.30. Calc. for $C_{16}H_{32}Cl_4CuN_4Zn$: C, 34.85; H, 5.85; N, 10.15%. Found for $[(\mathbf{Y})]ClO_4$: C, 33.10; H, 6.60; Cl, 17.95; N, 10.55. Calc. for $[Cu(C_{11}H_{23}N_3)Cl]ClO_4$: C, 33.40; H, 5.85; Cl, 17.90; N, 10.6%}. The amount of $[(\mathbf{13})][ZnCl_4]$ obtained after recrystallization was too small to perform an elemental analysis.

(*f*) *With* $CH_3COCH_2C(CH_3)_2OH$. The reaction between $CH_3COCH_2C(CH_3)_2OH$ (1.00 g, 8 mmol) and $[Cu(apip)_2][ClO_4]_2$ (1.0 g, 2 mmol) was carried out for 12 h in a way similar to (*e*). The products separated into five bands as in the case of (*e*). Yields: $[(\mathbf{12})][ZnCl_4]$, 0.05 g (5%) and $[(\mathbf{13})][ZnCl_4]$, 0.03 g (3%).

Reactions of $[Cu(ahaz)_2][ClO_4]_2$.—(*a*) *With* $CH_3COCH{=}CH_2$.—The reaction between $CH_3COCH{=}CH_2$ (0.57 g, 8 mmol) and $[Cu(ahaz)_2][ClO_4]_2$ (1.0 g, 2 mmol) was carried out for 2 h in a way similar to that with $[Cu(apip)_2]^{2+}$. A red precipitate of $[(\mathbf{7})][ClO_4]_2$ formed on cooling the reaction mixture. Complexes remaining in the mother solution separated into three bands {(**7**), (**14**), and $[Cu(ahaz)_2]^{2+}$} on an SP-Sephadex column. Yields: $[(\mathbf{7})][ClO_4]_2$, 0.50 g (41%); $[(\mathbf{7})][ZnCl_4]$, 0.02 g (2%); and $[(\mathbf{14})][ZnCl_4]$, 0.15 g (13%) {Found for $[(\mathbf{7})][ClO_4]_2$: C, 39.80; H, 6.00; N, 9.05. Calc. for $C_{20}H_{36}Cl_2CuN_4O_8$: C, 40.35; H, 6.10; N, 9.40%. Found for $[(\mathbf{14})][ZnCl_4]$: C, 34.80; H, 6.00; N, 10.15. Calc. for $C_{16}H_{32}Cl_4CuN_4Zn$: C, 34.85; H, 5.85; N, 10.15%}.

(*b*) *With* $CH_3COCH_2C(CH_3)_2OH$. The reaction between $CH_3COCH_2C(CH_3)_2OH$ (0.96 g, 8 mmol) and $[Cu(ahaz)_2][ClO_4]_2$ (1.0 g, 2 mmol) was carried out for 11 h in a way similar to that with $[Cu(apip)_2]^{2+}$. The products separated into five bands {a blue band, (**15**), (**16**), a red band, and $[Cu(ahaz)_2]^{2+}$}. Yields: $[(\mathbf{15})][ZnCl_4]$, 0.05 g (4%) and $[(\mathbf{16})][ZnCl_4]$, 0.03 g (3%). The amounts obtained after recrystallization were too small to perform elemental analyses.

Reactions of $[Cu(ampr)_2][ClO_4]_2$.—(*a*) *With* $CH_3COCH{=}CH_2$. The reaction between $CH_3COCH{=}CH_2$ (0.57 g, 8 mmol) and $[Cu(ampr)_2][ClO_4]_2$ (1.0 g, 2 mmol) was carried out for 2 h in a way similar to that with $[Cu(apip)_2]^{2+}$. A red precipitate of $[(\mathbf{17})][ClO_4]_2$ formed on cooling the reaction mixture. Complexes remaining in the filtrate separated into three bands [(**17**), (**18**), and (**19**)]. Yields: $[(\mathbf{17})][ClO_4]_2$, 0.21 g (17%); $[(\mathbf{17})][ZnCl_4]$, 0.20 g (16%); $[(\mathbf{18})][ZnCl_4]$, 0.05 g (5%); and



Scheme.

[(**19**)][$ZnCl_4$], 0.04 g (4%) {Found for [(**17**)][ClO_4]$_2$; C, 37.85; H, 5.50; N, 9.90. Calc. for $C_{18}H_{32}Cl_2CuN_4O_8$: C, 38.15; H, 5.70; N, 9.90%. Found for [(**18**)][$ZnCl_4$]: C, 32.10; H, 5.70; N, 10.45%. Calc. for $C_{14}H_{28}Cl_4CuN_4Zn$: C, 32.15; H, 5.40; N, 10.70%. Found for [(**19**)][$ZnCl_4$]: C, 31.85; H, 5.65; N, 10.40. Calc. for $C_{14}H_{28}Cl_4CuN_4Zn$: C, 32.15; H, 5.40; N, 10.70%}.

(*b*) *With* $CH_3COCH_2C(CH_3)_2OH$. The reaction between $CH_3COCH_2C(CH_3)_2OH$ (1.00 g, 8 mmol) and [Cu(ampr)$_2$][ClO_4]$_2$ (1.0 g, 2 mmol) was carried out for 11 h in a way similar to that with $[Cu(apip)_2]^{2+}$. Only a single band appeared on the column, which was pure (**20**). Yield: 0.95 g (80%) {Found for [(**20**)][$ZnCl_4$]: C, 34.50; H, 6.20; N, 9.80. Calc. for $C_{16}H_{32}Cl_4CuN_4Zn$: C, 34.85; H, 6.20; N, 9.80%}.

Measurements.—Infrared and visible absorption spectra were recorded on Shimadzu IR-400 and Shimadzu UV-210 spectrophotometers respectively. Circular dichroism (c.d.) spectra were recorded with a JASCO J-20 spectropolarimeter.

Table 1. I.r. spectroscopic data (cm^{-1}) for the complexes

Complex	Structure	ν_{NH}	$\nu_{C=N}$	δ_{NH_2}
(**8**)	(I)		1 660	
(**9**)	(II)	3 280, 3 230, 3 140	1 660	1 590
(**10**)	(I)		1 650	
(**11**)	(II)	3 300, 3 230, 3 140	1 660	1 580
(**13**)	(II)	3 300, 3 200	1 660	1 580
(**12**)	(III)	3 300, 3 230, 3 210	1 660	
(**Y**)		3 260, 3 220, 3 150	1 660	1 590
(**7**)	(I)		1 640	
(**14**)	(II)	3 230, 3 180, 3 110	1 640	1 570
(**16**)	(II)	3 230, 3 180, 3 110	1 640	1 570
(**15**)	(III)	3 160	1 650	
(**17**)	(I)		1 660	
(**19**)	(II)	3 230, 3 140	1 670	1 590
(**18**)	(III)	3 200	1 660	
(**20**)	(III)	3 200	1 660	

Results and Discussion

The possible structures of complexes formed from reactions of copper(II) complexes of *N*-substituted chiral diamines with ketones, which are expected from the results of reactions of $[Ni(ampr)_3]^{2+}$ with some methyl ketones,[7] can be classified into three categories (**I**), (**II**), and (**III**) (Scheme). When C–N single bond formation occurs at the primary amino group of the diamine a complex with structure (**III**) is obtained. Since this complex has no primary amino group remaining, the reaction with ketone does not proceed further. On the other hand, when C–N formation occurs at the secondary amino group, a complex with structure (**II**) will be formed. This complex, still having a primary amino group, can react with a further ketone to give a macrocyclic complex of structure (**I**). Thus these three structures differ in the number of ketone molecules reacted [two ketones for (**I**) and one for (**II**) and (**III**)], and in the relative orientation of the non-symmetric diamine groups [*trans* for (**I**) and (**II**), *cis* for (**III**)].

The route to either (**I**) and (**II**) or (**III**) should be determined at the stage of C–N bond formation at the β-position of the ketone. We considered, based on the results of reactions of $[Ni(ampr)_3]^{2+}$,[7] that the introduction of methyl group(s) to the β position of the ketone increases steric repulsion between the ketone and the diamine moiety and alters the selectivity for reaction at either the primary or secondary nitrogens, and thus gives information for exploring the factors which govern the selectivity. In the present study we used six ketones with substituent(s) at the β position to investigate the effect of substituents on the reactivity and selectivity of the condensation reaction.

Complexes (**7**)—(**20**), obtained from the reactions of bis(diamine)copper(II) complexes with methyl ketones, can be clearly classified into three categories (**I′**), (**II′**), and (**III′**) on the basis of their i.r. spectra (Table 1). All the reaction products give a strong absorption in the C=N stretching (*ca.* 1 640 cm^{-1}) region, while differences were acknowledged in the profiles of the N–H stretching (*ca.* 3 200 cm^{-1}) and NH_2 bending (*ca.* 1 580 cm^{-1}) regions. For complexes of category (**I′**), no amino protons remain so that absorptions around 3 200 and 1 580 cm^{-1} are absent. For complexes of category (**II′**), the existence of both primary and secondary amino groups is indicated by the appearance of absorptions at *ca.* 3 200 and 1 580 cm^{-1}. For complexes of category (**III′**), only secondary amino groups remain, thus giving an absorption at 3 200 cm^{-1} but not at 1 580 cm^{-1}. The i.r. characteristics observed among (**I′**), (**II′**), and (**III′**) correspond well with the general structures (**I**), (**II**), and (**III**) respectively (Scheme). Thus, the structures of (**7**)—(**20**) are those given in Figure 1. The c.d. and visible spectra (Table 2) of complexes of the same category resemble one another, implying their structural similarities. Elemental analyses were performed for representative complexes, and agree well with the proposed structures.

Reactions of Bis(diamine)copper(II) Complexes with But-3-en-2-one.—Reactions between $CH_3COCH{=}CH_2$ and copper(II) complexes of the optically active *N*-substituted 1,2-diamines

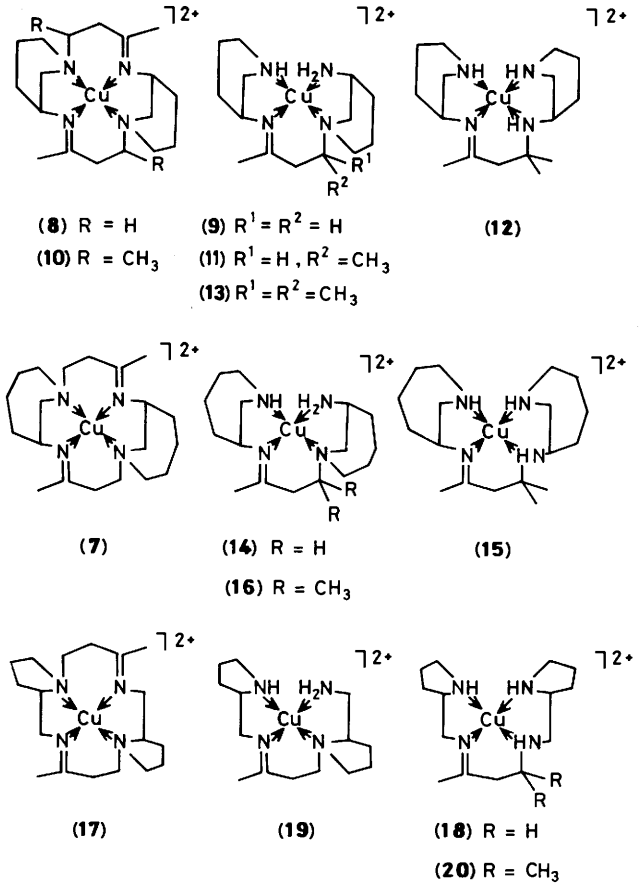


Figure 1. The structures of the isolated complexes

apip, ahaz, and ampr were carried out to examine the behaviour of the diamines in linkage formation. The reactions are found to give macrocyclic complexes (**I**) and their precursors (**II**), preferably. The tendency to form complexes with structures (**I**) and (**II**) indicates enhanced reactivity of the secondary amino groups. For apip and ahaz, the substituent at the secondary amino group necessarily takes an axial orientation upon co-ordination [Figure 2(*a*) and (*b*)].[10] For ampr, the N-substituent also tends to take an axial orientation due to the tendency of the C-substituent to take an equatorial orientation [Figure 2(*c*)]. These make the β carbon of the ketone molecule easier to approach and form the C–N bond at the secondary amino group.

The distribution of the reaction products between (**I**), (**II**), *vs.* (**III**), are, however, different for apip, ahaz, and ampr. In the case of $[Cu(apip)_2]^{2+}$ and $[Cu(ahaz)_2]^{2+}$, the macrocyclic complexes (**8**) and (**7**) were obtained in high yields. On the other hand, $[Cu(ampr)_2]^{2+}$ gave the macrocyclic complex (**17**) in a lower yield, and formed predominantly the open-chain tri-amino–imine complexes (**18**) and (**19**). It is evident that $[Cu(apip)_2]^{2+}$ and $[Cu(ahaz)_2]^{2+}$ only form complexes of structures (**I**) and (**II**), whose C–N linkages are formed between the β carbon of $CH_3COCH{=}CH_2$ and the secondary amino group of the diamine. On the contrary, $[Cu(ampr)_2]^{2+}$ forms all three types [(**I**), (**II**), (**III**)], indicating that the selectivity of C–N bond formation is lowered. The preference for C–N formation at the secondary amino group can be attributed to the difference in reactivity of the primary and secondary amino groups as nucleophiles. Nevertheless, the observed difference in selectivity between $[Cu(ampr)_2]^{2+}$ and $[Cu(apip)_2]^{2+}$ and $[Cu(ahaz)_2]^{2+}$ is striking, especially since all three complexes have one primary and one secondary amino groups in common, and do not appear to have differences which would give rise to such selectivity.

Table 2. Visible absorption and circular dichroism spectroscopic data for the complexes

		Visible		C.d.	
Complex	Structure	$\lambda_{max.}$/nm	ε*	$\lambda_{max.}$/nm	Δε*
(**8**)	(**I**)	506	206	492	+1.23
(**9**)	(**II**)	520	136	497	+1.30
(**10**)	(**I**)	506	176	488	+1.09
(**11**)	(**II**)	521	147	499	+1.42
(**13**)	(**II**)	521	112	494	+0.84
(**12**)	(**III**)	538	129	488	+0.36
				580	−0.35
(**7**)	(**I**)	508	192	479	+0.57
				549	−0.32
(**14**)	(**II**)	515	121	487	+0.93
				580	−0.30
(**16**)	(**II**)	517	95	485	+0.61
				580	−0.26
(**15**)	(**III**)	529	97	483	+0.28
				575	−0.50
(**17**)	(**I**)	526	223	504	−1.03
(**19**)	(**II**)	538	134	500	−0.41
				610	+0.10
(**18**)	(**III**)	530	94	505	−0.22
				585	+0.26
(**20**)	(**III**)	533	132	513	−0.02
				587	+0.06

* In $dm^3\ mol^{-1}\ cm^{-1}$

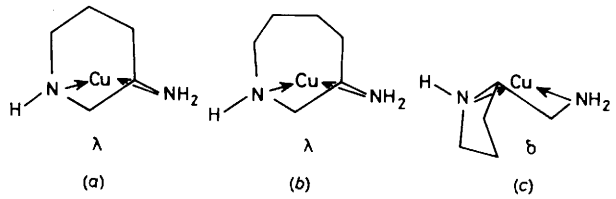


Figure 2. Structures of co-ordinating ligands: (*a*) (3*S*)-3-aminopiperidine; (*b*) (3*S*)-3-aminohexahydroazepine; (*c*) (2*S*)-2-(aminomethyl)pyrrolidine

A significant difference may arise when these diamines co-ordinate to copper(II) in the presence of ammonia used as a catalyst. The absorption maxima of $[Cu(apip)_2][ClO_4]_2$ in methanol shifted from 533 nm (violet) to *ca.* 620 nm (blue) by introducing ammonia into the solution. Similar colour changes were observed for $[Cu(ampr)_2]^{2+}$ and $[Cu(ahaz)_2]^{2+}$. Figure 3 shows the assumed structures in solution (structures of the ahaz complexes are omitted as they are analogous to the apip complexes). With regard to the apip and ahaz complexes [Figure 3(*a*)], it is clear that the major species in solution adopts the five-co-ordinate *trans* form, since the six- or seven-membered rings of the co-ordinating diamines sterically hinder one of the apical sites of Cu^{2+} and inhibit the formation of six-co-ordinate species. This is supported by the existence of the five-co-ordinate ahaz complex, $[Cu(ahaz)_2Br]ClO_4$, the structure of which has been established by an *X*-ray crystallographic study.[10]

It is reasonably assumed that (**I**) and (**II**) are derived from the five-co-ordinate *trans* form, and (**III**) from the *cis* form. Therefore, the reactions of $[Cu(apip)_2]^{2+}$ and $[Cu(ahaz)_2]^{2+}$

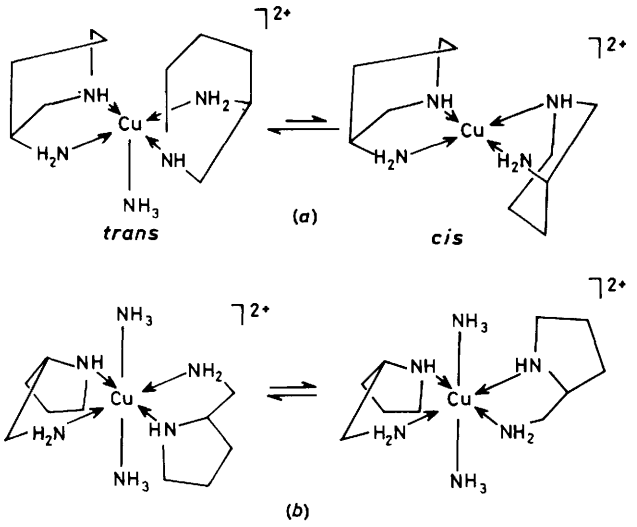


Figure 3. The structures of (*a*) $[Cu(apip)_2]^{2+}$ and (*b*) $[Cu(ampr)_2]^{2+}$ in ammonia saturated methanol solution

seem to proceed through the dominant *trans* species to give rise to complexes with structures (**I**) and (**II**).

For $[Cu(ampr)_2]^{2+}$, however, the steric regulation mentioned above is considered to be weak in comparison with $[Cu(apip)_2]^{2+}$ and $[Cu(ahaz)_2]^{2+}$. It should be noted that two *trans*-$(NO_2)_2$ isomers of $[Co(ampr)_2(NO_2)_2]^+$, in which the diamines take the *cis* and *trans* disposition, have been isolated.[11] This implies that an equilibrium exists between the *cis* and *trans* disposition for ampr in the six-co-ordinate complex *trans*-$[Cu(ampr)_2(NH_3)_2]^{2+}$ as shown in Figure 3(*b*). Although the distribution between these two isomers is not clear, the selectivity for C–N bond formation should be lowered to give all three categories of complexes. Thus we can conclude that the selectivity for reactions with $CH_3COCH{=}CH_2$ reflects the geometrical restrictions of the copper(II) complexes in solution.

Reactions of $[Cu(apip)_2]^{2+}$ *with several Alk-3-en-2-ones and 4-Hydroxyalkan-2-ones: Effects of β-Substituent(s) on Reactivity.*—As discussed in the preceding section, the macrocyclic complex (**8**) is formed selectively in the reaction of $[Cu(apip)_2]^{2+}$ with $CH_3COCH{=}CH_2$. However, the reactivity and selectivity will be affected by substituents introduced at the β position of the ketones.[7]

When one methyl group is introduced (*i.e.* $CH_3COCH{=}CHCH_3$) the yield of (**I**) decreases, while that of (**II**) increases. A similar tendency is observed for the reaction with $CH_3COCH_2CH_2OH$, having OH as a substituent at β position, and also for $CH_3COCH_2CH(CH_3)OH$ with an additional methyl group. The reaction to form the C–N single bond is considered to be a Michael addition for the alk-3-en-2-ones, and S_N2 type substitution for the 4-hydroxyalkan-2-ones. The difference between these two types of ketones was revealed by their reactivity; the former reacted faster than the latter. With regard to C–N bond formation, however, $CH_3COCH{=}CH_2$, $CH_3COCH{=}CHCH_3$, $CH_3COCH_2CH_2OH$, and $CH_3COCH_2CH(CH_3)OH$ react selectively at the secondary amino group of apip. The preference for forming (**II**) instead of (**I**) is due to the reduced reactivity of the ketones substituted by methyl and/or hydroxyl groups at the β position.

When two methyl groups are introduced [$CH_3COCH{=}C(CH_3)_2$ or $CH_3COCH_2C(CH_3)_2OH$], however, the reactivity is significantly lowered, and the selectivity of C–N bond formation disappears. The major product in this reaction is a blue complex, (**Y**), which is assumed to be a reaction product of one molecule each of apip, ketone, and ammonia, on the basis of elemental analysis, visible absorption, c.d., and i.r. spectral data. The optical activity indicates the presence of an apip moiety, and the presence of C=N and NH_2 groups is shown by i.r. spectroscopy.

The reason for such a distinct change brought about by the introduction of the second methyl group can be attributed to steric repulsion between two adjacent methyl groups and a diamine. When the β position of a ketone is fully substituted, as in the case of $CH_3COCH{=}C(CH_3)_2$ and $CH_3COCH_2C(CH_3)_2OH$, the approach of the β carbon to the secondary amino group of a diamine seems to be strongly disturbed. This should result in a low yield of a complex of structure (**II**). The steric repulsion appears to be weakened when one of the methyl groups is removed. On the other hand, the low yield of the type (**III**) complex can be attributed to the low population of *cis*-$[Cu(apip)_2]^{2+}$, the precursor of (**III**), although C–N bond formation would proceed more smoothly at a primary amino group.

Steric repulsions in the *trans* isomer and the low population of the *cis* isomer are responsible for the significantly retarded reaction of $CH_3COCH{=}C(CH_3)_2$ or $CH_3COCH_2C(CH_3)_2OH$ with the second diamine. Thus, ammonia whose nucleophilicity is rather poor but has less steric bulkiness, competes with a diamine in forming the C–N bond at the β carbon and gives the blue complex (**Y**) containing an ammonia moiety.

Reaction Products of $[Cu(ampr)_2]^{2+}$ *with* $CH_3COCH_2C(CH_3)_2OH$.—The previous discussion shows that $CH_3COCH_2C(CH_3)_2OH$ has the poorest reactivity on account of the steric repulsion brought about by the full substitution at the β position. The yields of type (**II**) and (**III**) complexes for $[Cu(apip)_2]^{2+}$ and $[Cu(ahaz)_2]^{2+}$ are, thus, very low. However, the reaction of $[Cu(ampr)_2]^{2+}$ proceeds selectively to give (**20**), a complex of structure (**III**), in a yield of 80%. This indicates that the formation of the type (**III**) complex in the reaction of $[Cu(ampr)_2]^{2+}$ is not prevented even though the β carbon of the ketone is fully substituted; in contrast the formation of the type (**II**) complex is strictly inhibited.

The regulation of relative configuration (*trans* over *cis*) of the co-ordinating diamines [Figure 3(*a*)] was the major inhibiting factor for the formation of (**III**) with $[Cu(apip)_2]^{2+}$ and $[Cu(ahaz)_2]^{2+}$. This factor can be neglected in the case of $[Cu(ampr)_2]^{2+}$ since the population of the *cis* and *trans* isomers is considered to be comparable.[11] The steric repulsion which is the main factor for the inhibition of formation of (**II**) with $[Cu(apip)_2]^{2+}$ and $[Cu(ahaz)_2]^{2+}$ should still apply in the case of $[Cu(ampr)_2]^{2+}$. In *trans*-$[Cu(ampr)_2(NH_3)_2]^{2+}$ [Figure 3(*b*)], the precursor of (**II**), steric repulsion will exist between the N and C substituents and the methyl groups of the approaching ketone. On the other hand, the steric repulsion in *cis*-$[Cu(ampr)_2(NH_3)_2]^{2+}$ [Figure 3 (*b*)], the precursor of (**III**), is small compared to the *trans* isomer because the pyrrolidine ring which contains C- and N-substituents is opposite the methyl groups of the approaching ketone. Thus complex (**20**), which has structure (**III**), is obtained selectively with a high yield (80%).

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