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Synthesis and Complex Formation of 2-Aminoethylthioacet(*N*-2-pyridylmethyl)amide

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Summary

A new ligand, 2-aminoethylthioacet(*N*-2-pyridylmethyl)-amide was synthesized. The complex formation of the ligand with Cu^{II}, Co^{II} and Co^{III} ions and that of the carbobenzoxy derivative of the ligand with Cu^{II} ions has been investigated. Structures are proposed for all complexes isolated and the factors influencing metal-sulphur bond formation in the complexes discussed.

Introduction

The previous paper(1) showed that the sulphur atom in thiodiaceticacid-bis(2-pyridylmethyl)amide does not participate in complex formation with transition metals. The same result was obtained also for complexes with bis(2-picolinoyl-aminoethyl)sulphide(2) where the relative position of the sulphur atom is similar. The fact that sulphur-metal bond formation occurs in transition metal complexes of ligands such as 1,5-diamino-3-thiapentane(3) and 1,8-diamino-3,6-dithiaoctane(4), while no such bond forms in the above examples was ascribed to steric factors rather than to electronic ones.

To investigate the factors which may influence the formation of metal-sulphur bonds in such transition metal complexes, 2-aminoethylthioacet(*N*-2-pyridylmethyl)amide (*1*) was synthesized. As this compound contains both the terminal groups mentioned, one at each end of the molecule, it was expected to possess steric and electronic properties in between those of the two ligands referred to above.

Results and Discussion

The 2-aminoethylthioacet(*N*-2-pyridylmethyl)amide ligand (*1*) was synthesized from thioacetic acid. S-alkylation with 2-(*N*-carbobenzoxy)aminoethyl bromide (*2*) followed by esterification of 2-(*N*-carbobenzoxy)aminoethylthioacetic acid (*3*) with chloroacetonitrile gave cyanomethyl 2-(*N*-carbobenzoxy)amino ethylthioacetate (*4*). Conversion of this ester with (2-pyridylmethyl)amide into the (*N*-2-pyridylmethyl)amide (*5*) followed by hydrogenolysis, in presence of dry hydrogen halide, of the protective carbobenzoxy group(6), gave the ligand.

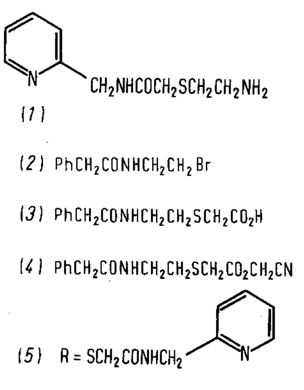

Figure 1. Route to the ligand.

The structures of the ligand and of all intermediates were elucidated by elemental analyses, u.v., i.r. and n.m.r. spectroscopy and by fragmentation patterns in the mass spectrum under electron impact.

The pK_a values of (*1*) were determined by potentiometric titration (Figure 2) as $pK_{a1} = 4.5$ and $pK_{a2} = 9.1$. These values are lower than the corresponding pK_a values of pyridine (5.2), ammonia (9.2) and methylamine (10.6), consequently the basicity of the ligand must be lower than that of the corresponding amine. This can be explained by the inductive effect of the arylaminomethyl substituent in the 2-position of the pyridine ring and by the vicinity of the sulphur atom to the aliphatic primary amino group.

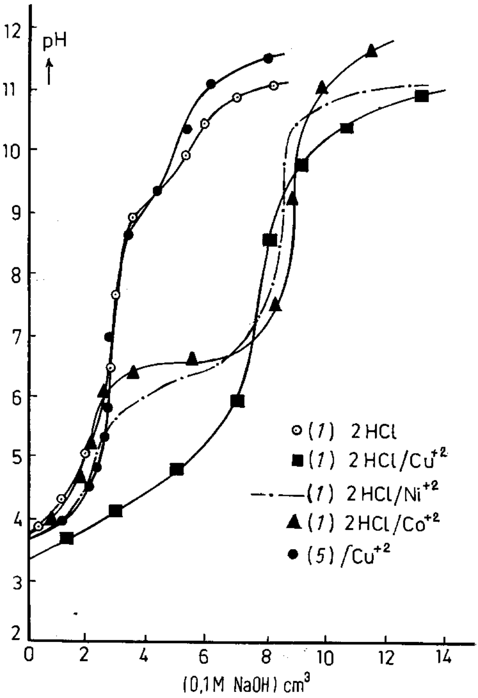

Figure 2. Potentiometric titration of the ligand (*1*), its carbobenzoxy derivative (*5*), and (*1*) in the presence of copper(II) and cobalt(II) ions.

Complexes of (*1*) with copper(II) and cobalt(II) were prepared in alcohol solutions as no solid product could be isolated from aqueous solutions at pH 7–8, the value shown by potentiometric titrations (Figure 2) to represent their optimum pH for complex formation. The same titration

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curves also indicate that the amide hydrogen is likely to be retained in the copper(II) complex (Figure 3) while in the cobalt(II) complex (Figure 4) it is likely to be lost due to cobalt-nitrogen bond formation, resulting in a lower net charge (+1) on the complex. An attempt to prepare a cobalt(II) complex in the presence of sodium nitrite, resulted in the formation of an octahedral nitrito-complex of cobalt(III) (Figure 5).

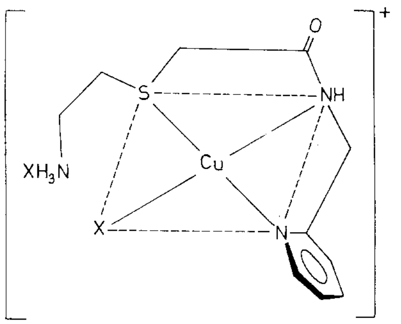

Figure 3. Cu^{II} complex of 2-aminoethylthioacet(*N*-2-pyridylmethyl)amide (X = Cl^- or Br^-).

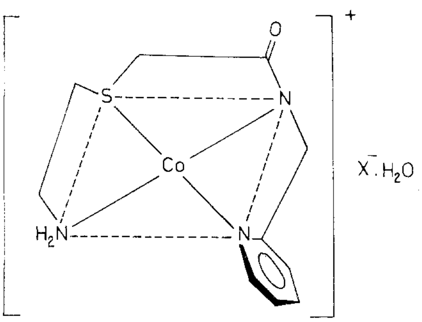

Figure 4. Co^{II} complex of 2-aminoethylthioacet (*N*-2-pyridylmethyl)amide (X = Cl^- or Br^-).

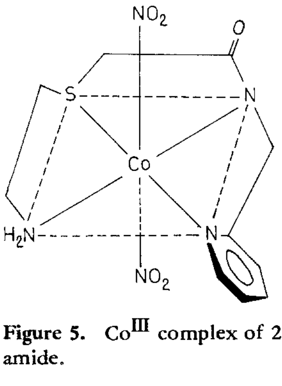

Figure 5. Co^{III} complex of 2-aminoethylthioacet (*N*-2-pyridylmethyl)amide.

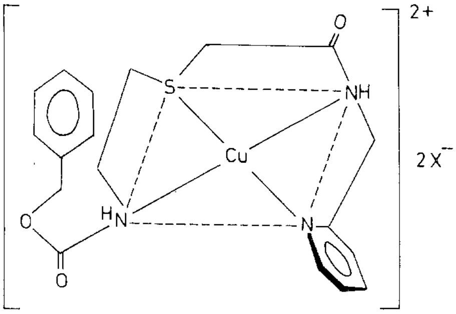

Figure 6. Cu^{II} diahalide complex of 2-(*N*-carbobenzoxy)aminoethylthioacet-(*N*-2-pyridylmethyl)amide (X = Cl^-or Br^-).

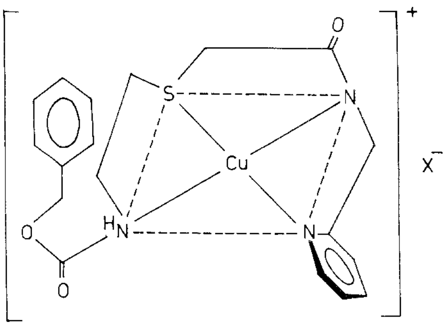

Figure 7. Cu^{II} mono halide complex of 2-(*N*-carbobenzoxy)aminoethylthioacet-(*N*-2-pyridylmethyl)amide (X^- = Cl^- or Br^-).

The carbobenzoxy derivative (*5*) of (*1*) is also capable of complex formation with copper(II). The complex (Figure 6) formed in alcoholic solution retains the amide hydrogen of (*5*).

However, if the above complex is dissolved in water and the pH of the solution is adjusted to 5.2, a new complex (Figure 7) is formed with the loss of the amide hydrogen closest to the pyridine ring.

All complexes show absorption at 1600–1610 cm^{-1} in the i.r. spectrum (KBr discs) characteristic of to the lactam carbonyl in transition metal complexes(7). In addition, the copper(II) complexes of (*5*) show a band also at 1695 cm^{-1} corresponding to the ester carbonyl, indicating that the carbobenzoxy group does not participate in the complex formation. The results obtained in this investigation show that the ability of the sulphur atom in 2-aminoethylthioacet-(*N*-2-pyridylmethyl)amide to form transition metal complexes lies in between that of the sulphur atom in 1,5-diamino-3-thiapentane(3) and in thioacetic acid-bis(2- in complex formation is influenced to a larger extent more by steric effects than by electronic ones.

The copper(II) complex of (*1*) does not involve the basic primary aliphatic nitrogen atom of the ligand in complex formation. Similar unusual results were found with diaminoglyoxime complexes of cobalt(II)(8) and more particularly of cobalt(III)(9), the structures of which have been established by x-ray crystallography.

Experimental

2(N-carbobenzoxy)aminoethylthioacetic acid (3)

Carbobenzoxy chloride (150 cm^3) was added slowly to a stirred solution of 2-bromoethylamine hydrobromide (205 g) in 4M NaOH (250 cm^3)(8). The solution was cooled in an ice bath, another 250 cm^3 of 4M NaOH was added dropwise, and stirred for a further 30 min. The precipitate formed was filtered and recrystallized from light petroleum to give the product (Yield 71%).

2-(N-carbobenzoxy)aminoethyl bromide (2)

This compound m.p. 43–44° was formed by dropwise addition of NaOH (68 g) in EtOH (400 cm^3) to an ice-cold stirred solution of (*2*) (129 g) and thioacetic acid (46 g) in EtOH (250 cm^3). The resulting solid was dissolved in H_2O and reprecipitated by acidification. Recrystallization from H_2O gave (*3*), m.p. 77–78° (Yield 85%). (Found: C, 53.7; H, 5.7; N, 5.1; S, 11.7. $C_{12}H_{15}O_4NS$ calcd.: C, 53.5; H, 5.6; N, 5.2; S, 11.9%).

Cyanomethyl-2-(N-carbobenzoxy)aminoethylthioacetate (4)

Chloroacetonitrile (38.2 cm^3) was added dropwise to a cooled and stirred solution of (*3*) (53.8 g) in NEt_3 (42 cm^3)(9). After completion of the addition the reaction mixture was warmed to and maintained at 70° for 2 h. Removal of NEt_3 *in vacuo* left a residue which was extracted with AcOEt. The extract was washed first with dil. HCl then thrice with saturated $NaHCO_3$ solution and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave (*4*) as a reddish viscous oil (Yield 77%) which was used without further purification for the next step.

2-(N-carbobenzoxy)aminoethylthioacet(N-2-pyridylmethyl)-amide (5)

2-Picolylamine (10.8 g) was added slowly to a stirred solution of (*4*) (30.8 g) in Et_2O (300 cm^3) and stirring was continued for 2 h(5). The precipitate formed was recrystallized from 19:1 Et_2O:EtOH to give colourless needles of (*5*), m.p. 65° (68% Yield). (Found: C, 60.1; H, 6.1; N, 11.5; S, 8.8. $C_{18}H_{21}N_3O_3S$ calcd.: C, 60.15; H, 5.9; N, 11.7; S, 8.9%.) N.m.r. ($CDCl_3$): δ 2.1 (2Ht, $S\underline{CH_2}CH_2$); δ 2.6 (2Hs, $Cp\underline{CH_2}S$; δ 2.7 (2Hm $NH\underline{CH_2}CH_2$, collapses to a t on D_2O exchange; δ 3.9 (2Hd, picolyl, collapses, to a s on D_2O exchange); δ 4.5 (2Hs benzyl); δ 5.6 (1Hbr, NH, disappears on D_2O exchange); δ 7.6 (1Hbr, NH, disappears on D_2O exchange); δ 6.7–8 (9H, phenyl and pyridyl).

The mass spectrum shows the molecular ion, M$^+$, at m/e 359 (15%) the base peak at m/e 150, $[PyCH_2NC(OH):CH_2]^+$ (McLafferty rearangement) and other significant peaks at m/e 107 (98%) $[Py{-}CH{=}NH_2]^+$; 135 (80%) ($150{-}CH_3$); 92 (95%) picolyl; 91 (95%) benzyl; 65 (75%) benzyl–C_2H_2.

2-Aminoethylthioacet(N-2-pyridylmethyl)amide (5)

The carbobenzoxy derivate (*5*) (22 g) was hydrogenolysed(6) at room temperature in glacial HOAc (300 cm^3) in presence of 10% Pd:C (1.5 g) by passing a mixture of dry H_2 and HBr gases through the solution for 15 days. Fresh catalyst (1 g) was added at 3 day intervals. After CO_2 evolution ceased, indicating completion of the reaction, the precipitate together with the catalyst, was filtered. The crude product was extracted from this solid by hot MeOH from which it was recovered by precipitation with Et_2O. Recrystallization from anhydrous EtOH gave colourless needles of the *dihydrobromide salt* of (*1*), m.p. 155° (Yield 43%). (Found: C, 31.2; H, 4.4; N, 10.95; S, 8.2; Br, 41.5. $C_{10}H_{17}Br_2N_3OS$ calcd.: C, 31.0; H, 4.4; N, 10.85; S, 8.3; Br, 41.3%).

The *dihydrochloride salt* of (*1*), m.p. 162° (Yield 40%), was prepared by the above method using HCl instead of HBr gas. (Found: C, 40.3; H, 5.7; N, 14.3; S, 10.5; Cl, 23.7. $C_{10}H_{17}Cl_2N_3OS$ calcd.: C, 40.3; H, 5.7; N, 14.1; S, 10.75; Cl, 23.8%).

The free base (*1*), was prepared by neutralizing a MeOH solution of either salts with an equivalent of solid NaOH, evaporating the solution to dryness and extracting the base from residue with CH_2Cl_2. Evaporating of the solvent gave (*1*) as a yellowish viscous oil which could not be crystallized.

N.m.r. ($CDCl_3$): δ 2.4 (2Hs NH_2 disappears on D_2O exchange); δ 2.6–3.0 (4Hm ethylene); δ 3.3 (2Hs $CO\underline{CH_2}S$; δ 4.6 (2Hd picolyl, collapses to a s on D_2O exchange); δ 7.2–8.6 (4H Pyridyl); δ 8.4 (1Hbr, NH). The mass spectrum shows the molecular ion, M$^+$, at m/e 225 (5%), the base peak at m/e 150, $[PyCH_2NHC(OH){=}CH_2]^+$. (McLafferty rearrangement) and other significant peaks at m/e 107 (98%) $[Py{-}CH{=}NH_2]^+$; 92 (90%) picolyl; 30 (80%) $[CH_2{=}NH_2]^+$.

Chloro-2-aminoethylthioacet(N-2-pyridylmethyl)amido-copper(II) chloride hydrochloride

To a stirred solution of (*1*) ·2 HCl (0.298 g) in EtOH (40 cm^3), $CuCl_2 \cdot 2H_2O$ (0.17 g) in EtOH (20 cm^3) was added and the mixture stirred for 45 min. The crystals which separated were filtered and recrystallized from 9:1 EtOH:H_2O to give green crystals of the complex, m.p. 141° (Yield 50%) (Figure 3). (Found: C, 30.0; H, 3.75; N, 10.8; S, 8.4; Cl, 26.4; Cu, 16.1. $C_{10}H_{16}Cl_3CuN_3OS$ calcd.: C, 30.1; H, 4.1; N, 10.1; S, 8.1; Cl, 26.8; Cu, 16.0%).

2-Aminoethylthioacet(N-2-pyridylmethylamidocobalt(II)-bromide, hydrate

A stirred solution of (*1*) · 2 HBr (0.387 g) in EtOH (20 cm^3) was neutralized with equivalent amount of solid NaOH, then $CoCl_2 \cdot 6H_2O$ (0.298 g) in EtOH (10 cm^3) was added. Precipitation of crystals was immediate. After 5 min stirring they were filtered and recrystallized from EtOH to give red crystals of the complex, m.p. 208° (Yield 40%). (Found: C, 31.15; H, 4.0; N, 10.7; S, 8.5; Br, 20.7; Co, 15.0. $C_{10}H_{16}BrCoN_3O_2$ calcd.: C, 31.5; H, 4.2; N, 11.0; S, 8.4; Br, 21.0; Co, 15.5%.)

Dinitro-2-aminoethylthioacet(N-2-pyridylmethyl)amido-cobalt(III)

$NaNO_2$ (0.365 g) was added in small portions to a stirred solution of (*1*), 2HCl (0.298 g) and $CoCl_2 \cdot 6H_2O$ (0.238 g) in 20:1 MeOH:H_2O (20 cm^3). Conc. HCl (0.165 cm^3) was then added and stirring was continued for 10 min. The crystals which formed were filtered, then recrystallized from 9:1 MeOH:H_2O to give the orange complex, m.p. 201° (Yield 24%) (Figure 5). (Found: C, 31.65; H, 3.7; N, 18.3; S, 8.3; Co, 15.1. $C_{10}H_{14}CON_5O_5S$ calcd.: C, 32.0; H, 3.8; N, 18.7; S, 8.5; Co, 15.7%).

2-(N-carbobenzoxy)aminoethylthioacet(N-2-pyridylmethyl)-amidocopper(II) dichloride

$CuCl_2 \cdot 2H_2O$ (0.341 g) in EtOH (20 cm^3) was added to a stirred solution of (*5*) (0.718 g) in EtOH (40 cm^3). After 30 min. the crystals which formed were filtered and recrystallized from 20:1 EtOH:H_2O to give green crystals of the complex, m.p. 177° (Yield 70%) (Figure 6). (Found: C, 43.2; H, 4.0; N, 8.1; S, 6.0; Cl, 13.0; Cu, 12.0. $C_{18}H_{21}Cl_2CuN_3O_3S$ calcd.: C, 43.8; H, 4.3; N, 8.5; S, 6.5; Cl, 14.4; Cu, 12.9%).

2-(N-carbobenzoxy)aminoethylthioacet(N-2-pyridylmethyl)-amidocopper(II) chloride

The previous complex (0.494 g) was dissolved in the minimum amount of H_2O and the pH of the solution was adjusted to 5.2. After standing overnight the blue crystals of the complex, m.p. 93°, separated in 50% yield (Figure 7). (Found: C, 47.1; H, 4.3; N, 9.2; S, 7.2; Cl, 7.7; Cu, 14.4. $C_{15}H_{20}ClCuO_3N_3S$ calcd.: C, 47.2; H, 4.4; N, 9.2; S, 7.0; Cl, 7.75; Cu, 13.9%).

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Equilibria in Complexes of *N*-Heterocyclic molecules, Part XXVI*. Reactions of Hydroxide and Water with the Tris-(2,2′-Bipyrazine)Iron(II) and Tris-[2,2′-bis-(5,6-dihydro-4-H-1,3-oxazine)]iron(II) Ions

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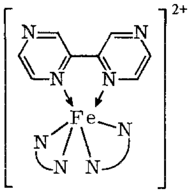
Summary

The reactions of $[Fe(bipyz)_3]^{2+}$ (bipyz = 2,2′-bipyrazine) and $[Fe(box)_3]^{2+}$ [box = 2,2′-bis-(5,6-dihydro-4-H-1,3-oxazine] with H_2O and HO^- in aqueous solution have been followed. The $[Fe(bipyz)_3]^{2+}$ ion is attacked at the ligand with both nucleophiles and the ligand is cleaved. A similar reaction between HO^- and $[Fe(box)_3]^{2+}$ is observed. Detailed kinetics for all reactions are reported.

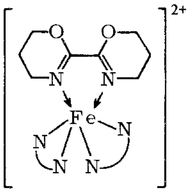
Introduction

Reactions of nucleophiles with coordinated *N*-heterocyclic ligands such as phen and bipy*** have been shown(1) to be common in the chemistry of such systems. However, as we have pointed out recently(2), the magnitude of the equilibrium constants for such interactions varies considerably. This is exemplified by the fact that Ru^{II} complexes of phen and bipy are very stable, even in concentrated basic solution. In an effort to cast some light upon reactions of these ligands with nucleophiles to form covalently-hydrated and pseudobase species, we have turned our attention to complexes containing multi-aza *N*-heterocyclic ligands such as bipym(2). Furthermore, Burgess and co-workers(3–5) have discussed recently at length the role that analogous reactions play in the chemistry of Schiff-base complexes of the first row transition metals. The ligands involved in these cases are related to phen and bipy in the sense that the diimine moiety is retained.

We have examined the reactions of HO^- and H_2O with the tris-(2,2′-bipyrazine)iron(II), $[Fe(bipyz)_3]^{2+}$ *(1)*, and tris-[2,2′-bis-(5,6-dihydro-4-H-1,3-oxazine)]iron(II), $[Fe(box)_3]^{2+}$ *(2)*, ions. Our results are presented below.



(1)



(2)

Experimental

Bipyz and box were prepared using known methods(6, 7). Slightly better yields of bipyz could be obtained by pyrolysing the cupric salt intermediate at a pressure of *ca.* 10 kNm^{-2}. $Fe(box)_3(ClO_4)_2 \cdot H_2O$ was prepared in the following way. Box (0.505 g, 3 mmole) was added to an aqueous solution (20 cm^3) of $FeSO_4 \cdot 7\ H_2O$ (0.28 g, 1 mmole). A deep-red solution was obtained. To this solution was added solid $NaClO_4$, with stirring, and the perchlorate salt slowly crystallized in small plates. The product was collected at the pump, washed with small amounts of ice-cold H_2O, MeOH and Et_2O then dried *in vacuo*. Water analyses were performed using a Stanton Redcroft TG 750 temperature programmed thermogravimetric balance. (Found: C, 37.6; H, 4.9; N, 11.0; H_2O, 3.0; $C_{24}H_{38}N_6O_{15}Cl_2Fe$ calcd: C, 37.1; H, 4.9; N, 10.8; H_2O, 2.3%). $Fe(bipyz)_3(ClO_4)_2 \cdot 4H_2O$ was synthesised in a similar way. To an aqueous solution (10 cm^3) of $FeSO_4 \cdot 7\ H_2O$ (0.185 g, 0.67 mmole) was added a cold MeOH solution of bipyz (0.32 g, 2 mmole; total vol. 50 cm^3). With gentle warming a deep-red solution was obtained. This solution was filtered, saturated with $NaClO_4$ and the red precipitate was collected at the pump, washed with ice-cold H_2O (5 cm^3) and ice-cold MeOH (10 cm^3). The solid was dried *in vacuo* over silica gel. (Found: C, 36.6; H, 3.2;

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*** phen = 1,10-phenanthroline; bipy = 2,2′-bipyridyl; bipym = 2,2′-bipyrimidine.

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