Tuning of N_2S_2 ligands in view of further applications in nuclear medicine: crystal structure of Ni^{II} and Cu^{II} complexes and first results concerning their stabilities

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Structural analyses of nickel and copper complexes obtained from N_2S_2 tetradentate ligands of the bis(enaminodithioester) type demonstrate the obtention of square planar complexes using the ligand derived from ethylenediamine (**1a**, **1b**) while a flattened tetrahedral structure was obtained for the copper complex **2b** using the ligand derived from 1,3-diaminopropan-2-ol. For complexes **1b** and **2b**, the bond lengths around the metal appear to be nearly unaffected by the nature of the ligand contrasted with the difference in the angles (shift from a square planar structure to a flattened tetrahedral one with increasing flexibility of the ligand). The kinetic and thermodynamic stabilities of the copper complexes **1b** and **2b** were roughly evaluated on the basis of transchelation experiments, competitive complexation experiments and electrochemical studies.

Adaptation de ligands N_2S_2 tetradentés en vue d'applications en médecine nucléaire: structure radiocristallographique de complexes de Ni^{II} et Cu^{II} et premiers résultats concernant leurs stabilités. L'étude structurale de complexes de nickel et de cuivre obtenus à partir de ligands N_2S_2 tetradentés du type bis(énaminodithioester) demontre l'obtention de complexes plan carré légèrement déformés lorsque l'on utilise des ligands dérivant de l'éthylènediamine (**1a**, **1b**) alors que le complexe du cuivre **2b** obtenu à partir d'un ligand dérivant du 1,3-diaminopropan-2-ol présente une structure de type tétraèdre aplati. Pour les complexes du cuivre **1b** et **2b**, les longueurs de liaison autour du métal apparaissent peu affectées par la nature du ligand à la différence des angles (évolution de plan carré vers tétraèdre aplati lorsque le ligand devient plus flexible). Les stabilités cinétiques et thermodynamiques des complexes du cuivre **1b** et **2b** ont été grossièrement évaluées à partir d'expériences de transchélation et de complexation compétitive ainsi que sur la base d'études électrochimiques.

We have recently obtained N_2S_2 tetradentate ligands of potential interest in nuclear medicine by reacting diamines with 3-methylthio-1,2-dithiolylium iodides.[1] The interest of the method lies in the fact that functionalized linkers bearing an *N*-hydroxysuccinimidyl ester group (NHS) can be easily attached to the ligand obtained from 1,3-diaminopropan-2-ol,[1] allowing further grafting on monoclonal antibodies able to recognize tumor cells and to vectorize radionuclides useful in immunoscintigraphy (IS) and in radioimmunotherapy (RIT).[2] Our initial experiments concerning complexation of ^{99}Tc as a $Tc^{V}N$ core by this ligand have led to several complexes,[3] while a similar N_2S_2 ligand derived from ethylenediamine was known to give cleanly a complex having a square pyramidal structure.[4] At this stage and due to the above difficulties, we decided to focus our studies on radionuclides having potential interest for RIT. Among the possible radionuclides, ^{67}Cu ($T_{\frac{1}{2}} = 2.576$ d) and ^{64}Cu ($T_{\frac{1}{2}} = 12.8$ h) appear to be interesting candidates since ^{67}Cu exhibits both β^- and γ emissions, allowing RIT and IS, while ^{64}Cu is a potential tool for positron emission tomography.[5]

However, before attempting experiments on radionuclides, we considered it of interest to examine the size of the chelating cavity on the structure of the complex since it appears possible to use ligands obtained directly from 1,3-diaminopropan-2-ol or from less accessible functionalized ethylenediamine derivatives[6] in order to have a convenient linker to bind the monoclonal antibody.

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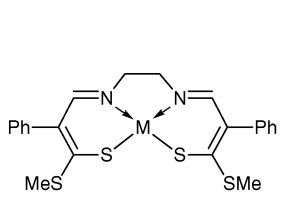
Results and Discussion

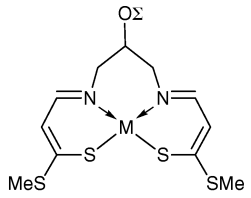
We decided to evaluate both the influence of the metal and ligand, and for this purpose, we examined complexes of copper derived from 1,2- and 1,3-diamines in comparison with those of nickel (Scheme 1).

These complexes **1a**,**b**,[7] **2a**,**b** and **2c**,**d** were obtained by reaction of the bis(enaminodithioester) ligands with Cu^{II} or Ni^{II} acetates in a chloroform–methanol mixture and isolated by chromatography on silica gel. The choice of the comparison between Cu^{II} and Ni^{II} complexes is justified by the similar size of these two elements (0.63 Å for Ni^{II} *versus* 0.71 Å for Cu^{II} in a square planar environment[8]), by their nearly identical complexation constant with EDTA[9] and by the fact that high resolution NMR studies are possible with Ni^{II} complexes while broad signals were obtained with Cu^{II}.

On the basis of the behaviour of these two elements in coordination chemistry, one can expect square planar complexes with nickel[8] while structures of copper complexes are less easy



1a, M = Ni, 81% yield
1b, M = Cu, 80% yield



2a, Σ = Ac, M = Ni, 84% yield
2b, Σ = Ac, M = Cu, 85% yield
2c, Σ = -CO-$(CH_2)_2$-COONHS, M = Cu, 68% yield
2d, Σ = -CO-$(CH_2)_2$-COONHS, M = Ni, 62% yield

Scheme 1

to predict since planar environments (eventually with orthogonal anionic ligands) or tetrahedral environments have been observed.[10] In our case, due to the relative propensity of copper to adopt a tetrahedral environment, the nature of the ligand might have a crucial influence on the geometry of the complexes and subsequently on their stability since larger distorsions from the plane can be accepted in ligands obtained from 1,3-diamines (type **2** complexes).

In order to obtain answers to these questions, we performed a crystal structural analysis of the complexes (the crystals were obtained by vapor diffusion methods from a 1 : 1 toluene–CH_2Cl_2 mixture). Complex **1a** (M = Ni), obtained as green-yellow needles, and complex **1b** (M = Cu), obtained as brown crystals, have a slightly distorted planar structure around the metal with phenyl rings out of the core plane by 73° (Ni) and 72° (Cu) for the C_9–C_{14} ring and by 63° (Ni) and 62° (Cu) for the $C_{9'}$–$C_{14'}$ ring (Fig. 1).

Complex **2a** (M = Ni) was obtained as an amorphous green powder but its NMR spectrum was consistent with a planar structure in solution (same chemical shifts and coupling constants for each couple of diastereotopic hydrogens on both branches of the ligand). Finally, complex **2b** (M = Cu), obtained as brown crystals, appears to have a flattened tetrahedral structure around the metal with a N—Cu—S 'diagonal' angle of about 150° (Fig. 2).

A comparison of the core of the complexes **1a**, **1b** and **2b** indicates a delocalization of the electrons along the N_2—C_3—C_4—C_5—S_8 arm, with a strong imino character in the complexes: N_2—$C_3 \approx 130$ pm, C_3—$C_4 \approx 143$ pm,

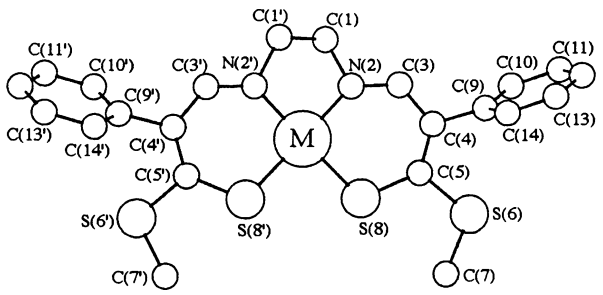


Fig. 1 Molecular structure for **1a** (M = Ni, hydrogens are omitted for clarity). Selected bond lengths/Å: Ni—S(8) 2.160(1), Ni—S(8′) 2.172(1), Ni—N(2) 1.875(2), Ni—N(2′) 1.876(2), N(2)—C(3) 1.310(3), N(2′)—C(3′) 1.301(3), C(3)—C(4) 1.415(4), C(3′)—C(4′) 1.423(4), C(4)—C(5) 1.375(4), C(4′)—C(5′) 1.360(4), C(5′)—S(8′) 1.717(3), C(5)—S(8) 1.708(3). Selected angles/°: N(2)—Ni—N(2′) 86.1(1), N(2′)—Ni—S(8′) 94.7(1), N(2)—Ni—S(8) 95.7(1), S(8)—Ni—S(8′) 83.8(1), N(2′)—Ni—S(8) 174.0(1), N(2)—Ni—S(8′) 176.5(1). Molecular structure for **1b** (M = Cu, hydrogens are omitted for clarity). Selected bond lengths/Å: Cu—S(8) 2.241(1), Cu—S(8′) 2.251(1), Cu—N(2) 1.949(3), Cu—N(2′) 1.953(3), N(2)—C(3) 1.304(4), N(2′)—C(3′) 1.297(4), C(3)—C(4) 1.412(5), C(3′)—C(4′) 1.426(4), C(4)—C(5) 1.377(5), C(4′)—C(5′) 1.373(5), C(5′)—S(8′) 1.715(3), C(5)—S(8) 1.711(3). Selected angles/°: N(2)—Cu—N(2′) 84.8(1), N(2′)—Cu—S(8′) 94.1(1), N(2)—Cu—S(8) 94.9(1), S(8)—Cu—S(8′) 87.0(1), N(2′)—Cu—S(8) 172.3(1), N(2)—Cu—S(8′) 173.7(1)

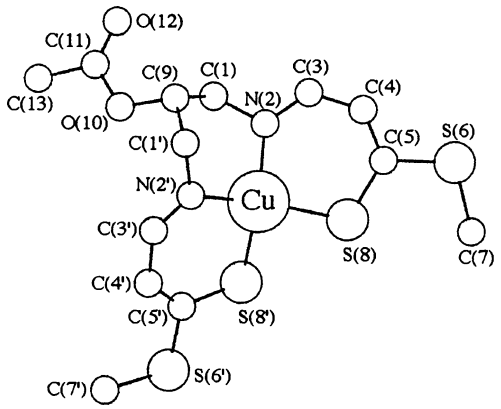


Fig. 2 Molecular structure for **2b** (hydrogens are omitted for clarity). Selected bond lengths/Å: Cu—S(8) 2.230(1), Cu—S(8′) 2.246(1), Cu—N(2) 1.971(3), Cu—N(2′) 1.947(3), N(2)—C(3) 1.277(4), N(2′)—C(3′) 1.318(5), C(3)—C(4) 1.428(4), C(3′)—C(4′) 1.406(5), C(4)—C(5) 1.358(5), C(4′)—C(5′) 1.360(5), C(5)—S(8) 1.708(3), C(5′)—S(8′) 1.711(4). Selected angles/°: S(8)—Cu—S(8′) 89.1(1), N(2)—Cu—S(8) 96.9(1), N(2′)—Cu—S(8′) 97.0(1), N(2)—Cu—N(2′) 92.3(1), N(2)—Cu—S(8′) 150.4 (1), S(8)—Cu—N(2′) 149.61

C_4—$C_5 \approx 137$ pm and C_5—$S_8 \approx 171$ pm. The usual values are considered to be near 136 pm for C_{sp_2}—N bonds compared to 128 pm for C=N bonds.[11] Similarly, the C—S bonds appear to have a higher resemblance with a C_{sp_2}—S bond than with a C=S one, this general trend being also in agreement with the length of the C—C bonds in this linkage. Concerning the close environment of the core, shorter bond lengths are observed for N—Ni (≈188 pm) and for Ni—S (≈217 pm) in **1a** compared with the bond lengths in the copper complexes **1b** and **2b** (N—Cu ≈ 197 pm and Cu—S ≈ 224 pm),[12] in agreement with the difference of the size of the cations in a square planar environment.[8] It is worth noticing that the higher distortion from the plane in complex **2b** compared to **1b** has no meaningful incidence on the bond lengths between the ligand and the metal, the modification of the angles allowing nearly identical bond lengths to be kept. In other words, it suggests that the stability of the complexes **1b** and **2b** might be expected to be similar, the higher adaptability of the ligand derived from 1,3-diaminopropan-2-ol for complexes having a tetrahedral character like **2b** acting as a counterbalance when compared to the nearly planar structure for complexes like **1b** derived from ethylenediamine.

Therefore, in a first step, due to their easier access with an appropriate linker, ligands giving complexes of type **2** appear more attractive than ligands affording complexes of type **1**. For instance, the ligand used in **2c** was coupled to the OC 125 Fab'_2 monoclonal antibody fragment (1.2 ligands per antibody without modification of its immunoreactivity) using usual experimental conditions.[13]

Furthermore, upon treatment with a large excess of EDTA (100 equiv.) in an acetone–water mixture for 20 h at room temperature, complex **2b** is recovered in a nearly quantitative yield (≈93%). The reverse experiment using a EDTA–Cu complex and the ligand used for **2b** (50 equiv.) in similar experimental conditions (acetone–water, pH = 6)[14] exhibits also a low rate of transchelation (≈5%). This means that there is a reasonably high kinetic stability of the title complexes and suggests an activation energy for decomplexation of copper in **2b** close to that obtained for EDTA–Cu, if one considers the transchelation rates and the relative concentrations. Furthermore, a competitive complexation of copper by the ligand derived from 1,3-diaminopropan-2-ol (5 equiv.) and by EDTA (5 equiv., used as the disodium salt) in an acetone–water mixture was achieved by addition of copper acetate (1 equiv.) at pH 6. Under such experimental conditions the ratio of **2b** : EDTA–Cu was 1 : 3, indicating a higher activation energy

(about 0.64 kcal mol^{-1} or 2.7 kJ mol^{-1}) for obtaining complex **2b**. Due to the uncertainty in the measurements of transchelation rates (weighing of **2b** after chromatography separation) the above results cannot be conclusive but demonstrate a fairly good kinetic stability for these complexes and suggest similar thermodynamic stabilities for both complexes.

Preliminary electrochemical studies were performed in order to obtain more information about the relative stabilities of complexes **1a**,**b** and **2a**,**b** using the Nernst equation according to an already described methodology[15] and assuming that in the case of reversible electrochemical systems the redox potentials measured electrochemically are equivalent to the thermodynamical potentials of the considered redox couples. As expected from already published results,[9] these experiments confirm the lower stability of **2a** (M = Ni) when compared to **1b** or **2b** (M = Cu), while discrimination between the two copper complexes is much more tedious. Due to the poor solubility of these complexes, experiments were done using DMSO as solvent but the degradation of the electrolyte/solvent system for high negative potentials prohibits the direct evaluation of the complexation constant and until now, only an approximate value ($\log K \approx 24.5$) has been obtained in DMSO for **1b**, and a value of $\log K$ above 24 for **2b** under similar experimental conditions.[16]

Conclusion

At this stage of our work, even if further studies are required to obtain a more accurate measurement of the complexation constants, it appears that complexes of type **1** (without phenyl substituents, but with an appropriate grafted linker on the ethylenediamine part) or of type **2** can be valuable ligands for further applications in nuclear medicine. The choice of the more appropriate ligand should be made taking into account the best compromise between the efficiency of the chelating structure and the nature of the grafted linker in terms of overall availability of the ligand–linker system (an argument highly favourable to **2c**) and of its *in vivo* biodegradability.

Experimental

All chemicals were of the highest commercially available purity. Solvents were purified by standard methods before use and stored on 0.3 nm molecular sieves. Glassware was washed with 3M HCl (to avoid free-metal contamination) and dried in an oven. Ligands used in this work were obtained according to our previously described method.[1]

NMR spectra were recorded on Bruker AC 200 or AC 250 apparatus. Chemical shifts (δ) are given relative to Me_4Si used as internal standard, and coupling constants (J) are given in Hz. Multiplicities were recorded as s (singlet), d (doublet), t (triplet) and m (multiplet). EI or FAB^+ mass spectra were obtained respectively on an HP 5989A or a JEOL SX102 mass spectrometer using nitrobenzyl alcohol as matrix in the last case. Melting points taken on a 9200 electrothermal apparatus were uncorrected. IR spectra were recorded in KBr plates on an FTIR Mattson 1000 apparatus. Cu : S ratio were obtained on a JEOL JM-35C scanning electron microscope (SEM) fitted with a Tracor TN 5500 micro Z system.

Synthesis of compounds 1 and 2

In a typical experimental procedure, a solution of nickel or copper acetate (2 mmol) in methanol (40 ml) was added to a solution of ligand (2 mmol) in chloroform (20 ml). After 10 min at room temperature, the resulting solution was evaporated to dryness and purified by chromatography on silica gel (elution conditions are given for each case). The corresponding metallic complexes were obtained in 62 to 85% yield.

Compound 1a. The reaction was performed with 890 mg of ligand and 497 mg of $Ni(OAc)_2 \cdot 4H_2O$. After purification using methylene chloride as eluent, 810 mg of green-yellow needles were obtained (81% yield, mp = 318 °C). MS (FAB^+): m/z 501/503 (MH^+, 100/57). IR (KBr): 3060, 2947–2800, 1579 ν(C=C) and ν(C=N), 1490, 1445, 1343 ν(S−C), 1285, 1270, 944, 771, 709 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 2.54 (s, 6H, CH_3); 3.39 (m, 4H, CH_2); 7.20–7.60 (m, 10H, H ar.); 8.40 (s, 2H, =CH); ^{13}C NMR (200 MHz, $CDCl_3$): 17.2 (2C, SCH_3); 61.5 (2C, CH_2); 124.1 (2C, C_{IV}); 128.6–130.5 (10C, CH ar.); 140.0 (2C, C_{IV}); 153.9 (2C, =CH); 175.7 (2C, C−S).

Compound 1b. The reaction was performed with 890 mg of ligand and 400 mg of $Cu(OAc)_2 \cdot H_2O$. After purification using methylene chloride as eluent, 810 mg of brown crystals were obtained (80% yield, mp = 195 °C). MS (EI): m/z 505/507 ($M^{\cdot+}$, 46/34); 457/459 (19/17); 411/413 (15/9); 366/368 (15/7); 303 (40); 188 (100); 147 (33); 63/65 (19/11). IR (KBr): 3060–2850, 1585 ν(C=C) and ν(C=N); 1417, 1334 ν(S−C), 1274, 937, 803, 707 cm^{-1}. SEM: 1 Cu : 4 S.

Compound 2a. The reaction was performed with 729 mg of ligand and 497 mg of $Ni(OAc)_2 \cdot 4H_2O$. After purification using methylene chloride–ethyl acetate (9 : 1, v/v) as eluent, 724 mg of green-yellow powder were obtained (84% yield, mp = 134 °C). MS (FAB^+): m/z 421/423 (MH^+, 75/45); 420/422 ($M^{\cdot+}$, 100/76); 373/375 (29/18); 279 (5); 149 (35). IR (KBr): 2967–2865; 1729 ν(C=O), 1583 ν(C=C) and ν(C=N), 1488, 1349 ν(S−C) cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ 2.05 (s, 3H, CH_3); 2.50 (s, 6H, SCH_3); 3.49 (dd, 2 × 1H, CH_2N, $^2J_{1H} = 13.2$, $^3J_{1H} = 4.9$); 3.87 (dd, 2 × 1H, CH_2N, $^2J_{1H} = 13.2$, $^3J_{1H} = 6.1$); 5.01 (tt, 1H, CH, $^3J_{2H} = 4.9$, $^3J_{2H} = 6.1$); 6.00 (d, 2H, =CH, $^3J_{1H} = 6.0$); 6.85 (d, 2H, =CH, $^3J_{1H} = 6.0$); ^{13}C NMR (250 MHz, $CDCl_3$): 16.9 (2C, SCH_3); 21.2 (1C, CH_3); 60.0 (2C, CH_2N); 71.3 (1C, CHO); 110.1 (2C, =CH); 158.9 (2C, =CH); 167.9 (2C, C_{IV}); 170.2 (1C, C=O).

Compound 2b. The reaction was performed with 729 mg of ligand and 400 mg of $Cu(OAc)_2 \cdot H_2O$. After purification using methylene chloride–ethyl acetate (9 : 1, v/v) as eluent, 724 mg of brown crystals were obtained (85% yield, mp = 164 °C). MS (FAB^+): m/z 426/428 (MH^+, 100/62). MS (EI): m/z 425/427 ($M^{\cdot+}$, 53/33); 377/379 (21/14); 331/333 (17/8); 184 (42); 124 (60); 98 (100); 94 (34); 71 (39); 48 (54); 47 (73); 45 (58); 43 (36). IR (KBr): 2941–2857, 1731 ν(C=O), 1593 ν(C=C) and ν(C=N), 1487, 1348 ν(S−C) cm^{-1}.

Compound 2c. The reaction was performed with 1038 mg of ligand[1] and 400 mg of $Cu(OAc)_2 \cdot H_2O$. After purification using methylene chloride–ethyl acetate (9 : 1, v/v) as eluent, 789 mg of brown powder were obtained (68% yield, mp = 116 °C). MS (FAB^+): m/z = 581/583 (MH^+, 4/2); 580/582 ($M^{\cdot+}$, 5/3); 486/488 (4/2); 391 (16); 279 (8); 167 (21); 149 (100); 113 (18). IR (KBr): 2956–2863, 1742 and 1717 ν(C=O) broad bands; 1589 ν(C=C) and ν(C=N), 1487, 1392 ν(S−C), 1292, 1205 cm^{-1}.

Compound 2d. The reaction was performed with 1038 mg of ligand[1] and 497 mg of $Ni(OAc)_2 \cdot H_2O$. After purification using methylene chloride–ethyl acetate (9 : 1, v/v) as eluent, 721 mg of green-black powder were obtained (62% yield, mp = 105 °C). MS (FAB^+): m/z 576/578 (MH^+, 82/57); 575/577 ($M^{\cdot+}$, 100/65); 528/530 (17/7). IR (KBr): 2981–2861, 1738 and 1715 ν(C=O) broad bands, 1589 ν(C=C) and ν(C=N), 1486, 1352 ν(S−C), 1205, 1081 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ 2.44 (s, 6H, SCH_3); 2.65 (m, 2H, CH_2); 2.78 (≈s, 4H, CH_2 from NHS); 2.87 (m, 2H, CH_2); 3.47 (dd, 2 × 1H, CH_2N, $^2J_{1H} = 13.2$, $^3J_{1H} = 4.8$); 3.80 (dd, 2 × 1H, CH_2N, $^2J_{1H} = 13.2$, $^3J_{1H} = 6.2$); 4.99 (tt, 1H, CH, $^3J_{2H} = 6.2$, $^3J_{2H} = 4.8$); 5.94 (d, 2H, =CH, $^3J_{1H} = 5.9$); 6.87 (d, 2H,

=CH, $^3J_{1H} = 5.9$); ^{13}C NMR (250 MHz, $CDCl_3$): 16.8 (2C, SCH_3); 25.6 (2C, CH_2 from NHS); 26.3 (1C, CH_2); 28.8 (1C, CH_2); 59.6 (2C, CH_2N); 72.1 (1C, CHO); 110.1 (2C, =CH); 159.1 (2C, =CH); 167.6 (2C, C_{IV}); 167.8 (2C, CO); 168.8 (1C, C=O); 170.2 (1C, C=O).

Crystal data for complexes 1a, 1b and 2b

1a and **1b** appear to be isomorphous. The replacement of Ni by Cu does not modify the basic crystal structure.

1a. $NiC_{22}H_{22}N_2S_4$, $M = 501.38$, thin green-yellow needles, monoclinic, space group $P2_1/c$, $a = 13.242(1)$, $b = 9.412(2)$, $c = 19.139(2)$ Å, $\beta = 109.75(1)°$, $U = 2245.1(5)$ Å^3 (by least-squares refinement on diffractometer angles from 25 centred reflections $20° \leqslant \theta \leqslant 35°$), $T = 293$ K, graphite-monochromated CuKα radiation, $\lambda = 1.54178$ Å, $Z = 4$, $D_c = 1.48$ Mg m^{-3}, crystal size $0.25 \times 0.05 \times 0.5$ mm^3, $\mu CuK\alpha = 38.85$ cm^{-1}, $F(000) = 1040$, semi-empirical absorption correction based on ψ scans, transmission factors 0.72–0.97, CAD4 Enraf-Nonius diffractometer, θ−ω scans, data collection range $1° \leqslant \theta \leqslant 60°$, three standard reflections showed no significant variation in intensity, 6603 reflections measured, 3254 unique ($R_{int} = 0.03$), which were used in all calculations. The structure was solved by Patterson methods and subsequent Fourier maps and refined anisotropically by full-matrix least-squares methods on F^2 (program SHELX 76),[17] hydrogen atoms were included in theoretical positions and refined isotropically. The weighting scheme was $w = 13.9406/\sigma^2(F_o) + 0.000204F_o^2$. The final wR was 0.038 with conventional $R = 0.033$ for 284 parameters, max. $\Delta/\sigma = 0.01$, max. $\Delta\rho = 0.2$ e Å^{-3}.

1b. $CuC_{22}H_{22}N_2S_4$, $M = 506.21$, thin dark brown needles, monoclinic, space group $P2_1/c$, $a = 13.329(1)$, $b = 9.445(1)$, $c = 19.107(3)$ Å, $\beta = 109.74(1)°$, $U = 2264.1(5)$ Å^3, $T = 293$ K, graphite-monochromated CuKα radiation, $\lambda = 1.54178$ Å, $Z = 4$, $D_c = 1.485$ Mg m^{-3}, crystal size $0.025 \times 0.1 \times 0.6$ mm^3, $\mu CuK\alpha = 38.73$ cm^{-1}, $F(000) = 1044$, semi-empirical absorption correction based on ψ scans, transmission factors 0.61–0.98, CAD4 Enraf-Nonius diffractometer, θ−ω scans, data collection range $1° \leqslant \theta \leqslant 60°$, three standard reflections showed no significant variation in intensity, 3842 reflections measured, 3708 unique, which were used in all calculations. The structure was solved by Patterson methods and subsequent Fourier maps and refined as for **1a**. The weighting scheme was $w = 1/\sigma^2(F_o) + 0.008391F_o^2$. The final wR was 0.05 with conventional $R = 0.043$ for 284 parameters, max. $\Delta/\sigma = 0.002$, max. $\Delta\rho = 0.6$ e Å^{-3}.

2b. $CuC_{13}H_{18}N_2O_2S_4$, $M = 426.08$, thin dark brown crystal, triclinic, space group $P\bar{1}$, $a = 8.388(1)$, $b = 11.315(2)$, $c = 11.653(2)$ Å, $\alpha = 117.01(1)$, $\beta = 107.65(1)$, $\gamma = 94.55(1)°$, $U = 907.9(2)$ Å^3, $T = 293$ K, graphite-monochromated CuKα radiation, $\lambda = 1.54178$ Å, $Z = 2$, $D_c = 1.56$ Mg m^{-3}, crystal size $0.025 \times 0.1 \times 0.4$ mm^3, $\mu CuK\alpha = 47.98$ cm^{-1}, $F(000) = 438$, semi-empirical absorption correction based on ψ scans, transmission factors 0.57–0.99, CAD4 Enraf-Nonius diffractometer, θ−ω scans, data collection range $1° \leqslant \theta \leqslant 60°$, three standard reflections showed no significant variation in intensity, 6532 reflections measured, giving 3421 independent ($R_{int} = 0.03$). The structure was solved by direct methods (program SHELX 86)[18] and Fourier difference techniques and refined anisotropically by full-matrix least-squares methods on F^2 (program SHELXS 76),[17] hydrogen atoms were included in theoretical positions. The weighting scheme was $w = 0.2562/\sigma^2(F_o) + 0.003879F_o^2$. The final wR was 0.044 with conventional $R = 0.034$ for 217 parameters, max. $\Delta/\sigma = 0.03$, max. $\Delta\rho = 0.6$ e Å^{-3}.

CCDC reference number 440/032.

Transchelation experiments

Complex 2b with excess of EDTA. To 26 mg (0.071 mmol, 1 equiv.) of complex **2b** in acetone (10 ml) was added 1880 mg of EDTA disodium salt (7.1 mmol, 100 equiv.) in water (5 ml, pH = 6). The reaction was stopped after 20 h of stirring. After addition of methylene chloride (15 ml), the organic phase was separated, dried and evaporated to dryness. The obtained residue was purified by chromatography on silica gel using methylene chloride as eluent. Complex **2b** ($R_f = 0.4$) was recovered (24 mg, 93% yield).

Complex EDTA–Cu with excess of N_2S_2 ligand. To 27 mg (0.076 mmol, 1 equiv.) of complex EDTA–Cu in water (5 ml, pH = 6),[14] was added 1386 mg of N_2S_2 ligand derived from 1,3-diaminopropan-2-ol (3.80 mmol, 50 equiv.) in 10 ml of acetone. The reaction was stopped after 20 h of stirring. After addition of methylene chloride (15 ml), the organic phase was separated, dried and evaporated to dryness. The separation between complex **2b** (due to transchelation) and excess of ligand was performed by chromatography on silica gel using methylene chloride as eluent ($R_f = 0.4$ for complex **2b** and 0.3 for N_2S_2 ligand). Complex **2b** was obtained (1.6 mg, ≈5% yield).

Competitive complexation

To a mixture of 200 mg (0.55 mmol, 5 equiv.) of N_2S_2 ligand derived from 1,3-diaminopropan-2-ol in acetone (5 ml) and 184 mg of EDTA disodium salt (0.55 mmol, 5 equiv.) in water (5 ml, pH = 6) was added 21.9 mg (0.11 mmol, 1 equiv.) of copper acetate monohydrate. The mixture was stirred 5 min and the reaction was stopped. After addition of methylene chloride (15 ml), the organic phase was separated, dried and evaporated to dryness. The complex **2b** and excess of N_2S_2 ligand were separated by chromatography on silica gel using methylene chloride as eluent ($R_f = 0.4$ for complex **2b** and 0.3 for N_2S_2 ligand). Complex **2b** was obtained (11.6 mg, 25% yield).

Electrochemical studies

Due to the difficulties encountered with the solubility of the complexes, the electrochemical behaviour of the Cu^{II} and Ni^{II} complexes was studied in DMSO. The experiments were carried out by cyclic voltammetry using a PAR 273 potensiostat-galvanostat in a three-electrode single compartment cell equipped with platinum microelectrodes of 7.85×10^{-3} cm^2 area, a platinum wire counter electrode and a saturated calomel reference electrode (SCE). The electrochemical curves were recorded on a Kipp–Zonen x–y recorder. All experiments were performed under an argon atmosphere at room temperature. KNO_3 was used in DMSO as supporting electrolyte at a 0.1 M concentration. Voltammograms were recorded using 10^{-3} M solutions of the complexes with a scanning speed of 100 mV s^{-1}.

Acknowledgements

This work was supported by grants from the 'Ligue Départementale Contre le Cancer de Loire-Atlantique' (G.C-J.) and from the 'Ligue Départementale Contre le Cancer des Deux-Sèvres' (E.B). We also acknowledge AGISMED for financial support and Pr M. Jubault (Angers) for fruitful discussions.

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Received in Montpellier, France, 23rd October 1997;
Paper 7/09182F