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The Synthesis and Properties of New 2-Pyrrolylthiones as Chelating Agents for Transition Metals and Technetium

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Abstract—A series of new 2-pyrrolylthiones was synthesized and found to be good chelating agents for transition metals and technetium. © 2001 Elsevier Science Ltd. All rights reserved.

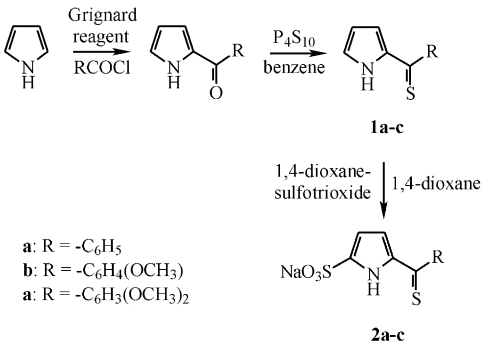
N,S-Bidentate ligands, in which nitrogen is part of a heterocycle and the sulfur donor atom is part of the thione group, attracted our attention as potential technetium and rhenium chelators.

It has been reported that di-2-pyrrolylthione forms complexes with mercuric chloride, although no structures or characteristics of such complexes were provided.[1]

Brückner et al. tried to use 2,2′-pyrrolylthiones as starting materials for the synthesis of 5,15-diphenylporphyrin by means of the Raney-nickel induced hydrodesulfurization of unsubstituted di-2,2′-pyrrolylthione, thereby obtaining di-2,2′-pyrrolylmethane—the key intermediate in the porphyrin synthesis.[2] The anticipated hydrodesulfurization, however, did not occur and a Ni(II)-2-pyrrolylthione complex was isolated from the reaction. This finding prompted the authors to take a close look at 2-pyrrolylthiones as N,S-donor chelating agents for transition metals. The 2-pyrrolylthionato complexes of Ni(II), Co(II), and Hg(II) were synthesized and characterized.[3]

The aim of the present work was to obtain various substituted 2-pyrrolylthiones in order to examine their potential to form complexes with transition metals and to study the properties of such complexes. Compounds of technetium and rhenium, containing N,S-donor ligands, constitute a prominent group among all bioinorganic drugs because of their importance in nuclear medicine.[4] We ventured to explore the suitability of novel 2-pyrrolylthione ligands as chelators for radiometals, such as the isotopes of technetium and rhenium, with a goal of creating a new class of radiopharmaceutical compounds for medical imaging.

The parent unsubstituted or substituted 2-pyrrolylketones served as precursors for the synthesis of lipophilic 2-pyrrolylthiones **1a**–**c**. These 2-pyrrolylketones were obtained from pyrrole and corresponding Grignard derivatives using the method suggested in the literature.[5]



Scheme 1. Synthesis of the 2-pyrrolylthiones **2a**–**c**.

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Synthesized 2-pyrrolylketones were converted into corresponding thiones **1a–c** using tetraphosphorus decasulfide P_4S_{10} as shown in Scheme 1. It should be noted that the unsubstituted 2-pyrrolyl-phenylthione **1a** was previously described in the literature.[6] Compounds **1b**,**c** were isolated chromatographically in good yields: **1b** as a bright red crystalline solid and **1c** as a red oil that subsequently crystallized.

While characterizing compounds **1b**,**c**, we have confirmed that these substituted 2-pyrrolyl-phenylthiones have the same tautomeric nature as the earlier described di-2,2-pyrrolylthione.[1] Thiones **1b** and **1c** show characteristic weak SH absorption in their IR spectra near $2550\,\text{cm}^{-1}$, corresponding to the thiol tautomer, along with intense maxima around $1036\,\text{cm}^{-1}$ that represent the C=S stretching frequencies. Thus, the ability of the pyrrolic group to release electron density in the thiol tautomer allows these novel 2-pyrrolylthiones to chelate the metals with large ionic radii: for example, certain transition metals.

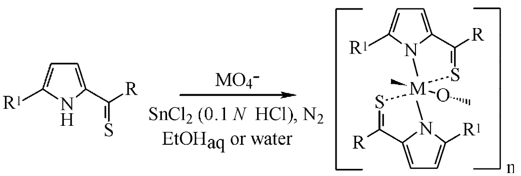
We have designed a synthetic procedure in order to obtain the water-soluble 2-pyrrolyl-phenylthiones **2a–c** (Scheme 1), as well as di-2,2′-pyrrolylthiones **2d** and **2e** (Scheme 2), using 1,4-dioxanesulfotrioxide[7] as the sulfonating agent and 1,4-dioxane as a solvent.[8]

These reactions take place at room temperature in an inert atmosphere and are usually completed in 10 min, thereby, in the case of 2-pyrrolyl-phenylthiones, yielding a single product, and two major products, **2d** and **2e**, when di-2,2′-pyrrolylthione **1d** is used as a substrate. The crude products obtained from the reaction mixture after evaporation of 1,4-dioxane are easily purified by means of extraction with acetone. Chromatographic purification on reverse-phase silica gel (either C-18 or Phenyl), using water or aqueous methanol as an eluent, furnished water-soluble sulfonated ligands, which were obtained in high yields as red crystalline solids.

These water-soluble ligands were then used to obtain the corresponding complexes **3** by employing transition metals such as Ni, Cd, Co, Cu, and Zn (Scheme 2). Such complexes were successfully synthesized, using metal acetates in solutions, and then purified via reverse-phase column chromatography. Generally, we found that the complexation takes place rapidly and results in stable chelates. In some instances, we obtained the complexes as precipitates. In other cases, we had to monitor the course of the reaction using spectrophotometry. All 2-pyrrolylthiones have their characteristic absorbency in UV–vis around 380 nm. These peaks became progressively red-shifted and broadened in shape upon addition of metal salts to the ligand solutions.

The ^{1}H NMR spectra of the purified complexes of ligands **1b**,**c** and **2a–c** show no proton at the pyrrolic nitrogen, which confirms the stability of these complexes in solutions.

Furthermore, the general procedure was developed for the synthesis of the complexes of novel 2-pyrrolylthiones with radioisotopes of technetium, thus representing a novel class of Tc-radiopharmaceuticals (Scheme 2).



1a-d, 2a-e

3

1a-c: R1 = H
1d: R1 = H, R = 2-pyrrolyl
2a-c: R1 = SO_3Na
2d: R1 = SO_3Na, R = 2-pyrrolyl
2e: R1 = SO_3Na, R = 5-sulfopyrrol-2-yl
M = Ni, Cd, Co, Cu, Zn, ^{99m}Tc, ^{99g}Tc, Re
n = 1-3

Scheme 2. Synthesis of metal complexes.

During the first stage of development of a therapeutic or a diagnostic radiopharmaceutical, it is essential to prove that the metallic radionuclide (e.g., ^{99m}Tc)—upon interaction with a chelating agent—should form a stable complex in high specific activity with a defined metal-to-ligand stoichiometry. Since the ^{99m}Tc is only available in minute concentrations, a detailed understanding of the coordination chemistry of new ligand systems with analogous non-radioactive rhenium or ground isotope ^{99g}Tc (a weak β-emitter) is important for the subsequent 'extrapolation' of these reactions at the tracer levels.

Thus, both the potassium [^{99g}Tc]pertechnetate and potassium perrhenate, which were reduced with stannous chloride, react smoothly with ligands **1** and **2** (Scheme 2), thereby forming 1:2 stable, soluble complexes, which were isolated in good yields. All synthesized ^{99g}Tc and Re compounds were isolated and characterized in terms of identity and purity. These complexes were obtained as brown crystalline solids, which either have high melting points (lipophilic) or decompose at high temperatures without melting (water-soluble). Crystallographic data suggest that some rhenium complexes exist as tri-nuclear layered structures ($n = 3$).

All synthesized compounds exhibited adequate analytical, spectroscopic and mass spectrometric data.[9]

As a result of our present work, we found that synthesized 2-pyrrolylthiones, either lipophilic or water-soluble, are good ligands for a wide range of transition metals—including rhenium and technetium. As it was shown, the periphery of these ligands can be modified easily in order to add desired specific properties to the resulting compounds. Therefore, 2-pyrrolylthiones might well find application in various biological, medical, and other fields where chelators play an important role. We shall publish elsewhere more detailed accounts of the use of these compounds in medical imaging.

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8. The general procedure. Solid 1,4-dioxanesulfotrioxide (2 mmol) was gradually added to a stirred solution of 2-pyrrolylthione (1 mmol) in 1,4-dioxane (25 mL) under a nitrogen atmosphere. The reaction mixture was allowed to stand for 10 min at room temperature. Next, the solvent was evaporated in a vacuum and the oily residue was dissolved in water (about 5 mL). The pH was adjusted to 3.5 using 1 M solution of NaOH. The acetone (40 mL) was added to the solution and the white precipitate was separated by centrifugation. The red supernatant was evaporated to dryness. The solid product was purified on the reverse-phase silica gel (C-18 or phenyl) using water as an eluant. Hydrate of sodium salt of sulfonated 2-pyrrolylthione was obtained as a red crystalline solid.
9. Selected data. Compound **2a**: Yield 50%; ^{1}H NMR (DMF-d_7) δ 11.81 (s, 1H), 7.69–7.66 (m, 2H), 7.60–7.50 (m, 2H), 7.48–7.45 (m, 2H), 6.75–6.76 (m, 1H); ^{13}C NMR (DMF-d_7) δ 214.80, 162.60, 138.00, 130.82, 130.69, 128.81, 128.30, 116.19; IR (KBr), cm^{-1}: 3364, 3121 (ν(N–H)), 1615 ($\delta(\text{C–H})_{\text{ar.}}$), 1591, 1531, 1458 (ν(C–C)), 1408, 1367 ($\nu_{\text{as.}}(\text{S}(=\text{O})_2)$), 1320 (ω(C–N)), 1211 (ν(C=S)), 1155 ($\nu_{\text{s.}}(\text{S}(=\text{O})_2)$), 1113, 1082 (ar.), 1059 (ν(O–Na)), 1041, 1026 (*ar.*), 968, 941, 852 (ν(S–*O*–Na)), 768 (γ(C–H)), 700, 667 (γ(C–C), δ(C–H)), 644, 629, 617; UV–vis (H_2O), $\lambda_{\max}$ (lg ε): 513 (2.11), 382 (4.34), 320 (4.05), 215 (4.07); LR–MS: 266 (M$^+$); anal. calcd for $C_{11}H_8NNaO_3S_2 \cdot H_2O$: C 42.99, H 3.28, N 4.56, S 20.86; found: C 42.32, H 2.73, N 4.41, S 20.44. Compound **2b**: Yield 40%; ^{1}H NMR (DMF-d_7) δ 11.71 (s, 1H), 7.92–7.74 (m, 2H), 7.57–7.56 (m, 1H), 7.14–7.04 (m, 2H), 6.81–6.80 (m, 1H); ^{13}C NMR (DMF-d_7) δ 141.11, 139.94, 137.49, 131.27, 131.13, 129.72, 125.32, 124.15, 116.53, 115.55, 114.84, 114.06, 113.61, 55.63. IR (KBr), cm^{-1}: 3570 (H bonds), 3283 (ν(N–H)), 1597, 1531, 1504, 1460 (ν(C–C)), 1408, 1367 ($\nu_{\text{as.}}(\text{S}(=\text{O})_2)$), 1310 (ω(C–N)), 1250 ($\nu_{\text{as.}}(\text{C–O–C})$), 1159 ($\nu_{\text{s.}}(\text{S}(=\text{O})_2)$), 1117 (ar.), 1057 (ν(O–Na)), 1041, 1024 (ar., $\nu_{\text{s.}}(\text{C–O–C})$), 950, 941, 860, 837 (ν(S–*O*–Na)), 785 (γ(C–H)), 671, 635 (γ(C–C), γ(C–H)), 580; UV–vis (H_2O), $\lambda_{\max}$ (lg ε): 511 (2.35), 375 (4.40), 221 (4.03); LR-MS: 296 (M$^+$); anal. calcd for $C_{12}H_{10}NNaO_4S_2 \cdot 3H_2O$: C 38.60, H 4.32, N 3.75, S 17.17; found: C 38.75, H 3.63, N 3.69, S 17.38. Compound **2c**: Yield 56%; ^{1}H NMR (DMF-d_7) δ 11.71 (s, 1H), 7.58–7.57 (m, 1H), 7.44–7.43 (m, 1H), 7.37–7.34 (m, 1H), 7.11–7.08 (m, 1H), 6.86–6.85 (m, 1H), 3.94 (s, 3H), 3.89 (s, 3H); ^{13}C NMR (DMF-d_7) δ 213.25, 152.69, 148.94, 139.94, 137.28, 129.67, 129.53, 122.60, 115.74, 113.48, 110.70, 55.89, 55.77; IR (KBr), cm^{-1}: 3443 (hydrogen bonds, ν(N–H)), 3125 (ν(N–H)), 1595, 1531, 1512, 1462, 1454 (ν(C–C)), 1420, 1366 ($\nu_{\text{as.}}(\text{S}(=\text{O})_2)$), 1331 (ω(C–N)), 1265 ($\nu_{\text{as.}}(\text{C–O–C})$), 1210 (ν(C=S)), 1138 ($\nu_{\text{s.}}(\text{S}(=\text{O})_2)$), 1043 (ν(O–Na)), 1016 ($\nu_{\text{s.}}(\text{C–O–C})$), 941, 862 (ν(S–O–Na)), 762, 663, 635 (γ(C–H)), 478; UV–Vis (H_2O), $\lambda_{\max}$ (lg ε): 508 (2.56), 382 (4.64), 264 (4.01), 221 (4.34); LR–MS: 326 (M$^+$); anal. calcd for $C_{13}H_{12}NNaO_5S_2 \cdot H_2O$: C 42.50, H 3.84, N 3.81; found: C 42.55, H 3.40, N 3.69.