The Molecular Structure of Indium Oxine

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The radiopharmaceutical use of [^{111}In]oxine for radiolabeling of blood products has recently met with FDA approval. The molecular structure of tris(8-quinolinolato) indium(III), "indium oxine", was determined by x-ray crystallography using a single yellow crystal grown from ethanol solution. The structural study reveals an asymmetric pseudo-octahedral N_3O_3 metal coordination sphere with meridional stereochemistry. This asymmetry is not detected in solution by proton NMR spectroscopy at room temperature; however, at −90°C spectroscopic changes suggest slowing of a fluxional process. The molecule unexpectedly crystallized with a molecule of ethanol hydrogen-bonded to an oxygen atom of one of the oxine ligands, suggesting that hydrogen-bonding will play a role in the solvation of this complex in protic solvents.

The radiopharmaceutical use of indium-111 (^{111}In) oxine for the radiolabeling of autologous leukocytes has recently received approval by the United States Food and Drug Administration (*1*). The effectiveness of [^{111}In]oxine for cell labeling derives from the ability of this moderately-stable lipophilic complex to diffuse across lipid membranes, allowing the indium-111 label to be trapped by ligand exchange with intracellular macromolecules (*2–5*).

The utility of [^{111}In]oxine as a mediator for the ^{111}In labeling of platelets and white blood cells (*6–12*) has led to some speculation in the nuclear medicine literature regarding the molecular structure of this metal chelate complex (*8–12*). In addition, estimates of the molecular dimensions of indium oxine have been used to explain the interactions of this complex with phospholipid membranes (*4*). The results of an x-ray crystallographic investigation of the molecular structure of tris(8-quinolinolato)indium(III), indium oxine, are presented in this report.

METHODS

Synthesis of In(oxine)$_3$·CH$_3$CH$_2$OH

A chloroform solution (60 ml) of 8-quinolinol (1.24 g, 8.5 mmol) was stirred overnight at room temperature in contact with an aqueous phase (30 ml) containing indium(III) acetate

(0.84 g, 2.9 mmol) and sodium acetate trihydrate (2.0 g). The chloroform phase was removed, washed with 2 × 50 ml H$_2$O, dried over sodium sulfate, and evaporated to dryness under reduced pressure. The product was dissolved in hot ethanol and deposited as transparent yellow crystals upon slow cooling. m.p. > 300°C.

The positive ion mass spectrum of the product was obtained by fast atom bombardment of a meta-nitrobenzylalcohol matrix. The following species were identified (m/e, (relative intensity), [assignment]): 548 (2.3) [In(oxine)$_3$H]$^+$; 547 (3.7) [In(oxine)$_3$]$^+$; 403 (12.7) [In(oxine)$_2$]$^+$; 259 (8.7) [In(oxine)]$^+$; (where oxine = C$_9$H$_6$NO).

Room temperature proton NMR spectrum (300 MHz) of In(oxine)$_3$·CH$_3$CH$_2$OH in deuterochloroform—Chemical Shift (multiplicity, coupling constant; intensity): 8.544 ppm (d, J = 4.6 Hz of d, J = 1.2 Hz; 3H); 7.398 ppm (d, J = 8.3 Hz of d, J = 4.6 Hz; 3H) 8.281 ppm (d, J = 8.3 Hz of d, J = 1.2 Hz; 3H); 7.175 ppm (d, J = 7.8 Hz of d, J = 0.7 Hz; 3H); 7.496 ppm (t, J = 8.0 Hz; 3H); 7.033 ppm (d, J = 8.0 Hz; 3H); 3.688 ppm ("quintet", J = 6.5 Hz; 2H) −CH$_2$−; 1.462 ppm (t, J = 5.2 Hz; 1H) −OH; 1.215 ppm (t, J = 7.0 Hz; 3H) −CH$_3$.

X-Ray Crystallography

The solid state structure of In(oxine)$_3$·CH$_3$CH$_2$OH was determined by x-ray crystallography. Crystal data for In(ONC$_9$H$_6$)$_3$·CH$_3$CH$_2$OH at −155°C: a = 11.215(4), b = 13.557(5), c = 16.626(7) Å; beta = 95.36(2)°; V = 2516.88 Å^3; Z = 4 in monoclinic space group P2$_1$/n (where a, b, and c are dimensions of the unit cell, beta is the angle between the b and c axes, V is the unit cell volume, Z is the number of molecules per unit cell, and the space group describes the symmetry of the crystal lattice (*13*)); R(F) = 0.0445, R$_w$(F) = 0.0434 for 2416 observed [F > 3.00 σ(F)] and absorption-corrected reflections using anisotropic thermal parameters for

all nonhydrogen atoms. Hydrogen atoms were refined isotropically. (Complete structural details are available in Molecular Structure Center Report No. 86821, which can be requested from the Chemistry Library, Indiana University, Bloomington, IN 47405 USA.).

RESULTS AND DISCUSSION

The solid state structure of tris(8-quinolinolato)indium(III), indium oxine, was determined by x-ray crystallography using a single yellow crystal grown from an ethanol solution of the complex. The structure is illustrated in Figures 1–3. Selected bond distances and angles are reported in Tables 1 and 2.

The structural study reveals the expected uncharged pseudo-octahedral complex with an asymmetric meridional arrangement of the N_3O_3 metal coordination sphere (rather than the facial geometry of C_3 symmetry). In chloroform solution at room temperature this inequivalence of the coordinated oxine ligands is not observed by proton NMR spectroscopy, indicating either a solution structure of higher symmetry or a predictably (*14*) rapid fluxional process. In d_2-methylene chloride at −90°C the downfield (8.5 ppm) proton NMR doublet (J ≅ 4 Hz) collapses to a broad singlet, suggesting that the asymmetric isomer is present but still undergoing relatively rapid interconversion of ox-
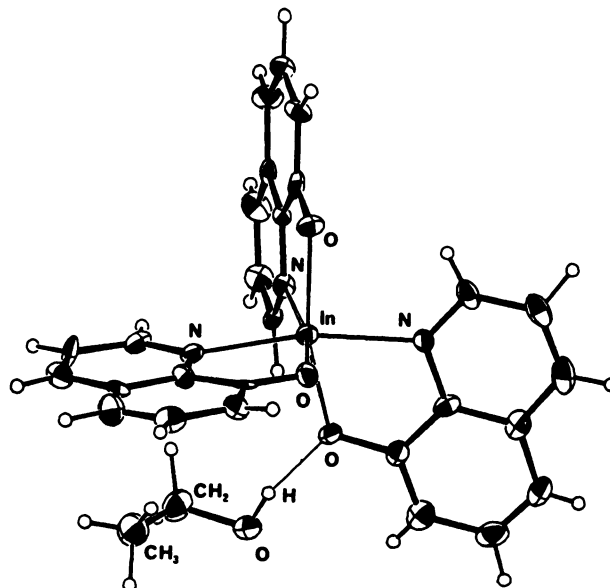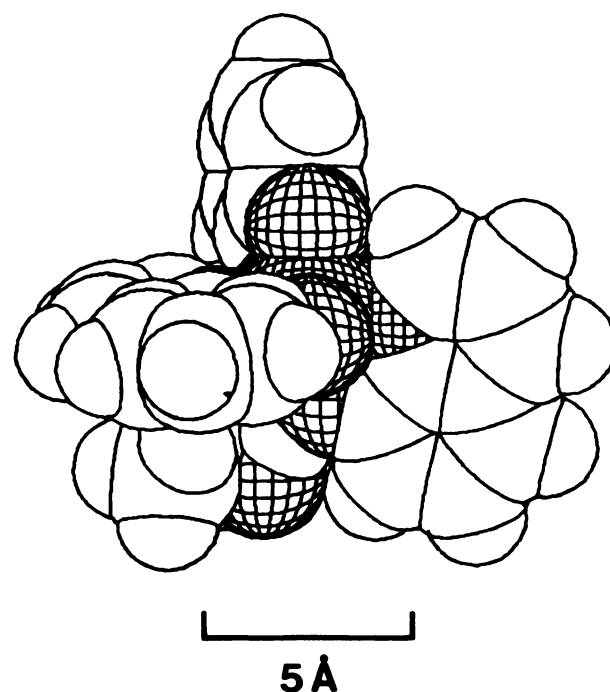

FIGURE 2
ORTEP drawing of the molecular structure of In(oxine)₃·CH₃CH₂OH.

ine ligand sites. (Exchange of free and coordinated oxine ligands is slow relative to the 300 MHz nuclear magnetic resonance (NMR) time scale. In chloroform solution at room temperature a 1:1 mixture of In(oxine)₃ and H(oxine) show no evidence of exchange—i.e., no signal averaging or significant line broadening).
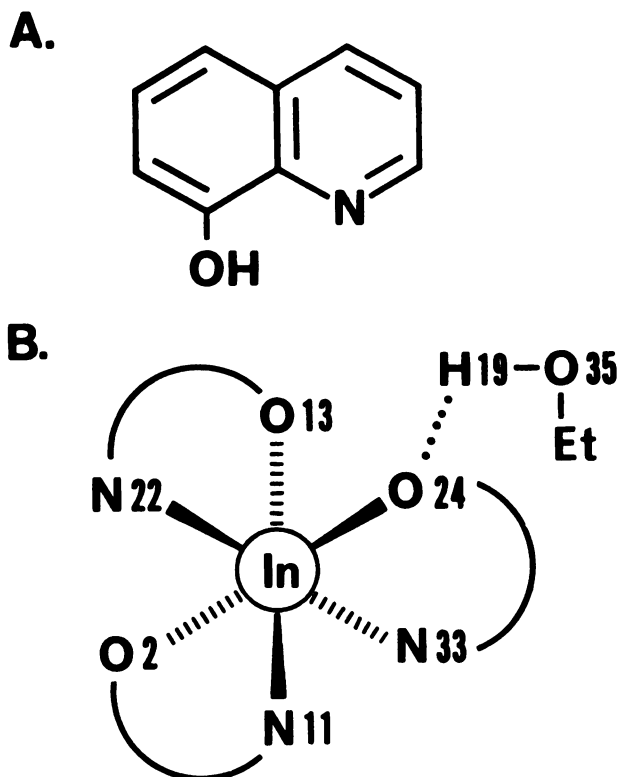
FIGURE 1
A: Structure of 8-quinolinol [H(oxine)]. B: Stereochemistry and atomic numbering scheme for In(oxine)₃·Ethanol.

FIGURE 3
Space-filling ORTEP drawing of the molecular structure of In(oxine)₃·CH₃CH₂OH, viewed as in Figure 2.

Unexpectedly, the indium oxine complex crystallized with a molecule of ethanol hydrogen-bonded to an oxygen atom, O(24), of one of the oxine ligands (Figs. 1–3). This hydrogen bond causes the In-O(24) bond distance to be slightly (0.046 Å) longer than the other two indium-oxygen bonds. The indium-oxygen (O(2) and O(13)) and indium-nitrogen bond distances are 0.17 Å and 0.15 Å longer than those found in the N₃O₃ coordination sphere of the gallium complex of 1,1,1-tris(5-methoxysalicylaldriminomethyl)ethane (*15,16*), corresponding roughly to the 0.19 Å difference in ionic radii (*17*) for these two metals.

While caution must be exercised in the use of solid state data to explain the chemistry of radiopharmaceuticals in aqueous solution, it is clear from this structural study that hydrogen-bonding will play a role in the solvation of indium oxine in protic media. In a cell labeling preparation the hydrogen-bond donor could be any of the protic species present in solution (water would obviously predominate in the aqueous (saline) phase). This hydrogen-bonding interaction should be sensitive to changes in the basicity of the coordinated metal ion. Thus, the lower basicity of the gallium(III) ion (*17*) is expected to diminish the importance of hydrogen-bonding in the solvation of gallium oxine. This is consistent with the greater thermodynamic (*18*)

and kinetic (*14*) stability of gallium oxine relative to indium oxine, since the strength of the hydrogen-bond and the strength of the metal-oxygen bond are inversely and synergistically related.

ACKNOWLEDGMENTS

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