Articles

Syntheses and Characterization of Anti-inflammatory Dinuclear and Mononuclear Zinc Indomethacin Complexes. Crystal Structures of $[Zn_2(Indomethacin)_4(L)_2]$ (L = *N*,*N*-Dimethylacetamide, Pyridine, 1-Methyl-2-pyrrolidinone) and $[Zn(Indomethacin)_2(L_1)_2]$ (L_1 = Ethanol, Methanol)

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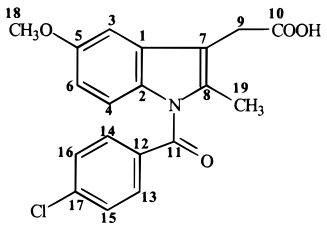
The syntheses and spectral and structural characterizations of Zn(II) indomethacin [1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indole-3-acetic acid = IndoH] complexes, as different solvent adducts, have been studied. The complexes are unusual in that both monomeric and dimeric complexes are formed and that this is the first example of the same carboxylato ligand binding via both carboxylate oxygen atoms in monomeric and dimeric Zn(II) complexes. The crystal structures of Zn−Indo complexes with *N*,*N*-dimethylacetamide (DMA), pyridine (Py), 1-methyl-2-pyrrolidinone (NMP), EtOH, and MeOH as solvent ligands, $[Zn_2(Indo)_4(DMA)_2]\cdot 2DMA$, **1**, $[Zn_2(Indo)_4(Py)_2]\cdot 2H_2O$, **2b**, $[Zn_2(Indo)_4(NMP)_2]$, **3**, *cis*-$[Zn(Indo)_2(EtOH)_2]$, **4**, and *cis*-$[Zn(Indo)_2(MeOH)_2]$, **5**, were determined. Complexes **1**, **2b**, and **3** crystallize in the triclinic space group $P\bar{1}$ (No. 2): $a = 13.628(2)$ Å, $b = 17.462(2)$ Å, $c = 11.078(1)$ Å, $\alpha = 99.49(1)°$, $\beta = 108.13(1)°$, $\gamma = 110.10(1)°$ for **1**; $a = 13.347(3)$ Å, $b = 16.499(5)$ Å, $c = 10.857(1)$ Å, $\alpha = 99.48(2)°$, $\beta = 108.25(2)°$, $\gamma = 106.24(2)°$ for **2**; $a = 14.143(3)$ Å, $b = 14.521(2)$ Å, $c = 11.558(2)$ Å, $\alpha = 109.07(1)°$, $\beta = 90.80(2)°$, $\gamma = 116.40(1)°$ for **3**. The three complexes exhibit dinuclear paddle-wheel structures with a Zn···Zn distance of 2.9686(6) Å, Zn−O_{RCOO} distances of 2.035(2)−2.060(2) Å, and a Zn−O_{DMA} distance of 1.989(2) Å in **1**, a Zn···Zn distance of 2.969(1) Å, Zn−O_{RCOO} distances of 2.020(3)−2.049(3) Å, and a Zn−N_{Py} distance of 2.036(3) Å in **2**, and a Zn···Zn distance of 2.934(1) Å, Zn−O_{RCOO} distances of 2.009(3)−2.051(3) Å, and a Zn−O_{NMP} distance of 1.986(3) Å in **3**. In these cases, the zinc ions are offset along the *z* direction such that the L−Zn···Zn−L moiety is nonlinear, unlike the Cu analogues. Each Zn has a square-pyramidal geometry bridged by four carboxylato ligands in the basal plane with the solvent ligands containing an O- or N-donor atom at the apex. Complexes **4** and **5** are isostructural, with space group *C*2/*c* (No. 15). For **4**, $a = 30.080(2)$ Å, $b = 5.3638(6)$ Å, $c = 24.739(2)$ Å, $\beta = 90.342(7)°$, and for **5**, $a = 29.419(2)$ Å, $b = 5.320(2)$ Å, $c = 24.461(2)$ Å, $\beta = 90.840(4)°$. The Zn resides on a 2-fold axis and the complexes have a distorted cis octahedral structure with Zn−O_{RCOO} bond lengths of 2.183(3) and 2.169(3) Å, a Zn−O_{EtOH} bond length of 2.015(3) Å in **4**, Zn−O_{RCOO} bond lengths of 2.195(2) and 2.151(2) Å, and a Zn−O_{MeOH} bond length of 2.022(3) Å in **5**.

Introduction

Indomethacin [1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indole-3-acetic acid = IndoH] is a nonsteroidal anti-inflammatory drug (NSAID) that exhibits favorable anti-inflammatory, analgesic, and antipyretic properties, but it has the undesirable side effects of inducing gastrointestinal ulceration and hemorrhages.[1] Numerous studies have been undertaken in order to reduce the side effects associated with the clinical use of IndoH and related carboxylate-containing NSAIDs. One strategy that has met with success has been the use of d-block metal complexes of the NSAIDs as therapeutic agents. In part this approach is based on the observation that some d-block metal ions, especially Cu(II) and Zn(II), can act as anti-inflammatory agents in their own right.[2−4] It has been demonstrated that the



Indomethacin

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Zn(II) complex of aspirin has a better therapeutic index (2.64 times) than aspirin itself and has improved physicochemical characteristics.[5] Furthermore, the Zn−aspirin complex displays more favorable therapeutic properties, is more effective, and less ulcerogenic than either aspirin alone or a physical mixture of aspirin and $ZnSO_4$.[1,5−6]

Recently, the Cu complex of IndoH was introduced for use as a veterinary anti-inflammatory drug. This drug is superior to uncomplexed IndoH for treatment of a range of conditions and most importantly induces considerably lower incidences of gastrointestinal damage.[7,8] Detailed studies of $[Cu_2(Indo)_4L_2]$ complexes have recently been reported,[9,10] and it was demonstrated that the complex adopts a dimeric structure similar to that found in Cu acetate and in the Cu−aspirin complex.[11,12] Weder and co-workers have shown that in the solid state the Indo units form a hydrophobic package containing the Cu_2O_8 core, and they postulated that this might contribute to its pharmaceutical efficacy.[9] In both the Cu−aspirin and Cu−Indo complexes, the sixth coordination site is occupied by a Lewis base, which is usually a molecule of the solvent.

Three Cu-acetate-like dinuclear carboxylato Zn(II) complexes have been described in the literature.[13−15] By contrast, $[Zn(O_2CR)_2(OH_2)_2]$ form six-coordinate monomeric species in the solid state for the acetato, salicylato, and acetylsalicylato ligands.[16−18] The Zn−Indo complexes have anti-inflammatory properties and have been patented as veterinary pharmaceutics.[19] A key step in understanding the biological function of these complexes is to establish their structures and to investigate the relative stabilities of the monomeric or dimeric arrangements. A Zn−aspirin structure has been described in the literature;[18] however, as far as we know, there have been no structural reports of Zn−Indo complexes. Accordingly, a number of Zn−Indo complexes have been prepared and characterized using a variety of coordinating solvents including *N*,*N*-dimethylacetamide (DMA), pyridine (Py), 1-methyl-2-pyrrolidinone (NMP), alcohols, dimethyl sulfoxide (DMSO), water, methylamine, and imidazole.

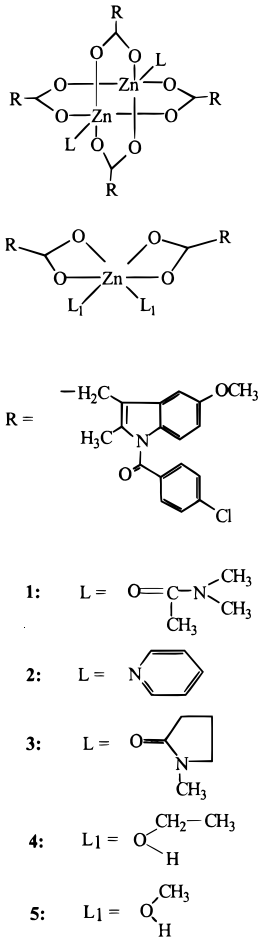
Experimental Section

Syntheses. IndoH was pharmaceutical grade (Sigma Pharmaceutical). All other chemicals were of high purity (Aldrich or Sigma) and were used without further purification.

Bis(*N*,*N*-dimethylacetamide)tetrakis-μ-(*O*,*O*′-Indo)dizinc(II)-2-*N*,*N*-dimethylacetamide, $[Zn_2(Indo)_4(DMA)_2]\cdot 2DMA$, 1. To a solution of IndoH (3.66 g, 10.23 mmol) in DMA (10 mL), a solution of $Zn(OAc)_2\cdot 2H_2O$ (1.24 g, 5.65 mmol) in DMA (10 mL) was added dropwise. The mixture was stirred and heated (ca. 60 °C) overnight, cooled to room temperature, and then set aside in a fume hood for 3 weeks, during which time small yellow crystals formed. These were collected by filtration under reduced pressure and air-dried. Further product was obtained on extended standing. Anal. Found: C, 57.67; H, 4.68; N, 5.97; Zn, 6.69%. Calcd for $Zn_2C_{84}H_{78}Cl_4N_6O_{18}\cdot 2C_4H_9NO$: C, 57.96; H, 5.08; N, 5.88; Zn 6.86%. ^{1}H NMR (in DMSO-d_6): δ (ppm) 7.76(H-13,14), 7.74(15,16), 7.13(H-3), 7.01(H-4), 6.78(H-6), 3.80(H-9), 3.42(H-18), 2.27(H-19).

Bis(pyridine)tetrakis-μ-(*O*,*O*′-Indo)dizinc(II)-2-acetonitrile, $[Zn_2(Indo)_4(Py)_2]\cdot 2CH_3CN$, 2. To a warm solution of IndoH (3.58 g, 10.01 mmol) in acetonitrile (100 mL) a solution of $Zn(OAc)_2\cdot 2H_2O$ (1.04 g, 4.74 mmol) in water (3 mL) and acetonitrile (3 mL) was slowly added. The mixture was briefly heated to 60 °C, then pyridine (2 mL) was added. The resultant mixture was stirred for 3 h, cooled to room temperature, and set aside in a fume hood overnight. The resulting yellow crystalline solid was filtered and washed with a small amount of dry diethyl ether and air-dried (1.74 g, 44.8%). Anal. Found: C, 59.91; H, 4.14; N, 6.34; Zn, 7.61%. Calcd for $Zn_2C_{86}H_{70}Cl_4N_6O_{16}\cdot 2CH_3CN$: C, 60.11; H, 4.26; N, 6.23; Zn, 7.27%. ^{1}H NMR (in DMSO-d_6): δ (ppm) 7.74(H-13,14), 7.72(15,16), 7.13(H-3), 7.01(H-4), 6.78(H-6), 3.81(H-9), 3.48(H-18), 2.27(H-19).

Bis(1-methyl-2-pyrrolidinone)tetrakis-μ-(*O*,*O*′-Indo)dizinc(II), $[Zn_2(Indo)_4(NMP)_2]$, 3. $Zn(OAc)_2\cdot 2H_2O$ (1.21 g, 5.51 mmol) in NMP (12 mL) was slowly added to IndoH (3.69 g, 10.31 mmol) in NMP (15



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mL). The mixture was heated overnight at 60 °C, then EtOH (60 mL) was added. The mixture was placed in a fume hood for 12 h during which time a crystalline solid formed (2.08 g, 45.9%). Anal. Found: C, 58.48; H, 4.32; N, 4.71; Zn, 7.33%. Calcd for $Zn_2C_{86}H_{78}Cl_4N_6O_{18}$: C, 58.82; H, 4.48; N, 4.79; Zn, 7.45%. ^{1}H NMR (in DMSO-d_6): δ (ppm) 7.74(H-13,14), 7.72(15,16), 7.12(H-3), 7.01(H-4), 6.78(H-6), 3.82(H-9), 3.51(H-18), 2.27(H-19).

***cis*-Bis(ethanol)bis(η^2-*O,O′*-Indo)zinc(II), *cis*-[Zn(Indo)$_2$(EtOH)$_2$], 4.** A solution of $Zn(OAc)_2 \cdot 2H_2O$ (2.16 g, 9.84 mmol) in DMA (10 mL) was added slowly to a solution of IndoH (7.26 g, 20.29 mmol) in DMA (10 mL). The mixture was stirred and heated at 50 °C overnight. The resultant yellow solution was cooled to room temperature, at which time ethanol (100 mL) was added. When the solution stood for a few days, a pale-yellow crystalline solid formed, which was collected by filtration under vacuum, washed with absolute ethanol (ca. 50 mL), and air-dried (7.43 g, 87%). Anal. Found: C, 57.49; H, 4.34; N, 3.29; Zn, 7.93%. Calcd for $ZnC_{42}H_{42}Cl_2N_2O_{10}$: C, 57.91; H, 4.86; N, 3.22; Zn, 7.51%. ^{1}H NMR (in DMSO-d_6): δ (ppm) 7.74(H-13,14), 7.72(15,16), 7.13(H-3), 7.02(H-4), 6.78(H-6), 3.83(H-9), 3.43(H-18), 2.27(H-19).

***cis*-Bis(methanol)bis(η^2-*O,O′*-Indo)zinc(II), *cis*-[Zn(Indo)$_2$(MeOH)$_2$], 5.** To a solution of IndoH (3.61 g, 10.09 mmol) in DMF (10 mL), a solution of $Zn(OAc)_2 \cdot 2H_2O$ (1.24 g, 5.65 mmol) in DMF (10 mL) was added slowly. The mixture was stirred and heated at ca. 50 °C for 6 h and cooled to room temperature. Then methanol (50 mL) was added. When the solution stood overnight, colorless crystals were formed that were collected through filtration and air-dried (3.04 g, 71.5%). Anal. Found: C, 57.18; H, 4.26; N, 3.45; Zn 7.74%. Calcd for $ZnC_{40}H_{38}Cl_2N_2O_{10}$: C, 56.99; H, 4.54; N, 3.32; Zn, 7.76%. ^{1}H NMR (in DMSO-d_6): δ (ppm) 7.75(H-13,14), 7.73(15,16), 7.13(H-3), 7.02(H-4), 6.78(H-6), 3.83(H-9), 3.44(H-18), 2.27(H-19).

Bis(1-butanol)bis(η^2-*O,O′*-Indo)zinc(II)·2.25H$_2$O, [Zn(Indo)$_2$(1-butanol)$_2$]·2.25H$_2$O, 6; Bis(2-butanol)bis(η^2-*O,O′*-Indo)zinc(II)·3.25H$_2$O, [Zn(Indo)$_2$(2-butanol)$_2$]·3.25H$_2$O, 7; and Bis(2-methyl-2-propanol)bis(η^2-*O,O′*-Indo)zinc(II)·2.5H$_2$O, [Zn(Indo)$_2$(*t*-butanol)$_2$]·2.5H$_2$O, 8. $Zn(OAc)_2 \cdot 2H_2O$ (0.58 g, 2.64 mmol) in the appropriate warm butanol (20 mL) was slowly added to a warm solution of IndoH (1.85 g, 5.17 mmol) in butanol (20 mL). The mixture was heated at ca. 60 °C for 3 h, during which time a precipitate rapidly formed. Upon cooling to room temperature, the mixture was then filtered and the isolated solid was washed with a small amount of EtOH and finally air-dried. For **6**, yield 88.4%. Anal. Found: C, 56.71; H, 4.99; N, 2.85; Zn 7.11%. Calcd for $ZnC_{46}H_{50}Cl_2N_2O_{10} \cdot 2.25H_2O$: C, 57.09; H, 5.68; N, 2.89; Zn, 7.05%. ^{1}H NMR (in DMSO-d_6): δ (ppm) 7.76(H-13,14), 7.73(15,16), 7.13(H-3), 7.02(H-4), 6.78(H-6), 3.83(H-9), 3.46(H-18), 2.27(H-19). For **7**, yield 80.0%. Anal. Found: C, 55.57; H, 5.43; N, 2.71; Zn 7.52%. Calcd for $ZnC_{46}H_{50}Cl_2N_2O_{10} \cdot 3.25H_2O$: C, 56.05; H, 5.78; N, 2.84; Zn, 7.05%. ^{1}H NMR (in DMSO-d_6): δ (ppm) 7.75(H-13,14), 7.74(15,16), 7.13(H-3), 7.01(H-4), 6.78(H-6), 3.83(H-9), 3.49(H-18), 2.27(H-19). For **8**, yield 68.6%. Anal. Found: C, 56.49; H, 5.05; N, 2.81; Zn 7.12%. Calcd for $ZnC_{46}H_{50}Cl_2N_2O_{10} \cdot 2.5H_2O$: C, 56.83; H, 5.70; N, 2.88; Zn, 7.05%. ^{1}H NMR (in DMSO-d_6): δ (ppm) 7.75(H-13,14), 7.73(15,16), 7.13(H-3), 7.01(H-4), 6.78(H-6), 3.82(H-9), 3.46(H-18), 2.27(H-19).

Bis(dimethyl sulfoxide)bis(η^2-*O,O′*-Indo)zinc(II), [Zn(Indo)$_2$(DMSO)$_2$], 9. This complex was prepared in a manner similar to that of **1** except that dimethyl sulfoxide was used as the solvent. The mixture was heated with stirring for 7 h, then cooled to room temperature. The precipitate that formed after a few weeks was collected by filtration and washed with ethanol, then air-dried (0.95 g, 21.1%). Anal. Found: C, 53.48; H, 4.49; N, 3.09; Zn, 6.84%. Calcd for $ZnC_{42}H_{42}Cl_2N_2O_{10}S_2$: C, 53.94; H, 4.53; N, 3.00; Zn, 6.99%. ^{1}H NMR (in DMSO-d_6): δ (ppm) 7.71(H-13,14), 7.69(15,16), 7.09(H-3), 6.97(H-4), 6.74(H-6), 3.79(H-9), 3.45(H-18), 2.23(H-19).

Diaquabis(η^2-*O,O′*-Indo)zinc(II), [Zn(Indo)$_2$(OH$_2$)$_2$], 10. To a solution of IndoH (3.00 g, 8.38 mmol) in NaOH (0.1 M, 50 mL) a solution of $Zn(OAc)_2 \cdot 2H_2O$ (0.90 g, 4.10 mmol) in water (10 mL) was slowly added. The mixture was stirred and heated at 60 °C for 3 h, during which time a pale-yellow precipitate formed. After the mixture was cooled, the precipitate was collected by filtration, washed with water and EtOH, and air-dried (2.91 g, 89.3%). Anal. Found: C, 55.64; H, 3.95; N, 3.04; Zn, 8.38%. Calcd for $ZnC_{38}H_{34}Cl_2N_2O_{10}$: C, 56.00; H, 4.20; N, 3.44; Zn, 8.02%. ^{1}H NMR (in DMSO-d_6): δ (ppm) 7.73(H-13,14), 7.71(15,16), 7.11(H-3), 6.99(H-4), 6.76(H-6), 3.81(H-9), 3.44(H-18), 2.25(H-19).

Aqua(methylamine)bis(η^2-*O,O′*-Indo)zinc(II)·1.25H$_2$O, [Zn(Indo)$_2$(NH$_2$Me)(OH$_2$)]·1.25H$_2$O, 11. [Zn(Indo)$_2$(OH$_2$)$_2$] was slowly added to a THF solution of methylamine (2.0 M, 15 mL) until a saturated solution was formed. The mixture was stirred for 1.5 h at 45 °C, then set aside in a fume hood overnight. The white precipitate was collected by filtration, washed with a small amount of EtOH, and air-dried. Anal. Found: C, 54.75; H, 4.19; N, 4.95; Zn, 7.73%. Calcd for $ZnC_{39}H_{37}Cl_2N_3O_9 \cdot 1.25H_2O$: C, 55.07; H, 4.68; N, 4.94; Zn, 7.69%. ^{1}H NMR (in DMSO-d_6): δ (ppm) 7.7(H-13,14), 7.71(15,16), 7.12(H-3), 7.03(H-4), 6.75(H-6), 3.82(H-9), 3.43(H-18), 2.26(H-19).

Aquaimidazolebis(η^2-*O,O′*-Indo)zinc(II)·1.25H$_2$O, [Zn(Indo)$_2$(Im)(OH$_2$)]·1.25H$_2$O, 12. [Zn(Indo)$_2$(OH$_2$)$_2$] (0.40 g, 0.49 mmol) was slowly added to a solution of imidazole (0.034 g, 0.50 mmol) in MeOH (10 mL). The resultant mixture was stirred for 2 h, then filtered and washed with a small amount of MeOH, and air-dried. Anal. Found: C, 55.20; H, 4.30; N, 6.16; Zn, 6.89%. Calcd for $ZnC_{41}H_{36}Cl_2N_4O_9 \cdot 1.25H_2O$: C, 55.48; H, 4.37; N, 6.31; Zn, 7.37%. ^{1}H NMR (in DMSO-d_6): δ (ppm) 7.75(H-13,14), 7.73(15,16), 7.14(H-3), 7.04(H-4), 6.78(H-6), 3.80(H-9), 3.41(H-18), 2.28(H-19).

Physical Methods. Infrared spectra were recorded using a KBr matrix on a BIO-Rad Win-IR FTS-40 infrared spectrometer. Elemental microanalyses were performed by the Department of Chemical Engineering, University of Sydney. A Varian AA-800 air−acetylene flame atomic absorption spectrophotometer was used for the Zn analyses. ^{1}H and ^{13}C NMR spectra were recorded at room temperature in DMF-d_7, DMSO-d_6, or pyridine-d_5 on a Bruker AM400 spectrometer using the solvents as internal standards but with shifts cited versus tetramethylsilane (TMS).

X-ray Crystallographic Analyses. Crystal data and processing parameters of complexes **1**−**5** are listed in Table 1. Diffraction data were collected at 21 ± 1 °C on a Rigaku AFC7R diffractometer employing graphite monochromated Cu Kα radiation (λ = 1.541 78 Å) from a rotating anode generator. There were no significant changes in the intensities of three representative reflections measured every 150 reflections during the data collections for complexes **1**, **2**, and **4**. A generator anomaly during the data collection for complex **3** resulted in a 30.0% increase in the reference reflections intensities, whereas the intensities of the complex **5** standards decreased by 23.0% during the data collection. A polynomial correction factor was accordingly applied to the data for complexes **3** and **5**. An empirical absorption correction based on azimuthal scans of three reflections was applied to the data for complexes **1**, **3**, and **5**, and an analytical correction was applied to the complex **2** and **4** data. The diffraction data were also corrected for Lorentz and polarization effects.

All calculations were undertaken with the teXsan[20] crystallographic software package. Neutral atom scattering factors were taken from Cromer and Waber.[21] Anomalous dispersion effects were included in F_c,[22] and the values for $\Delta f'$ and $\Delta f''$ were those of Creagh and McAuley.[23] The values for the mass attenuation coefficients were those of Creagh and Hubbell.[24] The structures were solved by direct methods[25] and expanded using Fourier techniques.[26] The least-squares planes were

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Table 1. Crystal Data and Processing Parameters for Complexes **1**−**5**

	complexes				
	1	**2**	**3**	**4**	**5**
empirical formula	$C_{92}H_{96}Cl_4N_8O_{20}Zn_2$	$C_{86}H_{70}Cl_4N_6O_{18}Zn_2$	$C_{86}H_{78}Cl_4N_6O_{18}Zn_2$	$C_{42}H_{42}Cl_2N_2O_{10}Zn$	$C_{40}H_{38}Cl_2N_2O_{10}Zn$
fw	1906.38	1748.10	1756.18	871.09	843.05
cryst color, habit	yellow, prism	yellow, prism	colorless, blade	yellow, blade	colorless, columnar
cryst syst	triclinic	triclinic	triclinic	monoclinic	monoclinic
cryst size (mm)	0.38 × 0.17 × 0.15	0.25 × 0.09 × 0.06	0.35 × 0.12 × 0.08	0.50 × 0.15 × 0.05	0.25 × 0.05 × 0.03
lattice type	primitive	primitive	primitive	C-centered	C-centered
space group	$P\bar{1}$ (#2)	$P\bar{1}$ (#2)	$P\bar{1}$ (#2)	$C2/c$(#15)	$C2/c$(#15)
Z value	1	1	1	4	4
a (Å)	13.628(2)	13.347(3)	14.143(3)	30.086(2)	29.419(2)
b (Å)	17.462(2)	16.499(5)	14.521(2)	5.3638(6)	5.320(2)
c (Å)	11.078(1)	10.857(1)	11.558(2)	24.739(2)	24.461(2)
α (deg)	99.49(1)	99.48(2)	109.07(1)		
β (deg)	108.13(1)	108.25(2)	90.80(2)	90.342(7)	90.840(4)
γ (deg)	110.10(1)	106.24(2)	116.40(1)		
V (Å^3)	2241.0(7)	2094(1)	1973.6(8)	3992.2(5)	3827(1)
D_{calc} (g cm^{-3})	1.412	1.386	1.472	1.429	1.463
F_{000}	992.0	900.0	902.0	1808.0	1744.0
μ(Cu Kα) (cm^{-1})	23.81	24.75	26.27	26.01	26.95
total data	7981	7418	6124	4079	3508
total unique data	7622	7077	5834	3799	3437
no. variables	568	532	524	257	249
no. observations	6531 [$I > 2.50\sigma(I)$]	5667 [$I > 3.00\sigma(I)$]	4697 [$I > 2.50\sigma(I)$]	2400 [$I > 3.00\sigma(I)$]	2393 [$I > 3.00\sigma(I)$]
final diff map$_{maxi}$ (e$^-$/Å^3)	0.71	0.63	0.50	0.43	0.67
final diff map$_{mini}$ (e$^-$/Å^3)	−0.70	−0.58	−0.65	−0.59	−0.63
residuals:[a] R; R_w	0.043; 0.044	0.053; 0.056	0.050; 0.058	0.050; 0.055	0.042; 0.046

[a] $R = \sum(|F_o| - |F_c|)/\sum |F_o|$. $R_w = (\sum w(|F_o| - |F_c|)^2/\sum w|F_o|^2)^{1/2}$, $w = 1/\sigma^2(F_o)$.

calculated with the XTAL software package.[27] In general non-hydrogen atoms were modeled with anisotropic atomic displacement parameters and hydrogen atoms were included in the model at calculated positions with group thermal parameters. The crystals of complexes **1** and **2** are isomorphous, and the complexes are isostructural and centered about inversion sites in $P\bar{1}$ (No. 2), as is the isostructural complex **3**. The asymmetric unit of the complex **1** structure contains two solvent molecules, and the asymmetric unit for complex **2** includes two sites treated as the oxygen atoms of two water molecules, with 50% occupancies. There are no additional molecules in the asymmetric unit for complex **3**. The crystals of complexes **4** and **5** are isomorphous, and the complexes are isostructural with the metal ion residing on a 2-fold axis in $C2/c$ (No. 15). The ethanol ligand of complex **4** is disordered, with the occupancies of the isotropically modeled C(20a) and C(20b) sites initially refined and then fixed at 0.5. There were no hydrogen atoms included in the model for the ethanol ligand of complex **4**. The methanol oxygen hydrogen site of complex **5** could not be located; however, the inclusion in the complex **5** model of a hydrogen at a calculated position corresponding to an sp^2-hybridized oxygen lowered the refinement residuals by 0.1%. Placement of the hydrogen at an sp^3 position resulted in no change in the residuals in one position and an increase of 0.2% in the second position. Projections of the complex molecules were generated with ORTEP.[28]

Results

Synthesis and Spectroscopic Characterization. Highly crystalline samples of all the complexes were prepared in good yields, with diffraction-quality single crystals for **1**−**5** being obtained on prolonged standing of the reaction solutions. Elemental analyses and IR spectroscopy showed that the complexes contained varying amounts of solvent molecules, and structural studies demonstrated that these act as ligands to the Zn(II), as well as occupy noncoordinated solvent sites. The presence of noncoordinated solvent molecules was confirmed during the crystallographic study of **1**. In the case of the imidazole complex a mixed aquaimidazole complex of the type $[Zn(Indo)_2(Im)(OH_2)]$ was obtained, even when an excess of imidazole was used in the reaction.

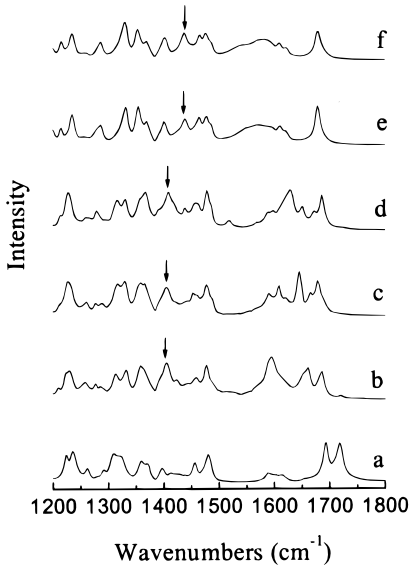

Figure 1. IR spectra in KBr of (a) IndoH, (b) $[Zn_2(Indo)_4(DMA)_2]$, (c) $[Zn_2(Indo)_4(Py)_2]$, (d) $[Zn_2(Indo)_4(NMP)_2]$, (e) $[Zn(Indo)_2(EtOH)_2]$, and (f) $[Zn(Indo)_2(MeOH)_2]$.

The IR spectra of all the complexes show strong absorptions near 1680 and 1700 cm^{-1} (Supporting Information and Figure 1) corresponding to the amide and carbonyl C═O stretches in the Indo ligand. Whereas the amide C═O frequency is essentially constant in all the complexes, the carbonyl stretching frequency shows two distinct patterns. The IR spectra of complexes **1**−**3** are similar, as are those of **4**−**12**, but the spectra of these two groups of complexes are clearly different. This is most evident in the region around 1400 cm^{-1}, where in the spectra of complexes **4**−**12,** there is a strong band near 1440 cm^{-1} that is absent in complexes **1**−**3**. This moderately strong

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(28) Johnson, C. K. *ORTEP*; Report ORNL-5138; Oak Ridge National Laboratory: Oak Ridge, TN, 1976.

Table 2. Selected Bond Lengths (Å) and Angles (deg) for Complexes **1**−**3**

	1	**2**	**3**
Zn(1)−Zn(1)	2.9686(6)	2.969(1)	2.934(1)
Zn(1)−O(1)	2.036(2)	2.040(3)	2.048(3)
Zn(1)−O(2)	2.035(2)	2.048(3)	2.051(3)
Zn(1)−O(5)	2.038(2)	2.020(3)	2.009(3)
Zn(1)−O(6)	2.060(2)	2.049(3)	2.028(3)
Zn(1)−O(9)	1.989(2)	2.036(3)[a]	1.986(3)
O(1)−C(1)	1.245(3)	1.237(4)	1.240(5)
O(2)−C(1)	1.244(3)	1.242(4)	1.260(5)
O(5)−C(20)	1.249(3)	1.262(5)	1.252(6)
O(6)−C(20)	1.253(3)	1.235(5)	1.249(6)
O(1)−Zn(1)−O(2)	158.70(8)	158.4(1)	160.0(1)
O(1)−Zn(1)−O(5)	88.24(9)	89.2(1)	88.0(1)
O(1)−Zn(1)−O(6)	89.36(9)	88.5(1)	89.2(1)
O(1)−Zn(1)−O(9)	102.83(8)	98.3(1)[a]	103.2(1)
O(2)−Zn(1)−O(5)	87.50(9)	87.9(1)	88.1(1)
O(2)−Zn(1)−O(6)	87.26(9)	86.3(1)	87.7(1)
O(2)−Zn(1)−O(9)	98.47(8)	103.1(1)[a]	96.8(1)
O(5)−Zn(1)−O(6)	159.18(8)	158.4(1)	159.8(1)
O(5)−Zn(1)−O(9)	103.06(8)	107.3(1)[a]	101.1(1)
O(6)−Zn(1)−O(9)	97.64(8)	94.3(1)[a]	99.0(1)
Zn(1)−O(1)−C(1)	129.4(2)	134.9(3)	122.2(3)
Zn(1)−O(2)−C(1)	125.6(2)	120.6(3)	131.8(3)
Zn(1)−O(5)−C(20)	125.0(2)	122.4(3)	126.0(3)
Zn(1)−O(6)−C(20)	129.1(2)	132.4(3)	128.3(3)
O(1)−C(1)−O(2)	126.1(2)	125.8(4)	125.9(4)
O(1)−C(1)−C(2)	117.4(2)	117.5(3)	118.3(4)
O(2)−C(1)−C(2)	116.5(2)	116.7(3)	115.8(4)

[a] In complex **2**, atom O(9) is replaced by N(3).

band near 1440 cm^{-1} is assigned to the symmetric carboxyl stretching frequency $\upsilon_s(COO^-)$. The analogous asymmetric stretching frequency $\upsilon_{as}(COO^-)$ for complexes **1**−**3** is near 1600 cm^{-1}, and the positions and separations, ca. 200 cm^{-1}, of these bands are indicative of a bridging bidentate coordination mode of the carboxylate groups, as occurs in copper acetate like dimers[29] and in the $[Cu_2(Indo)_4L_2]$[9] complexes. In the spectra of **4**−**12**, the intensity of the band near 1400 cm^{-1} is considerably lower than those in the spectra of **1**−**3**, and it is probable that this band also contains the symmetric carboxylate stretch υ_s (COO^-). The smaller separations between υ_{as} and υ_s in the spectra of complexes **4**−**12** are indicative of a chelating geometry, as occurs in monomeric species.[30]

The ^1H NMR spectra do not differ significantly for the complexes. The ^{13}C NMR spectra in the various complexes were collected in three different solvents. The spectra reveal a downfield chemical shift of the carboxylate carbon atom in all the complexes relative to that of IndoH, and there is no significant difference between spectra of the monomeric and dimeric complexes. This suggests that either the species rapidly equilibrate or the ^{13}C NMR resonance is not sensitive to the type of carboxylate coordination. We note that the ^{13}C NMR and IR spectral properties previously reported for a Zn−Indo complex prepared in aqueous solutions are similar to those found here for the monomeric complexes, and this indicates that the complex formed in the previous study is most likely the monomer $[Zn(Indo)_2(H_2O)_2]$.[1]

X-ray Crystallography. The single-crystal structures of complexes **1**−**3** are isostructural, space group $P\bar{1}$ (No. 2), and they are also isostructural with the related Cu complexes $[Cu_2(Indo)_4(L)_2]$, L = DMF, DMSO.[9,10] Selected bond angles and distances for complexes **1**−**3** are given in Table 2. The structures consist of centrosymmetric dinuclear Zn units and are typical of dinuclear $[M_2(carboxylate)_4L_2]$ complexes, with the Indo ligands providing the four metal-bridging bidentate carboxylate residues. The Indo ligands display a paddle wheel like arrangement about the Zn···Zn axis. Each Zn(II) cation has a square-pyramidal coordination geometry, with the apex provided by axial coordination of a solvent ligand (DMA, Py, or NMP). The metal to apical atom distances are 1.989(2), 2.036(3), and 1.986(3) Å for DMA, Py, and NMP, respectively, and the mean Zn−O(carboxylate) bond length is 2.042 Å in **1**, 2.039 Å in **2**, and 2.034 Å in **3**. These distances are typical and unremarkable.[13−15] The metal displacement from the square-pyramid-base least-squares plane is 0.0373(1), 0.0382(1), and 0.0355(1) Å for **1**, **2**, and **3**, respectively, and this pattern follows the donor capacity of the axial ligands. Charge donation from the axial ligand would cause a nephelauxetic swelling of the metal-based orbitals that would tend to electrostatically displace the metal from the basal plane. Additionally, the charge donation would lift the metal-based orbital energies and so slightly weaken the basal bonding.

The tetracarboxylate bridging framework can accommodate metal−metal separations of up to 3.452 Å.[31] The Zn···Zn separations of 2.9686(6), 2.969(1), and 2.934(1) Å for **1**, **2**, and **3**, respectively, are shorter than this maximum but much longer than the corresponding Cu···Cu distance observed in $[Cu_2(Indo)_4(DMF)_2]$ (2.630 Å). This may reflect attractive metal−metal interactions in the copper complex. The average Zn−O distance is also somewhat longer than that determined for the analogous Cu complex (1.965 Å).[9] Interestingly, the L−Zn···Zn−L units are not collinear as they are in the Cu dimers.[9,10] There is a small lateral shift of the two zincs, with respect to the principal dimer axis, of 0.13 Å for complex **1**, 0.34 Å for complex **2**, and 0.20 Å for complex **3**. Additionally, the metal to apex atom bond forms an angle of 3.43(5), 6.85(8), and 3.38(9)° with the base least-squares plane normal of **1**, **2**, and **3**, respectively. The Zn···Zn···apex atom angle is 175.21(6)°, 166.93(9)°, and 172.6(1)° for complexes **1**, **2**, and **3**, respectively. Dinuclear $[Zn_2(carboxylate)_4L_2]$ complexes have previously been observed to be either collinear[13,14] or similarly offset.[15]

The methanol and ethanol complexes are isostructural with the metal residing on a 2-fold axis in *C*2/*c* (No. 15). As shown in the ORTEP diagram for the methanol complex (Figure 3), the complexes are pseudo-octahedral, with the equatorial plane defined by the carboxylate atoms O(1), O(2), and O(2*) (where O(2*) is generated from O(2) with $1 - x, y, 0.5 - z$) and O(5) of the methanol ligand. The methanol O(5*) is then axial with the angle between the equatorial atoms least-squares plane normal and the Zn(1)−O(5*) line being 5.53(5)°. The angle between the Zn to carboxylate O(1*) bond line and the equatorial atoms least-squares plane normal is 21.56(5)°. The analogous angles for **5** are 5.23(5)° and 21.71(5)°, respectively. Apparently the bidentate carboxylate geometry hinders metal−ligand orbital overlap. The $Zn-O_{RCOO}$ bond distances of 2.183(3) and 2.169(3) Å in **4** and 2.196(2) and 2.152(2) Å in **5** are similar to those observed in zinc acetate dihydrate.[26] Other selected bond angles and distances are listed in Table 3.

Discussion

The structures of several monomeric, dimeric, trimeric, and polymeric zinc carboxylates have been described and attempts have been made to relate the physical properties of these with

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(31) Allman, T.; Goel, R. C.; Jha, N. K.; Beauchamp, A. L. *Inorg. Chem.* **1984**, *23*, 914−918.

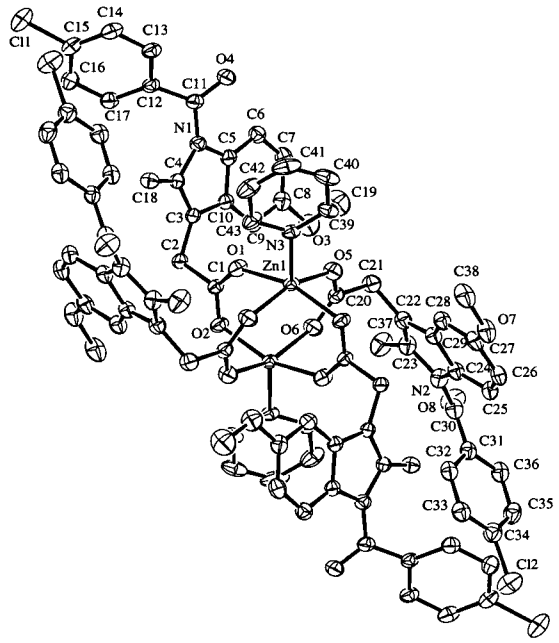

Figure 2. ORTEP[28] depiction of $[Zn_2(Indo)_4(Py)_2]$, with atomic displacement ellipsoids shown at the 25% level.

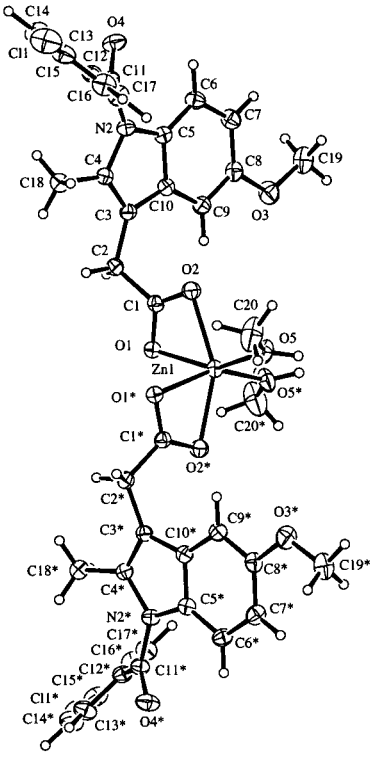

Figure 3. ORTEP[28] depiction of $[Zn(Indo)_2(MeOH)_2]$, with atomic displacement ellipsoids shown at the 25% level.

the structural changes.[13−18,32−37] In the case of the zinc carboxylates only three dimeric complexes have been structurally characterized,[13−15] whereas monomeric complexes are more common,[16−18,32−37] although these invariably have aqua donor groups. No examples of monomeric and dimeric zinc complexes with the same bidentate carboxylate group have been reported previously, although examples are known where the ligand acts as a bidentate in a dimer and a monodentate in a monomer.[13]

Table 3. Selected Bond Length (Å) and Bond Angles (deg) for **4** and **5**

	4	**5**
Zn(1)−O(1)	2.183(3)	2.195(2)
Zn(1)−O(2)	2.169(3)	2.151(2)
Zn(1)−O(5)	2.015(3)	2.022(3)
O(1)−C(1)	1.275(4)	1.274(4)
O(2)−C(1)	1.244(5)	1.245(4)
O(1)−Zn(1)−O(1)	85.9(1)	85.8(1)
O(1)−Zn(1)−O(2)	60.1(1)	60.03(8)
O(1)−Zn(1)−O(2)	99.6(1)	98.66(9)
O(1)−Zn(1)−O(5)	152.8(1)	152.90(9)
O(1)−Zn(1)−O(5)	96.2(1)	94.7(1)
O(2)−Zn(1)−O(2)	153.8(2)	152.4(1)
O(2)−Zn(1)−O(5)	105.0(1)	93.2(1)
O(2)−Zn(1)−O(5)	92.9(1)	105.0(1)
O(5)−Zn(1)−O(5)	94.2(2)	96.9(2)
Zn(1)−O(1)−C(1)	89.2(2)	88.6(2)
Zn(1)−O(2)−C(1)	90.7(2)	91.4(2)
O(1)−C(1)−O(2)	119.7(4)	119.4(3)
O(1)−C(1)−C(2)	118.3(4)	118.3(3)

Hence, the present series of compounds provides the first opportunity to compare the bonding contacts in monomeric and dimeric zinc complexes. In general the $Zn-O_{RCOO}$ bond lengths in the monomers are longer (average 2.175 Å) than those in the dimeric complexes (average Zn−O 2.038 Å). This is a consequence of the higher coordination number and hindered orbital overlap in the bidentate carboxylate groups. The O−C−O bond angle is reduced to ∼119° in the monomers compared to ∼126° in the dimers. These angles are similar to those observed in other monomeric and dimeric carboxylate groups, including zinc acetate dihydrate[16] and $[Cu_2(Indo)_4(DMF)_2]$.[9] These differences account for the observed shifts in carboxylate stretching frequencies observed in the IR spectra.

It is believed that the biological activity of Cu(II) complexes of Indo such as $[Cu_2(Indomethacin)_4(DMF)_2]$ is related to their dimeric structure.[7,9] The Cu(II) complex has a lower level of gastric toxicity than IndoH itself, and this may be because the dimeric complex presents a more effective "lipophilic package".[7,9,13] Partial decomposition of the dimeric Cu(II) complex to monomeric species is observed under certain conditions appropriate to their pharmaceutical preparation, and this may increase the side effects and limit the efficacy of the drug. Thus, the pharmaceutical effectiveness of Zn(II) Indo complexes of Indo may critically depend on the relative stability of the dimeric and monomeric forms.

The Py, DMA, or NMP adducts are dinuclear with pentacoordination about the metal, whereas the alcohol adducts are mononuclear with hexacoordination of the metal. Singh et al.[13] have shown that the Zn−acetate−py system can yield monomeric, dimeric, or polymeric products depending on the solvents used. Interestingly and significantly, the monomeric $[Zn(Py)_2(O_2CCH_3)_2]$ complex is four-coordinate with unidentate carboxylate coordination.[13] The polymeric $\{[Zn(O_2CCH_3)(Py)]_n\}$ complex is five-coordinate,[13] and the 4-vinylpyridinezinc carboxylate trimer reported by Clegg et al.[15] is also five-coordinate. By contrast, the eight literature $[Zn(OH_2)_2(O_2CR)_2]$

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(35) O'Reilly, E. J.; Smith, G.; Kennard, C. H. L.; Mak, T. C. W. *Aust. J. Chem.* **1987**, *40*, 1147−1159.
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(37) Mak, T. C. W.; Yip, W. H.; Smith, G.; O'Reilly, E. J.; Kennard, C. H. L. *Inorg. Chim. Acta* **1984**, *84*, 57−64.

complexes[16−18,32−37] and **4** and **5** are six-coordinate when the additional neutral ligand is a relatively weak Lewis base such as water, methanol, or ethanol. This circumstantially suggests that the water and the alcohols are unable to support a less than six-coordinate metal center. Stronger Lewis bases such as Py, DMA, or NMP apparently reduce or remove the need for hexacoordination. Presumably the stronger Lewis bases elevate the metal-based target orbitals beyond the reach of a sixth ligand ($[Zn(Py)_2(O_2CCH_3)_2]$ uses only two of the four available carboxylate oxygen atoms). The determining factor in Zn(II) carboxylate dimer formation may simply be the ability of theavailable ligand set to support a less than six-coordinate metal ion center.

What is clear is that dimeric carboxylate complexes are preferred for Cu(II) relative to Zn(II). This may be a contribution to the observation in preliminary animal studies that $[Cu_2(Indo)_4(DMF)_2]$[9] has low toxicity to both the stomach and the small intestine, whereas $[Zn_2(Indo)_4(DMA)_2]$ has low toxicity in the small intestine but is toxic to the stomach.[38] This prompts the hypothesis that the pharmacokinetics and efficacy of Indo−metal ion anti-inflammatory drugs may depend on the relative stability of the dinuclear Indo complexes. This aspect will be the subject of further research.

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Supporting Information Available: Tables of crystal data, bond distances, bond angles, hydrogen atom coordinates and parameters, anisotropic thermal parameters for **1**−**5**, IR stretching frequencies and ^{13}C NMR spectra for **1**−**12**, and figures of ORTEP projections for **1**, **3**, and **4**. This material is available free of charge via the Internet at http://pubs.acs.org. Structure factors may be obtained directly from the authors.

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(38) Davies, N. Department of Pharmacy, University of Sydney. Personal communication, 1999.