Azolidene Carbenes Derived from Biologically Relevant Molecules.[1] Synthesis and Characterization of Iridium Complexes of Imidazolidene Ligands Based upon the Antifungal Drugs Econazole and Miconazole

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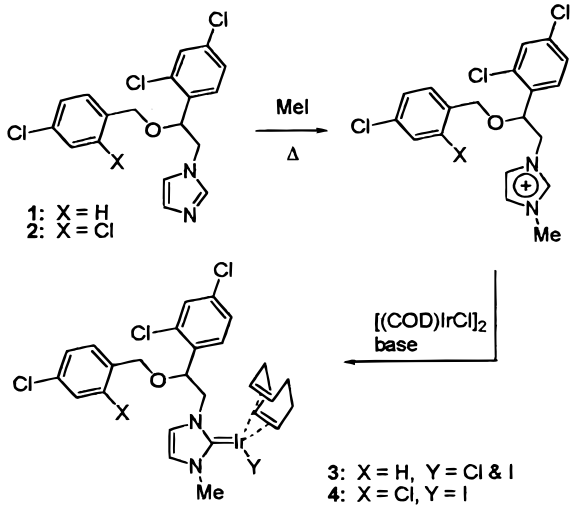
Imidazole and other -azole ring systems are structural features of many drugs and natural products.[2] Azoles are typically susceptible to N-alkylation, forming azolium cations.[3] Many of the latter undergo deprotonation of a ring C−H α to the nitrogen, generating an azolidene carbene.[4] In at least one case, that of thiamine (vitamin B_1), such a carbene is thought to be involved in the biological function of the molecule.[5] In turn, the capacity of azolidene carbenes to function as ligands in transition-metal complexes is well-established.[6] Consequently, biologically relevant molecules containing azoles are candidates as carbene sources for metal complexation. We consider the utilization of drugs or natural products in this role to be a potentially useful approach for the development of compounds of interest for medicinal and biochemical applications. Further, since N-methylation is a common metabolic event,[7] studies of such molecules may ultimately provide new insights into possible modes of metal−azole interactions in biological systems.[8]

We report here the results of our initial work in this area, the utilization of the antifungal drugs econazole and miconazole as carbene ligand precursors for complex formation with iridium (Scheme 1). The new complexes are the first to link a drug-based ligand to a metal via a metal−carbon σ bond, and they complement a small family of antifungal drug−metal conjugates possessing metal−nitrogen linkages.[9]

Both econazole and miconazole were prepared as the respective free bases from the commercially available nitrate salts.[10] The salts were dissolved in water and the solutions brought to pH = 8 with aqueous base and then extracted with Et_2O. Evaporation of the ether solutions yielded the free bases in essentially quantitative yield. Alkylation of the free bases was accomplished by refluxing each in neat methyl iodide, followed by evaporation to dryness.[11] The off-white powders (**1**, econazole derivative; **2**, miconazole derivative) obtained in this fashion are used without purification.

Scheme 1



In THF at 0 °C, the econazolium salt **1** reacted with the phosphazene base P_4-*t*-Bu,[12] as ascertained by a change in color of the solutions from near colorless to yellow upon mixing. Subsequent addition at 0 °C of the putative free-carbene solution to a light orange, THF suspension of $[\eta^4$-(1,5-COD)IrCl$]_2$ resulted in a color change of the latter to dark yellow-orange, accompanied by the complete dissolution of the iridium complex. After an additional 15 min of stirring, no further color change was observed and the THF was removed in vacuo. The residue was extracted into CH_2Cl_2 and filtered through silica to remove the putative P_4-*t*-Bu:HX byproduct. Removal of the solvent in vacuo produced a yellow-orange microcrystalline product, the ^{1}H and ^{13}C NMR spectra of which support its being an iridacarbene.[13] A key spectroscopic element in this assignment is the appearance of a

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(10) Sigma Chemical Company, St. Louis, MO.
(11) **Caution!** Methyl iodide is highly toxic. Handle with care in an efficient fume hood.
(12) Pietzonka, T.; Seebach, D. *Chem. Ber.* **1991**, *124*, 1837.
(13) ^{13}C NMR(75.57 MHz, δ, $CDCl_3$): 29.18, 29.99, 33.09, 34.11 (all COD); 37.62 (N−CH_3); 50.81, 51.90, 54.48 (all COD); 68.64 (N−CH_2−); 77.52 (PhCH_2O−); 84.64 (COD); 85.19(O−CH_2−PhCH_2); 120.90, 122.64 (imidazole C4 and C5); 122.64, 127.65, 128.49, 129.05, 129.32, 129.52, 129.81, 129.95, 133.53, 134.68, 135.55, 136.26 (all aryl); 181.26 (carbene C). ^{1}H NMR (300.53 MHz, δ, $CDCl_3$): 1.27−1.67 (m, br, 4H, COD); 2.14−2.16 (m, br, 4H, COD); 2.75 (m, 1H, COD); 2.97 (m, 1H, COD); 3.99 (s, 3H, N−CH_3); 4.04 (dd, 1H, PhOC*H*PhCH_2); 4.30 (s, br, 2H, NCH_2CH−); 4.60 (m, br, 2H, PhCH_2O); 4.85 (m, 1H, COD); 5.41 (m, 1H, COD); 6.76 (d, 1H, imidazole H); 6.99 (d, 1H, imidazole H); 7.10−7.18 (m, 2H, aryl); 7.23−7.34 (m, 3H, aryl); 7.44 (m, 1H, aryl); 7.54 (m, 1H, aryl). All reported data for major (chloro) derivative.

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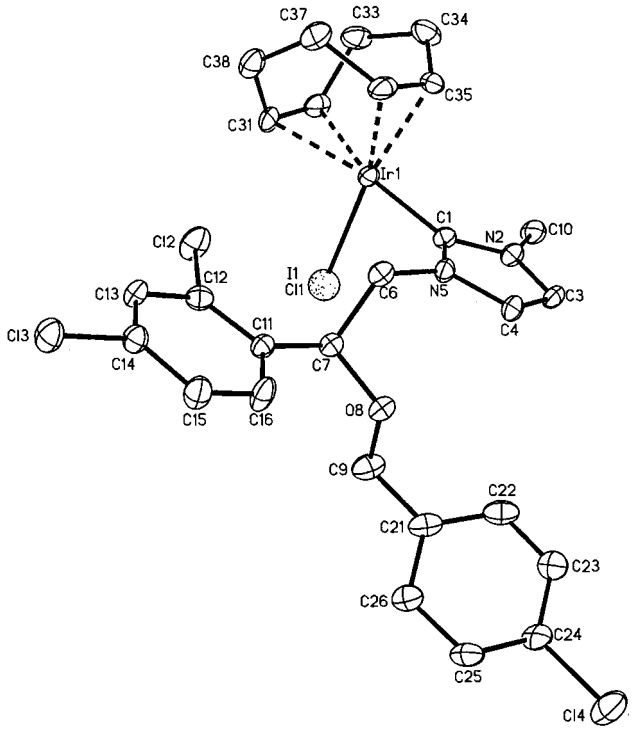

Figure 1.

resonance in the ^{13}C spectrum at 181.26 ppm, characteristic of an iridium-bound carbene carbon.[14]

X-ray quality crystals of **3** were grown by the slow diffusion of hexane vapor into a CH_2Cl_2 solution of the product. The crystal structure and the labeling of the atoms of **3** are shown (Figure 1). The $16e^-$ iridium center adopts a distorted square planar geometry which includes a hybrid iodo/chloro halogen site and the econazolidene carbene. The carbene-carbon to iridium distance of 2.017(7) Å is similar to that of other published iridium−carbene complexes.[14] The crystal structure exists as discrete molecules of **3** with no anomalous intermolecular contacts.[15]

The related miconazolidene−Ir complex **4** was prepared utilizing finely divided sodium acetate as a base. The base, *N*-methylmiconazolium iodide (**2**), and $[\eta^4$-(1,5-COD)IrCl$]_2$ were combined in THF and refluxed for 3 h. After cooling, the dark brown-orange suspension was filtered through 1 cm of silica, yielding a bright orange solution. Subsequent vapor diffusion of hexane into the solution produced yellow microcrystals of **4**. The ^{13}C NMR spectrum[21] of **4** exhibits a singlet at δ 181.26, confirming the incorporation of a carbene ligand. The spectrum also exhibits the expected resonances for the remaining components of the miconazolidene ligand. Between 127 and 135 ppm are peaks for the dichlorophenyl carbons, while singlets for the imidazolidene C4 and C5 atoms appear at 120.98 and 122.51 ppm. A total of eight COD-carbon resonances between 29.21 and 84.70 ppm are observed, consistent with the asymmetric nature of the complex imposed by the racemic carbene ligand. Peaks at 85.16, 78.37 and 68.64 ppm arise from the miconazolidene benzyl ether and $N-CH_2$ units. The resonance for the terminal $N-CH_3$ carbon is observed at 37.61 ppm. The FAB-MS and elemental analysis data of **4** are consistent with the proposed formulation.[22]

The preparation of compounds **3** and **4** demonstrates the feasibility of assembling stable drug−metal complex conjugates by means of linking the two species via $M-C_{carbene}$ interactions. Other studies currently underway in our laboratory have given encouraging results for the utilization of a variety of natural products as carbene precursors. We expect to report on the results of these experiments in due course.

Acknowledgment. J.H.D. thanks the University of South Alabama Research Council for support of this work. We also thank Dr. N. Dale Ledford for the acquisition of the NMR data.

Supporting Information Available: Tables of crystal data, thermal parameters, bond distances and angles, and atomic coordinates for complex **3** (7 pages). Ordering information is given on any current masthead page.

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(15) X-ray data collection, structure determination, and refinement for **3**: A single crystal of **3** (dimensions 0.25 × 0.20 × 0.20 mm) was sealed into a thin-walled glass capillary under aerobic conditions. It was then mounted and aligned upon an Enraf-Nonius CAD4 single-crystal X-ray diffractometer (Mo Kα radiation, λ = 0.710 73 Å). Details of the data collection are collected in the Supporting Information. Unit cell parameters demonstrate that the crystal belongs to the triclinic system. Intensity statistics clearly favored the centrosymmetric space group $P\bar{1}$ (No. 2) over the noncentrosymmetric space group $P1$ (No. 1). This was later verified by successful solution and refinement of the crystal structure. All crystallographic calculations were carried out with the use of the Siemens SHELXTL-PC program package.[16] The potential and anisotropic thermal parameters of all non-hydrogen atoms were refined (except for the disordered halogen, which was refined isotropically). Hydrogen atoms were included in their idealized staggered geometries with d(C−H) set at 0.96 Å.[17] The treated model was refined until convergence, with the final residual indices being R = 3.87% and R_w = 5.23% for all 3519 independent reflections and R = 3.25% for those 3089 data with $|F| > 6\sigma(|F_o|)$. After refinement, the anomalous features present on the difference Fourier map were a peak of 2.11 e Å^{-3} and a hole of −1.32 e Å^{-3}, both of which were associated with the substitutional disorder at the halogen site.[18]

(16) *Siemens SHELXTL-PC Manual*, release 4.1; Siemens Analytical Instruments: Madison, WI, 1990.

(17) *International Tables for Crystallography*; Kluwer Academic Publishers: Dordrecht, The Netherlands, 1995; Vol. C, pp 713−791.

(18) The crystal was discovered to be a mixture of both the iodo and chloro derivatives. The static disorder problem was initially identified by the anomalous iridium−halogen bond length. The distance Ir−X was determined to be 2.512(2) Å, which is intermediate between the distances expected for Ir−Cl and Ir−I bonds (2.390 and 2.729 Å, respectively).[19] This anomaly led to further examination of the difference Fourier map. The peak height associated with the halogen site had a height equivalent of 34.42% of that associated with the Ir center. This corresponds to approximately 26.5 e^-, which again is clearly between chloride and iodide. This clearly demonstrates that the overall crystal structure must be the result of a statistical averaging of both chloro and iodo derivatives (bromide being excluded by other experimental data). The percent composition of the crystal was estimated to be 26.4% iodo and 73.6% chloro.[20] The disordered chlorine and iodine atoms are in too close a proximity to be effectively resolved by the X-ray study. The resulting Ir−X bond distance is a statistical average of these two different Ir−halogen distances. During refinement, a hybrid iodo/chloro atom was inserted into the halogen site with occupancy k = 0.264 for I and 0.736 for Cl.

(19) Churchill, M. R. *Inorg. Chem.* **1973**, *12*, 1213.

(20) Determined by the algebraic expression $53X + 17(1 - X) = 26.5$ (iodine = 53 e^-; chlorine = 17 e^-; unknown peak = 26.5 e^-).

(21) ^{13}C NMR (75.57 MHz, δ, $CDCl_3$): 29.21, 29.96, 33.14, 34.06 (all COD); 37.61 ($N-CH_3$); 50.87, 51.89, 54.46 (all COD); 71.22 ($N-CH_2-$); 84.69 (COD); 85.16 ($O-CH_2-PhCH_2$); 120.30, 122.51 (imidazole C4/C5); 127.06, 127.64, 129.00, 129.11, 129.77, 130.70, 134.03, 134.12, 134.74, 135.29 (all aryl); 181.26 (carbene C). ^1H NMR (300.53 MHz, δ, $CDCl_3$): 1.50−1.80 (m, br, 4H, COD); 2.04−2.23 (m, br, 4H, COD); 2.75 (m, 1H, COD); 2.96 (m, 1H, COD); 3.97 (s, 3H, $N-CH_3$); 4.11 (dd, 1H, PhOC*H*PhCH$_2$); 4.43 (dd, 2H, NCH_2CH−); 4.60 (m, br, 2H, PhCH_2O); 4.86 (dd, 1H, COD); 5.44 (dd, 1H, COD); 6.75 (d, 1H, imidazole H); 6.99 (d, 1H, imidazole H); 7.13−7.28 (m, 4H, aryl); 7.44 (m, 1H, aryl); 7.52 (d, 1H, aryl).

(22) C, H, N analytical data calcd for **4**, $C_{27}H_{28}N_2Cl_4IIrO$: C, 37.82; H, 3.29; N, 3.27. Found: C, 37.75; H, 3.23; N, 3.10.