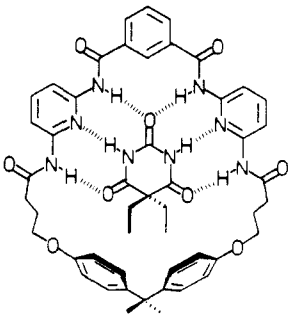
Table I. Association Constants for the Receptor-Barbiturate Interaction[a]

receptor	barbiturate	K_a, M^{-1} (25 °C, $CDCl_3$)
6	barbital (**1b**)	2.08×10^4
5	mephobarbital (**1d**)	6.80×10^2
5	phenobarbital (**1c**)	1.97×10^5
5	barbital (**1b**)	1.37×10^6

[a] At 250 MHz: [receptor] = 2.0×10^{-3} M, [barbiturate] = 4.0×10^{-2} M. Measurements made on isophthaloyl-2H and both amide-NHs by using 12-15 points. In all cases titration curves showed distinct 1:1 stoichiometry.

the hexa-hydrogen-bonded complex **7**.[14] The CH_2 and CH_3 resonances of the barbital ethyl groups were shifted upfield by 0.25 and 0.23 ppm, respectively, confirming their proximity to the diphenylmethane cleft in **7**. Furthermore, the isophthaloyl resonances in uncomplexed **5** are broadened due to the conformational mobility of the macrocycle. In complex **7** the motion of the isophthaloyl group is restricted and its ^1H resonances sharpen. CPK molecular modeling suggests that in **7** the isophthaloyl-2 proton is forced to lie in the deshielding region of the barbital-2-carbonyl group, and, indeed, this resonance is shifted downfield by 0.4 ppm.



7

Association constants for the receptor-barbiturate complexes were determined from ^1H NMR titration data by using either Foster-Fife[15] or nonlinear least-squares analysis and are collected in Table I. The three key design features of the receptors (their macrocyclic structure, the six H-bonding interactions, and the 5,5-binding region) are confirmed by these measurements. Good complementarity between barbiturate **1b** and macrocyclic receptor **5** results in a large association constant (1.37×10^6 M^{-1}). When the inwardly pointing binding site is no longer enforced, with acyclic **6**, association to **1b** diminishes by almost 100-fold. Removal of three H-bonds from the binding interaction, as with mephobarbital **1d**, leads to a more than 1000-fold decrease in binding to **5**. Incorporation into the barbiturate-5 position of a bulky substituent which cannot fit neatly into the receptor cavity, e.g., with phenobarbital **1c** and **5**, causes a 10-fold reduction in the binding constant.

In summary, we have shown that complementary positioning of H-bonding groups within a cavity can lead to strong complexation between uncharged molecules. We are currently seeking to increase the recognition characteristics of these receptors, particularly in the 5,5-region, and to extend the approach to other key biological molecules such as urea, uric acid, and xanthine.

Acknowledgment. We thank KOSEF, Korea for a fellowship to S.K.C. and the National Institutes of Health for financial support of this work.

(14) Complex (1:1) between **1b** and **5**: ^1H NMR ($CDCl_3$) 12.40 (2 H, s, barb NH), 9.80 (2 H, s, isophth CONH), 9.55 (2 H, s, CH_2 CONH), 8.49 (1 H, s, isophth-2H), 8.20 (2 H, d, J = 8 Hz, pyr-3H), 8.15 (2 H, d, J = 8 Hz, pyr-5H), 7.98 (2 H, d, J = 8 Hz, isophth-4H), 7.84 (2 H, t, J = 8 Hz, pyr-4H), 7.64 (1 H, t, J = 8 Hz, isophth-5H), 7.04 (4 H, d, J = 9 Hz, phenol-3,5H), 6.73 (4 H, d, J = 9 Hz, phenol-2,6H), 4.06 (4 H, t, J = 5.5 Hz, CH_2O), 2.66 (4 H, t, J = 7 Hz, CH_2CO), 2.15 (4 H, m, CH_2CH_2O), 1.78 (4 H, q, J = 7.5 Hz, CH_3CH_2), 1.65 (6 H, s, CH_3), 0.65 (6 H, t, J = 7.5 Hz, CH_3CH_2).

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Lewis Acid Promoted Carbon-Carbon Bond Formation between Bridging Isocyanides

Jianxin Wu, Phillip E. Fanwick,† and Clifford P. Kubiak*[1]

Department of Chemistry, Purdue University
West Lafayette, Indiana 47907

Received November 2, 1987

We report the direct formation of a carbon-carbon bond between two aryl isocyanides of a binuclear iridium(0) complex by using a Lewis acid promoter. Carbon-carbon bond-forming reactions are among the most important organic chemical transformations mediated by transition-metal complexes. There has been a particularly keen interest recently in coupling pairs of coordinated carbonyl[2-4] or isocyanide[5] ligands of mononuclear[3,5] and binuclear[2,4] transition-metal complexes. The coupling of the isocyanide ligands of the complex $Ir_2(CNR)_4(dmpm)_2$[8,9] (**1**, R = 2,6-$Me_2C_6H_3$, dmpm = $Me_2PCH_2PMe_2$), described herein, is unusual in several respects. Coupling is mediated by a late transition-metal complex, a d^9-d^9 Ir(0) system. The reaction does not require two external reducing electronic equivalents. Instead, coupling is effected by formal addition of a single $^{\bullet}AlEt_2$ radical to two μ-isocyanides resulting in annulation to a five-membered C_2N_2Al ring.

In view of the theoretical criteria for isocyanide coupling enumerated recently,[6] complex **1** appears to be extremely promising. The complex possesses the "cradle" type[10] structure I[9,11,13-15]

† Address correspondence pertaining to crystallographic studies to this author.

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(8) Complex **1** was prepared by Na/Hg reduction of $[Ir_2(2,6\text{-}Me_2C_6H_3CN)_5(dmpm)_2][PF_6]_2$[7] in benzene. Anal. Calcd for $C_{48}H_{66}N_4P_4Ir_2$ ($\mathbf{1}\cdot{}^1/_3C_6H_6$): C, 47.75; H, 5.51; N, 4.64. Found: C, 47.55; H, 5.72; N, 4.43. (A solvated benzene molecule is confirmed by the X-ray structural study and is partially removable under high vacuum.) Spectroscopic data: IR (KBr) ν(CN) 2038 (s), 1996 (s, br), 1600 (m), 1564 (m) cm^{-1}; ^{31}P NMR (81 MHz, benzene, reference to external H_3PO_4) δ -34.7 (s, br); ^1H NMR (200 MHz, toluene-d_8) δ 6.9 (m, 12 H, $C_6H_3(CH_3)_2$), 2.51 (s, 12 H, $C_6H_3(CH_3)_2$), 2.37 (s, 12 H, $C_6H_3(CH_3)_2$), 1.70 (s, 12 H, PCH_3), 1.08 (s, 12 H, PCH_3), 0.89 (m, 4 H, PCH_2P).

(9) Crystal data for $\mathbf{1}\cdot C_6H_6$: $C_{52}H_{70}N_4P_4Ir_2$, fw = 1259.5, monoclinic, space group $P2_1$, a = 10.615 (2) Å, b = 16.883 (3) Å, c = 15.044 (3) Å, β = 94.23 (1)°, V = 2689 (2) Å^3, Z = 2, d_{calcd} = 1.555 g cm^{-3}. The structure was solved by MULTAN least-squares Fourier methods and was refined to R and R_w values of 0.033 and 0.044, respectively, for 528 variables and 3229 unique observations with $I > 3\sigma(I)$ with Mo Kα radiation. Data were corrected for absorption empirically. Changing the enantiomer did not significantly change the R factors.

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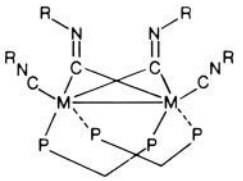

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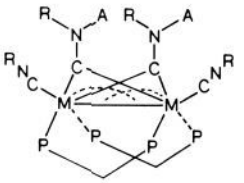
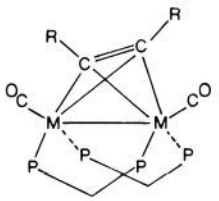


II

1, M = Ir; R = 2,6-$Me_2C_6H_3$ [9] 2, M = Ir; R = 2,6-$Me_2C_6H_3$; A = BH_3



III

with a short 2.37 (2) Å separation between the two bridging isocyanide carbon atoms. Both the terminal and bridging ν(CN) bands, 2038 (s), 1996 (s) cm^{-1} and 1600 (m), 1564 (m) cm^{-1}, are at extremely low energies, reflecting an abundance of electron density on the iridium(0) centers. Complex **1** also reacts readily with Lewis acids, including BH_3[16] and CO_2[17] to form N-adducts. Indeed, the aminocarbyne complex $Ir_2(CN)(A)R)_2(CNR)_2$-$(dmpm)_2$ (A = BH_3), **2**, was structurally characterized and found to possess a "cradle" framework essentially identical with **1** and uncoupled aminocarbyne groups, structure II.[16] An η^2-alkyne, complex of structure III (M = Rh, R = Ph) is also now known,[18] suggesting a plausible pathway for isocyanide coupling via aminocarbynes of structure II. This "rational" approach to isocyanide coupling however met with several surprising results as described below.

Addition of 1 equiv of neat Al_2Et_6[19] to a toluene solution of **1** at 25 °C causes an immediate reaction. The terminal ν(CN) bands do not change noticeably; however, the bridging ν(CN) bands lose intensity to a new band at 1520 cm^{-1}. The $^{31}P\{^1H\}$ NMR spectra of **1** + Al_2Et_6 shows the disappearance of **1** at δ −34.7 ppm and appearance of a doublet of triplets centered at δ −38.6 and δ −47.8 ppm (J = 40 Hz).[20] These observations are consistent with the addition of $AlEt_3$ to one of the N atoms of the bridging isocyanide ligands. A second slow reaction ensues, and after 24 h a product of stoichiometry $Ir_2(CNR)_4(AlEt_2)$-$(dmpm)_2$, **3**, was obtained as red-purple crystals. The FTIR spectrum of **3** displays two ν(CN) bands at 2047 and 1996 cm^{-1}. These are very similar to those displayed by **1** and suggest no formal change of oxidation state in the transformation: **1** + Al_2Et_6 → **3**. The ν(CN) bands of the μ-isocyanides of **3** are replaced by new bands below 1440 cm^{-1}. Complex **3** is also paramagnetic,

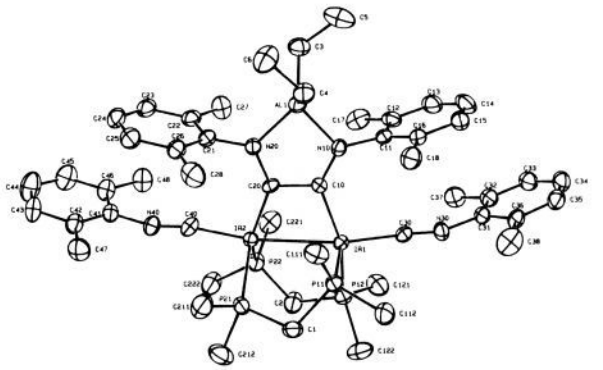


Figure 1. ORTEP drawing of $Ir_2\{C_2(NR)_2AlEt_2\}(CNR)_2(dmpm)_2$ (**3**, R = 2,6-$Me_2C_6H_3$) with 30% probability thermal ellipsoids.

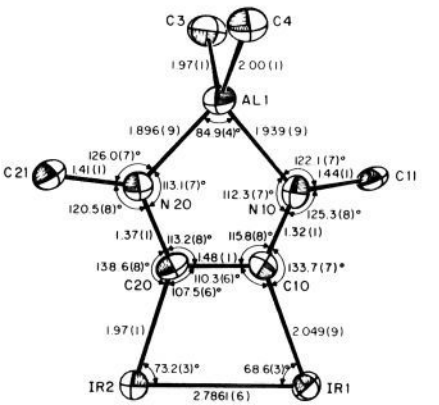


Figure 2. Skeletal view of **3** with selected bond distances and angles.

thus preventing characterization by NMR.

The molecular structure[21] of **3** is shown in Figure 1. A skeletal view with selected bond distances and angles is given in Figure 2. The structure of **3** reveals the coupling of two isocyanide ligands and their condensation with one $AlEt_2$ fragment. The C10–C20 bond distance, 1.48 (1) Å, is intermediate between typical values for C–C single and double bonds. The bond distance Al–N10 is significantly longer (0.043 (9) Å) than Al–N20, suggesting dative and covalent bonds, respectively.[27] There are also significant differences of 0.058 (12) Å between C10–N10 and C20–N20 in the C_2N_2Al ring. The structure displays the "1,2-dimetallated" or parallel mode of alkyne coordination for binuclear complexes.[25] This is in contrast to the parent complex **1** and to many other known binuclear acetylene complexes,[8,22–25] in which the vector formed by the bridging carbon atoms is perpendicular to the M–M bond.[26] Complex **3** also differs significantly from the known binuclear alkyne complexes which exhibit 1,2-dimetallated olefin structures. The typical 1,2-dimetallated olefin complex is of the "A-frame" type structure with no metal–metal bond.[31,32] Complex **3** possesses the "cradle"

(11) The structure of complex **1** is similar to the bridged form of $Co_2(CO)_8$. See: (a) Sumner, G. G.; Klug, H. P.; Alexander, L. E. *Acta Crystallogr.* **1964**, *17*, 732. (b) Bor, G.; Noack, K. *J. Organomet. Chem.* **1974**, *64*, 367. (c) Onaka, S.; Shriver, D. F. *Inorg. Chem.* **1976**, *15*, 915, and is also related to various homoleptic isocyanide complexes of the cobalt group. See: ref 13–15.

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(16) The single crystal structure of **2** has also been determined and will be reported separately.

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(20) Initial addition of 0.5 equiv, 2 equiv, or 3 equiv of Al_2Et_6 lead to unclean ^{31}P spectra, and the final product could not be obtained.

(21) Crystal data for **3**: $C_{50}H_{74}N_4AlP_4Ir_2$, fw = 1266.5, monoclinic, space group $P2_1/c$, a = 11.444 (1) Å, b = 19.072 (1) Å, c = 25.602 (3) Å, β = 102.91 (1)°, V = 5446 (2) Å^3, Z = 4, d_{calcd} = 1.544 g cm^{-3}. The structure was solved by MULTAN least-squares Fourier methods and was refined to R and R_w values of 0.035 and 0.040, respectively, for 550 variables and 5330 independent observations with $I > 3\sigma(I)$ with Mo Kα radiation. Data were corrected for absorption empirically.

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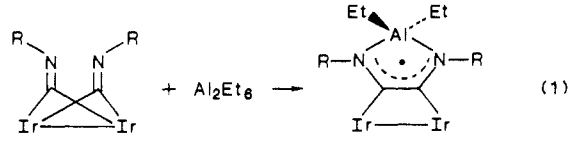
(26) From a theoretical calculation a perpendicular structure would be expected for **3** while a parallel structure would be expected for an A-frame complex where two diphosphine ligands are trans to each other. See ref 25.

geometry and a metal-metal bond, d(Ir-Ir) = 2.7861 (6) Å.

Complex **3** has one unpaired electron, which is introduced by the addition of a neutral $^{\bullet}AlEt_2$ radical to the diamagnetic complex **1**. At −150 °C the EPR powder spectrum of **3** exhibits a completely isotropic signal with g = 2.005. The isotropic nature of the low-temperature powder spectrum suggests that the unpaired electron **3** resides in a molecular orbital with essentially no contribution from the iridium atoms. This result is in accord with FTIR ν(CN) data which suggest no change in the formal oxidation state of **3** compared to **1** and indicates the unpaired electron likely is delocalized exclusively within the C_2N_2Al ring of **3**.

The formation of **3** by annulation of two μ-isocyanides with an $AlEt_2$ radical is unprecedented, eq 1. The $^{\bullet}AlEt_2$ radical is



(1)

1 3

presumably formed by $AlEt_3$ abstraction of $C_2H_5^-$ from an N-complexed $AlEt_3$ followed by electron transfer. The complexation of 1 equiv of $AlEt_3$ to **1** is observed in the early stages of reaction (vide supra). Upon abstraction of $C_2H_5^-$ from the initial adduct, one would expect formation of the species $[Ir_2\{C_2(NR)_2AlEt_2\}(CNR)_2(dmpm)_2]^+[AlEt_4]^-$, $[3^+][AlEt_4^-]$. We note Schmidbaur has reported an apparently similar disproportionation of Al_2Me_6 to $[AlMe_2^+]/[AlMe_4^-]$ and annulation of $[AlMe_2^+]$ in the case of bis(trialkylphosphoranylimino)silanes.[31] We find the molecular cation 3^+ can be prepared by one-electron oxidation of **3**. Cyclic voltammetric studies of **3** in THF reveal one reversible oxidation, $E_{1/2}(3^+/3)$ = −0.22 V versus SCE. Chemical oxidation of **3** with $[FeCp_2][PF_6]$ affords $[3^+][PF_6^-]$. The cationic species 3^+ does not show any ν(CN) band in the 1700–1450-cm^{-1} region, suggesting that the carbon-carbon bond in the C_2N_2Al ring of **3** is not cleaved by one-electron oxidation. The diamagnetic cation 3^+ is however reducible by $AlEt_4^-$ to yield the isolated radical product **3**. Our results thus imply that it is the condensation of an $AlEt_2^+$ fragment with two bridging isocyanide ligands which induces carbon-carbon bond formation, not the injection of an electron from $AlEt_4^-$, formed during the coupling reaction. Our studies of the relative importance of the Lewis acid employed in ligand coupling versus electron transfer are continuing.

Acknowledgment. This work was supported by the National Science Foundation (CHE-8411836 and CHE-8707963). NSF support of the Chemical X-ray Diffraction Facility at Purdue is also gratefully acknowledged.

Supplementary Material Available: Tables consisting of crystal data and data collection parameters for **1** and **3** (Table I), positional parameters for **1** and **3** (Tables II and VII, respectively), temperature factor expressions for **1** and **3** (Tables III and VIII, respectively), bond distances and angles for **1** and **3** (Tables IV and IX, respectively), least-squares planes and dihedral angles for **1** and **3** (Tables V and X, respectively) (30 pages); tables consisting of observed and calculated structure factors for **1** and **3** (Tables VI and XI, respectively) (51 pages). Ordering information is given on any current masthead page.

(27) The Al-N bond distances of 1.939 (9) Å and 1.896 (9) Å lie at the extrema for known Al-N distances, 1.937 (5)–1.902 (4) Å.[28]

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(29) The detailed studies of complex **1**, **2**, and **3** will be reported in a full paper.

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Total Synthesis of (+)-CC-1065 and *ent*-(−)-CC-1065

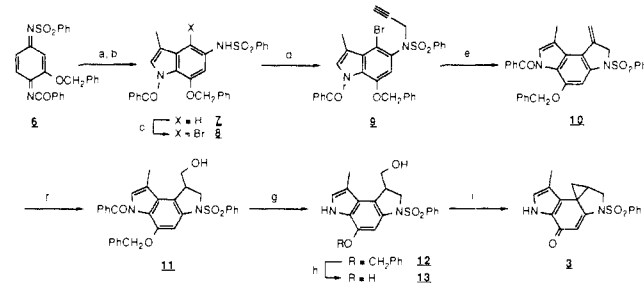
Dale L. Boger*[1a] and Robert S. Coleman[1b]

Department of Chemistry, Purdue University
West Lafayette, Indiana 47907

Received October 7, 1987

CC-1065 (**1**, NSC-298223), an antitumor-antibiotic isolated from *Streptomyces zelensis*[2] initially identified by spectroscopic techniques[3a] and confirmed in a single-crystal X-ray structure determination,[3b] has been shown to possess exceptional, potent in vitro cytotoxic activity, antimicrobial activity, and confirmed, potent in vivo antitumor activity.[4] In sharp contrast to the early observations made with simplified analogues of CC-1065 bearing modified central and right-hand subunits, e.g., U-71,184,[5] in which the antitumor activity and DNA binding properties have been found to be restricted primarily to the agent enantiomer bearing the natural 3*bR*,4*aS*-CPI left-hand segment,[6] recent efforts have

Scheme I[a]



[a] (a) 1.10 equiv of 1-piperidino-1-propene, CH_2Cl_2, 0–23 °C, 12 h; (b) 10% aqueous HCl–THF (1:5), 23 °C, 12 h; (c) 1.0 equiv of *N*-bromosuccinimide, THF, H_2SO_4 (catalyst), −23 °C, 1 h, 97%; (d) 1.1 equiv of NaH, DMF, 23 °C, 15 min; 3 equiv of 3-bromopropyne, DMF, 23 °C, 3 h, 67% from **7**; (e) 2.1 equiv of *n*-Bu_3SnH, AIBN (catalyst), benzene, 80 °C, 4–5 h; (f) 2–3 equiv of $BH_3{\cdot}SMe_2$, THF, 0–23 °C, 1–3 h; 1 equiv of 2 N aqueous NaOH, 3 equiv of 30% H_2O_2, 45 °C, 30 min, 40% from **9**; (g) 5% anhydrous HCl–CH_3OH, 50 °C, 2 h, 83%; (h) 1 atm of H_2, 10% Pd/C, EtOAc, 23 °C, 20 h, 85%; (i) 1.5 equiv of Ph_3P, 1.95 equiv of diethyl azodicarboxylate, THF, 23 °C, 3 h, 50%.

(1) (a) National Institutes of Health research career development award recipient, 1983–1988 (CA 01134). Alfred P. Sloan research fellow, 1985–1989. (b) National Institutes of Health predoctoral trainee, 1984–1985 (GM 07775). David Ross Fellow, Purdue University, 1986–1987.

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