Table II. Quantitative Nuclear Overhauser Enhancement Data[a]

IRR	OBS
Ortho	3 - 3%, 10_A - 3%
21	20 - 4%, 17eq - 4%, 22 - 10%
13	7 - 4%, 15ax - 5%
22	21 - 5%, 20 - 2%
12_A	12_B - 25%, 7 - 3%
14	13 - 3%, 8 - 3%
12_B	12_A - 25%, CH_3 11 - 1%
20	21 - 4%, 22 - 5%, 20_{OH} - 9%, 19ax - 1%, 19eq - 1%
7	13 - 4%, 12_A - 2%, 7_{OH} - 3%
3	10_A - 2%, CH_3 11 - 1%, Ortho - 2%, NH - 5%
8	14 - 4%, 5 - 9%, 4 - 3%
5	4 - 4%, CH_3 11 - 1%
4	5 - 4%, 8 - 3%, Ortho - 3%
10_A	Ortho - 3%, 3 - 3%, CH_3 11 -1%
10_B	Ortho - 2%, 3 - 3%, CH_3 11 - 1%
15eq	CH_3 16 - 10%, 15ax - 4%
19ax	20 - 4%, 19eq - 4%
17eq	17ax - 18%, 21 - 11%, 19eq - 3%, 16 - 1%
15ax	15eq - 15%, 13 - 4%
19eq	19ax - 15%, 20 - 5%, 21 - 2%
18ax	19ax - 7%, CH_3 16 - 2%, 17eq - 2%, 17ax - 2%
18eq	19ax - 3%, 17eq - 3%
16	14 - 2%, 15eq - 2%, CH_3 16 - 2%, 17eq - 2%
CH_3 16	15eq - 1%, 16 - 3%
CH_3 11	12_B - 8%, 3 - 7%, 5 - 9%, 4 - 3%
17ax	17eq - 12%, 18ax - 2%

[a] Nuclear Overhauser enhancements were determined by NOE difference at 360 MHz in acetone-d_6. Spectra were obtained with a 3-s irradiation, a 1-ms delay, and a 90° observe pulse.

ketone) from X-ray crystallographic data.[13] NMR data collected on cytochalasin A (data not shown) agrees very well with the solid-state conformation. The only X-ray data for cytochalasin B was collected on a $AgBF_4$ adduct,[14] and the conformation of the macrocyclic ring is significantly different in this case. The silver adduct, then, has resulted in distortions in the macrocyclic ring that are not present in solution. The solid-state conformation of cytochalasin B has been used to explain its high affinity for inhibition of the facilitated diffusion glucose transport system of human erythrocytes.[15] In light of these NMR results and the small energy difference (<2 kcal) between the dissociation constants of cytochalasin A and B, it seems more reasonable to assume that the two macrocyclic rings are of very similar conformation.[16]

The 2D exchange experiment provides access to data that can identify the trans-annular nonbonded and torsional arrangements that are inherently present in medium- and large-ring natural products. This information is critical in establishing the conformation and in assigning relative stereochemistry to such systems. The rapid mapping of these interactions should facilitate studies directed at understanding the chemical reactivity[2,17] and biological activity[18] of such systems.

Acknowledgment. Support from NIH through the Diabetes Research and Training Center at the University of Virginia is gratefully acknowledged.

Registry No. Cytochalasin B, 14930-96-2.

(13) Griffin, J. F.; Rampal, A. L.; Jung, C. Y. *Proc. Natl. Acad. Sci. U.S.A.* **1982**, *79*, 3759-3763.
(14) McLaughlin, G. M.; Sim, G. A.; Kiechel, J. R.; Tamm, C. *J. Chem. Soc., Chem. Commun.* **1970**, 1398-1399.
(15) Rampal, A. L.; Pinkotsky, H. B.; Jung, C. Y. *Biochemistry* **1980**, *19*, 679-673.
(16) It is noteworthy that these NMR studies were done in organic solvents rather than H_2O, but changes in solvent polarity from chloroform-*d*, to acetone-d_6, to dimethyl-d_6 sulfoxide showed no alteration of the cytochalasin B conformation.
(17) The stereospecific reduction of cytochalasin A to cytochalasin B is readily explained by the steric inaccessibility of the α-face of the C-20 ketone in cytochalasin A (see ORTEP drawing).
(18) For example, see: Egan, R. S.; Pesun, T. J.; Martin, J. R.; Mitscher, L. A. *Tetrahedron* **1973**, *29*, 2525-2538. Egan, R. S.; Freiberg, L. A.; Washburn, W. H. *J. Org. Chem.* **1974**, *39*, 2492-2494. Egan, R. S.; Martin, J. R.; Peran, T. J.; Mitschner, L. A. *J. Am. Chem. Soc.* **1975**, *97*, 4578-4583.

Reversible C-H Insertion/Reductive Elimination in (η^5-Pentamethylcyclopentadienyl)(trimethylphosphine)-iridium Complexes. Use in Determining Relative Metal-Carbon Bond Energies and Thermally Activating Methane

Michael J. Wax, Jeffrey M. Stryker, J. Michael Buchanan, Caroline A. Kovac, and Robert G. Bergman*

Materials and Molecular Research Division
Lawrence Berkeley Laboratory
and the Department of Chemistry
University of California, Berkeley, California 94720
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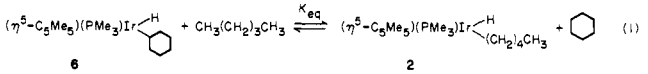
Heating causes reductive elimination of alkane from (η^5-pentamethylcyclopentadienyl)(trimethylphosphine)hydridoalkyliridium complexes, leading to an intermediate capable of undergoing oxidative addition to the C-H bonds in other alkanes.[1] We have used this property to achieve two goals in the C-H activation field that we wish to report: (a) establishment of reversible equilibrium between a pair of alkanes and hydridoalkyl complexes, allowing measurement of the equilibrium constant for this process and providing a method for determining relative metal-carbon bond energies, and (b) solution-phase thermal oxidative addition of methane[2] leading directly to a stable hydridoalkylmetal complex.

The equilibration studies began with the mixture of dihydride (**1**) and alkyl hydrides (**2-5**) formed on irradiation of **1** in *n*-pentane. As reported earlier and illustrated in Scheme I, heating this mixture to 110 °C in *n*-pentane caused disappearance of all the resonances in the ^1H NMR spectrum due to the secondary hydrides and a corresponding increase in the signal due to the primary hydride.[1] We judged from this observation that isomerization of secondary to primary hydridoalkyl complexes is possible by thermal activation at this temperature and that (as expected[3]) the primary complex is thermodynamically more stable. Evidence that this isomerization occurs by intermolecular reductive elimination/oxidative addition was obtained by carrying out the reaction in cyclohexane, rather than pentane, solvent. In this case, the amount of primary hydride remained constant, and the secondary hydrides were converted into hydridocyclohexyl complex **6** rather than primary hydridopentyl complex **2** (Scheme I).

This experiment also suggests that both the primary *n*-pentyl and secondary cyclohexyl complexes are stable to reductive elimination at 110 °C. In fact, higher temperatures are required to bring these materials into the reductive elimination/oxidative addition equilibrium illustrated in eq 1. The equilibrium constant



6 2 (1)

$$K_{eq} = \frac{[2][\text{cyclohexane}]}{[6][n\text{-pentane}]} \quad (2)$$

for this process (eq 2) can be conveniently measured by heating either the primary complex **2** or the hydridocyclohexyl complex **6** in a solvent containing 91.5% cyclohexane and 8.5% *n*-pentane. With either starting material, equilibrium is reached after 50 h at 140 °C; the ratio of **6** to **2** under these conditions[4] is 1.0 ± 0.1. This allows calculation of an equilibrium constant of 10.8, which

(1) Janowicz, A. H.; Bergman, R. G. *J. Am. Chem. Soc.* **1983**, *105*, 3929.
(2) For discussions and examples of transition-metal-based methane activation see: (a) Goldschleger, M. B.; Tyabin, M. B.; Shilov, A. E.; Shteinman, A. A. *Zh. Fiz. Khim.* **1969**, *43*, 2174. (b) Webster, D. E. *Adv. Organomet. Chem.* **1977**, *15*, 147. (c) Shilov, A. E.; Shteinman, A. A. *Coord. Chem. Rev.* **1977**, *24*, 97. (d) Lavrushko, V. V.; Lermontov, S. A.; Shilov, A. E. *React. Kinet. Catal. Lett.* **1980**, *15*, 269. Watson, P. L. *J. Am. Chem. Soc.* **1983**, *105*, 6491. (e) Hoyano, J. K.; McMaster, A. D.; Graham, W. A. G. *Ibid.* **1983**, *105*, 7190. (f) Ozin, G. A.; McIntosh, D. F.; Mitchell, S. A. *J. Am. Chem. Soc.* **1981**, *103*, 1574. (g) Halle, L. F.; Armentrout, P. B.; Beauchamp, J. L. *Organometallics* **1982**, *1*, 963. (h) Remick, R. J.; Asunta, T. A.; Skell, P. S. *J. Am. Chem. Soc.* **1979**, *101*, 1320.
(3) (a) Halpern, *J. Acc. Chem. Res.* **1982**, *15*, 238. (b) Schwartz, J.; Labinger, J. A. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 333.
(4) Slow decomposition of the hydridoalkylmetal complexes takes place under these conditions; however, the isomerization is rapid enough that the equilibrium concentrations of **2** and **6** are not significantly perturbed.

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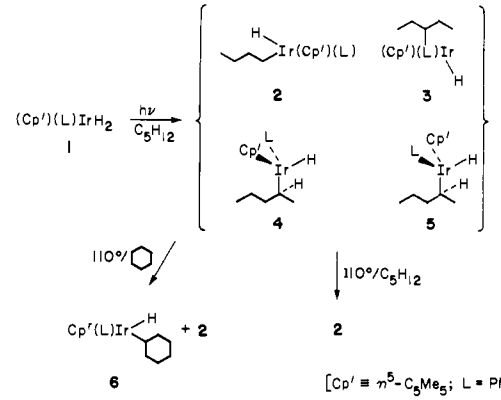
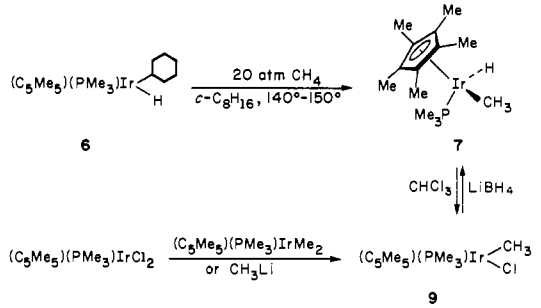
Scheme I



corresponds to $\Delta G^\circ_{reaction} = -2.0$ kcal/mol at 140 °C. Making the reasonable assumption that ΔS° for reaction 1 is close to 0 and using 94.5 kcal/mol for the secondary C-H bond energy in cyclohexane and 98 kcal/mol for the primary C-H bond energy in *n*-pentane,[5] we calculate[6] from this ΔG° that the metal-carbon bond energy in primary complex **2** is 5.5 kcal/mol stronger than the secondary metal-carbon bond in **6**.

Attempted photolysis of dihydride **1** in perfluoroalkane solvents under 4 atm of CH_4 gave no detectable methane activation (in contrast to Graham's observations[2e] on the methane-activating photolysis of $(C_5Me_5)Ir(CO)_2$), perhaps because of the very low solubility of **1** in these solvents. Photolysis in cyclooctane, a "slow" substrate for C-H insertion of the presumed intermediate $(\eta^5\text{-}C_5Me_5)(PMe_3)Ir$, under CH_4 gave only the previously observed[1] hydridocyclooctyl complex (**8**). However, we were able to achieve methane activation thermally and in high yield under reversible conditions by taking advantage of the presumption that the hydridomethyl complex **7** would be thermodynamically more stable even than primary alkyl complexes such as **2**. Thus, as shown in Scheme II, heating hydridocyclohexyl complex **6** in cyclooctane solvent in a sealed Pyrex vessel under 20 atm of CH_4 at temperatures between 140 and 150 °C for 14 h led to a 58% yield (NMR)[7] of hydridomethyl complex **7** (^{1}H NMR δ 1.87 (dd, J = 2.0, 0.7 Hz, C_5Me_5), 1.22 (d, J = 9.8 Hz, PMe_3), 0.71 (d, J = 5.8 Hz, IrMe), -17.22 (d, J = 35.9 Hz, IrH)) along with 8% of dihydride **1**. Attempted isolation of the hydridomethyl complex by crystallization or chromatography proved difficult, as it has in other cases,[1] and so the material was treated with $CHCl_3$, converting it to the corresponding chloromethyl complex **9**, which could be purified and characterized by conventional means.[8] The isolated yield of **9** from starting hydridocyclohexyl complex **6** was

Scheme II



50%. Confirmation of these structural assignments was obtained by independent synthesis: chloromethyl complex **9** was prepared by either ligand interchange between the corresponding dichloro and dimethyl complexes (82% yield) or treatment of the dichloro complex with methyllithium (80% yield) (Scheme II); it was converted to hydridomethyl complex **7** in >90% yield by treatment with excess $LiBH_4$ in THF.

In the methane experiment, we assume that the hydridocyclohexyl complex **6** and hydridocyclooctyl complex **8** are formed reversibly but do not build up due to their thermodynamic instability relative to the hydridomethyl complex **7**; i.e., **7** is the "thermodynamic sink" for the system. The ability to functionalize methane thermally and convert it quantitatively to a metalated species is an essential step in the development of possible catalytic functionalization schemes for this molecule; work along these lines is continuing. Efforts are also under way aimed at applying our method for determining relative metal-carbon bond energies to additional pairs of alkyliridium complexes.

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(5) Benson, S. W. "Thermochemical Kinetics"; Wiley: New York, 1976.

(6) As pointed out by a referee, this calculation also assumes, since bond dissociation energies are defined for the gas phase, that the heats of solution and vaporization of the compounds in eq 1 do not perturb the equilibrium constant significantly. Data appropriate to resolve this question fully are not available. Although it has often been assumed that heats of sublimation of structurally related organometallic complexes are identical, other data indicate that heats of sublimation of organometallic complexes vary with relatively subtle changes in structure.[6a,b] Given this situation, and the presently crude level of our data, we would prefer to make the assumption (as we did for contributions to the entropy change for the system) that contributions to heats of sublimation are approximately additive—that is, that the difference in heats of vaporization between *n*-pentane and cyclohexane (about 1.0 kcal/mol) is approximately balanced by the estimated difference in heats of sublimation of complexes **6** and **2**. (a) Adedeji, F. A.; Brown, D. L. S.; Connor, J. A.; Leung, M. L.; Paz-Andrade, I. M.; Skinner, H. A. *J. Organomet. Chem.* **1975**, *97*, 221. (b) Connor, J. A.; Zafarani-Moattar, M. T.; Bickerton, J.; El Saied, N. I.; Suradi, S.; Carson, R.; Al Takhin, G.; Skinner, H. A. *Organometallics* **1982**, *1*, 1166.

(7) The yield was obtained by NMR integration vs. a known amount of hexamethyldisiloxane added as internal standard. Control experiments demonstrated that no hydridomethyl complex is formed in the absence of CH_4.

(8) Data on chloromethyliridium complex **8**: ^{1}H NMR (200 MHz; C_6D_6) δ 1.47 (d, J = 1.9 Hz, C_5Me_5), 1.17 (d, J = 10.3 Hz, PMe_3), 1.08 (d, J = 7.0 Hz, IrMe); ^{13}C NMR (C_6D_6) δ 90.86 (d, J = 3.8 Hz, C_5Me_5), 13.88 (d, J = 37.2 Hz, PMe_3), 8.87 (s, C_5Me_5), -18.09 (d, J = 10.9 Hz, Ir-*Me*). Exact mass: three resolvable isotopomers for $C_{14}H_{27}ClPIr$ M^+: calcd 456.1139, 454.1160 (weighted average of two peaks), 452.1145; found 456.1148, 454.1133, 452.1123.

anti-6-Tetracyclo[4.4.0.1^{1,4}.1^{7,10}]dodecyl Cation Cascade. Sequencing of Rearrangement Routes in a Norbornyl-Fused Norbornyl System

Leo A. Paquette,*[1a] George DeLucca,[1a] James D. Korp,[1b] Ivan Bernal,[1b] John K. Swartzendruber,[1c] and Noel D. Jones[1c]

Departments of Chemistry, The Ohio State University Columbus, Ohio 43210
University of Houston, Houston, Texas 77004
The Lilly Research Laboratories, Eli Lilly and Company Indianapolis, Indiana 46285

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Intense current interest is focused on understanding the electronic origins and consequences of π bond deformation in norbornenes and methylenenorbornanes. Crystallographic data[2] and supporting theoretical calculations[3] reveal that internally positioned

(1) (a) The Ohio State University. (b) University of Houston. Inquiries concerning the X-ray crystal structure of **5**-OPBB should be directed to I.B. (c) The Lilly Research Laboratories. Inquiries concerning the X-ray crystal structure of **4**-OPBB should be directed to N.D.J.

(2) (a) Paquette, L. A.; Schaefer, A. G.; Blount, J. F. *J. Am. Chem. Soc.* **1983**, *105*, 3642. (b) Watson, W. H.; Galloy, J.; Bartlett, P. D.; Roof, A. A. M. *Ibid.* **1981**, *103*, 2022. (c) Pinkerton, A. A.; Schwarzenbach, D.; Stibbard, J. H.; Carrupt, P.-A.; Vogel, P. *Ibid.* **1981**, *103*, 2095. (d) Ermer, O.; Bödecker, C.-D. *Helv. Chim. Acta* **1983**, *66*, 943. (e) Mackenzie, K.; Miller, A. S.; Muir, K. W.; Manojlovic-Muir, Lj. *Tetrahedron Lett.* **1983**, 4747 and additional references cited in these papers.

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