In summary, the first potent inhibitor of squalene synthase, ether **6**, was rationally designed on the basis of a proposal for the mechanism of the enzymatic reaction. This study revealed a surprisingly large enhancement in differential binding energy resulting from the replacement of a CH_2 with an ether oxygen. We speculate that the tight binding of **6** to squalene synthase is due to H bonding of the ether oxygen with a key active-site acid catalyst.[11,13]

Acknowledgment. We thank the Bristol-Myers Squibb Analytical Chemistry Department for obtaining elemental analyses, mass spectra, IR spectra, and certain NMR spectra.

Supplementary Material Available: Detailed procedure for the synthesis of **6** including spectral data and Lineweaver–Burk plot for the inhibition of rat liver microsomal squalene synthase by **6** (8 pages). Ordering information is given on any current masthead page.

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(13) All inhibitors described herein exhibited ^1H NMR, ^{13}C NMR, infrared, and mass spectra, as well as microanalyses (C, H, P), which were consistent with the assigned structures. The final target salts were purified by chromatography on CHP20P gel, as described in ref 4b.

Evidence for an Unprecedented $Ir(H)(NH_3) \rightleftharpoons Ir(H_2)(NH_2)$ Equilibrium and Hydrogen Exchange between NH and CH Bonds

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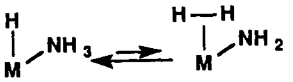
During our studies on ammonia activation, we have obtained complexes **1** and **2** by reaction of ammonia with $[Ir(C_8H_{14})_2Cl]_2$ (C_8H_{14} = cyclooctene) followed by anion exchange.[1] Complexes **3–5** are obtained by substitution reactions of **1** and **2** with PEt_3.[2,3] Our evidence suggests that these complexes are involved in an unprecedented, albeit slow, equilibrium (eq 1). When combined with a parallel equilibrium between alkyl and olefin-hydride configurations in the same complex, the result is C–H/N–H exchange.



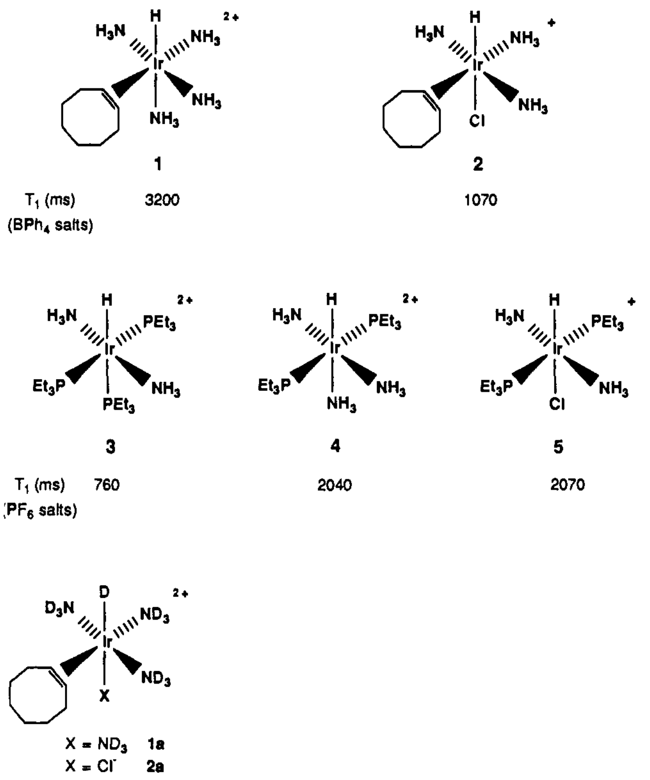
$$\mathrm{M(H)(NH_3)} \rightleftharpoons \mathrm{M(H{-}H)(NH_2)} \qquad (1)$$

T_1 measurements[4] (Scheme I) indicate that complexes **1–5** are present in solution as classical hydrides.[5,6] Compatible with this, ^{15}N NMR measurement of the ^{15}N-enriched complexes indicates only ammine (NH_3) and no amide (NH_2) ligands.

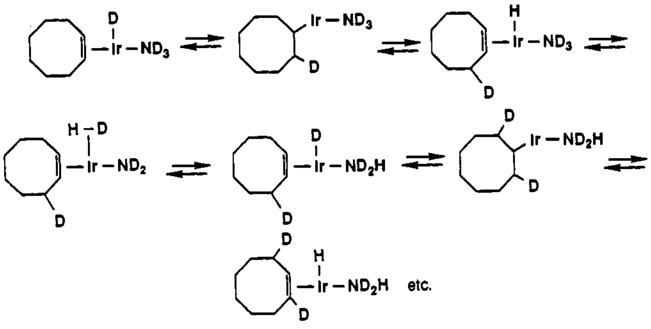
Surprisingly, when the deuterido complexes **1a** and **2a**, obtained from reaction of $[Ir(C_8H_{14})_2Cl]_2$ with ND_3, are left standing at room temperature in THF under nitrogen, Ir–H and N–H bonds are formed. ^2D NMR measurements reveal formation of C–D bonds. This process is quite slow: when a THF solution of complexes **1a** and **2a** in a 1:1 ratio was utilized, 25% deuteration of the cyclooctene ligand (ca. 4 deuterium atoms/ligand) was observed after 20 days at room temperature. After 1 day at 65 °C, 20% olefin deuteration was obtained.[7] Interestingly, the ammine ligands differ in their degree of exchange. The NH_3 trans to the cyclooctene ligand undergoes this process most readily, and the NH_3 cis to both hydride and cyclooctene ligands exchanges to a lesser extent, whereas almost no hydrogen incorporation is observed in the ammine trans to the hydride.

The H/D exchange process between the ammine and olefin ligands most probably proceeds via an η^2-H_2 intermediate[8] formed as a result of interaction of the electronegative hydride with the more acidic N–D. Indications for $H^{\delta+}\cdots H^{\delta-}$ interaction were observed in *cis*-$Ir(H)(OH)(PMe_3)_4^+$.[9,10] The reverse of this

Scheme I



Scheme II



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(1) Koelliker, R.; Milstein, D. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 707.

(2) Complexes **3** and **4** are obtained by dropwise addition of 3 or 2 equiv of PEt_3, respectively, to a THF solution of **1** (PF_6 salt) at room temperature under nitrogen. Addition of 2 equiv of PEt_3 to **2** (PF_6 salt) under the same conditions leads to **5**.

(3) Spectral characterization of **3**: ^1H NMR (acetone-d_6) δ −12.15 (dt, 1 H, $J_{PH,trans}$ = 145.4 Hz, $J_{PH,cis}$ = 18.0 Hz); $^{31}P\{^1H\}$ NMR (THF) δ −18.3 (d, 2 P, J = 15.6 Hz), −33.1 (t, 1 P, J = 15.6 Hz); ^{15}N NMR (THF/THF-d_8) δ −473.0 (q, 2 N, J_{NH} = 71.3 Hz). **4**: ^{15}N NMR (THF/THF-d_8) δ −425.3 (dq, 1 N, J_{NH} = 68.5 Hz, J_{NIrH} = 170 Hz), −466.1 (q, 2 N, J_{NH} = 70.7 Hz); $^{31}P\{^1H\}$ NMR (THF) δ −9.6 (s); ^1H NMR (acetone-d_6) δ −21.64 (t, 1 H, J = 15.6 Hz; with $^{15}NH_3$: dt, J_{NH} = 17 Hz, J_{PH} = 15.6 Hz). **5**: ^1H NMR (acetone-d_6) δ −23.14 (t, 1 H, J = 14.6 Hz); $^{31}P\{^1H\}$ NMR (THF) δ −10.1 (s); ^{15}N NMR (THF/THF-d_8) δ −461.2 (q, 2 N, $^1J_{NH}$ = 70.6 Hz).

(4) T_1 experiments were performed at 20 °C using a Bruker WH-270 NMR spectrometer at 270 MHz. The BPh_4 salts of **1** and **2** and PF_6 salts of **3–5** were used in THF-d_8.

(5) Crabtree, R. H.; Lavin, M.; Bonneviot, L. *J. Am. Chem. Soc.* **1986**, *108*, 4032.

(6) (a) Crabtree, R. H. *Acc. Chem. Res.* **1990**, *23*, 95. (b) Hamilton, D. G.; Crabtree, R. H. *J. Am. Chem. Soc.* **1988**, *110*, 4126. (c) Ammann, C.; Isaia, F.; Pregosin, P. S. *Magn. Reson. Chem.* **1988**, *26*, 236.

(7) At equilibrium, equal scrambling between 10 D and 14 C–H atoms would lead to 41.6% D incorporation into the cyclooctene ligand.

(8) (a) Kubas, G. J. *Acc. Chem. Res.* **1988**, *21*, 120. (b) Crabtree, R. H. *Acc. Chem. Res.* **1990**, *23*, 95.

(9) (a) Milstein, D.; Calabrese, J. C.; Williams, I. D. *J. Am. Chem. Soc.* **1986**, *108*, 6387. (b) Stevens, R. C.; Bau, R.; Milstein, D.; Blum, O.; Koetzle, T. F. *J. Chem. Soc., Dalton Trans.* **1990**, 1429.

(10) Although less relevant, participation of metals in hydrogen-bonding interactions was recently addressed: (a) Brammer, L.; Charnock, J. H.; Goggin, P. L.; Goodfellow, R. J.; Orpen, A. G.; Koetzle, T. F. *J. Chem. Soc., Dalton Trans.* **1991**, 1789. (b) Kristjánsdóttir, S. S.; Norton, J. R.; Moroz, A.; Sweany, R. L.; Whittenburg, S. L. *Organometallics* **1991**, *10*, 2357.

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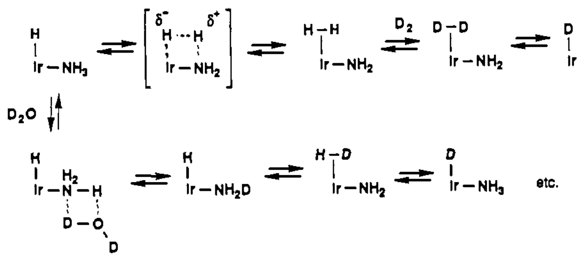
Scheme III



process may be viewed as an intramolecular version of the deprotonation of a dihydrogen ligand.[11,12] A similar equilibrium involving an η^2-H_2 intermediate was proposed for $Ir(H)(H_2O)(bq)(PPh_3)_2^+$ (bq = benzoquinolinate) although the H_2O ligand is easily displaced upon treatment with H_2[5] as opposed to the tightly bound NH_3 in **1**–**5**. Also relevant is the reaction of complexes of the ligand $N(SiMe_2CH_2PPh_2)_2$ with H_2 to yield the corresponding amine metal hydrides.[13] Dihydrogen complexes containing nitrogen donor ligands have been reported.[14]

The degree to which the ammine ligands undergo H/D exchange reflects (a) the requirement for the NH_3 and hydride ligands to be mutually cis and (b) the higher acidity of the NH_3 trans to the π-accepting cyclooctene ligand.

Parallel to the NH_3/Ir–H exchange process, an olefin–hydride/alkyl equilibrium in complexes **1** and **2** results in label transfer from the ammine ligand to the olefin (Scheme II). The lack of scrambling between the three types of ammine ligands suggests a square-pyramidal structure for the alkyl intermediate. Obviously, the olefin–hydride arrangement prevails over that of the alkyl, which could not be detected spectroscopically. This may be a result of the importance of π-back-bonding to the olefin, the only π-acceptor present in these electron-rich complexes. The fairly slow exchange rate has precluded attempts to quantify it by spin saturation transfer experiments.

The phosphine complexes **3**–**5** also show interesting exchange reactivity. Although they are classical hydrides on the basis of T_1 measurements, exposure to D_2 leads to deuterium incorporation into both Ir–H and N–H bonds. When THF solutions of the complexes are placed under 30 psi of D_2 for 7 days at room temperature, **3**–**5** incorporate 4.7, 20, and 47% deuterium, respectively, the ratio of N–D/Ir–D being 1.4:1. The order of exchange reactivity **3** < **4** < **5** parallels the trend of increasing electron density on the metal center. The monocationic complex **5** experiences higher electron density than the dicationic **4**, which, in turn, is more electron rich than the phosphine complex **3**.

Since amines do not undergo exchange with D_2 in the absence of a catalyst,[15,16] intermediacy of a nonclassical dihydrogen complex is implied (Scheme III). Generation of such an intermediate may be favored with increasing electron density at the metal, as a result of a more "basic" hydride, facilitating the intramolecular "deprotonation" of bound NH_3. Intermediacy of an η^2-H_2 complex was suggested for the D_2O/H_2 exchange catalyzed by $Ru(OEP)(THF)_2$ in the presence of KOD.[12]

An alternative mechanism of Ir–H/N–H exchange involving generation of an ammonium salt by deprotonation of the hydride ligand with a dissociated ammonia molecule is highly unlikely. Such a mechanism is not compatible with preferential D incorporation in the *cis*-NH_3 groups of **1** and **2**. Moreover, exposure of complex **1** to $^{15}NH_3$ did not lead to ^{15}N incorporation.

As expected, complexes **1**–**5** also undergo exchange with D_2O. N–H/O–D scrambling is the fastest process occurring after minutes at room temperature and is followed by slow generation of Ir–D and (in complexes **1** and **2**) C–D bonds occurring to a noticeable extent after a few hours. In principle, complete deuteration of the bound cyclooctene ligand can be achieved in this way, representing several cycles of C–H/O–D exchange. Similar exchange occurs between **1**–**5** and ND_3.

The equilibrium processes described here open up a new means of labeling coordinated olefins by, e.g., D_2O, ND_3, or D_2. We are now exploring the possibility of a catalytic process under conditions which allow equilibrium between free and coordinated olefins. Utilization of complexes such as **5** as catalysts for labeling water and ammonia may also be possible.

Acknowledgment. This research was supported by Grant No. 89-00374 from the U.S.–Israel Binational Science Foundation (BSF), Jerusalem, Israel, and by the Fund for Basic Research, administered by the Israel Academy of Sciences and Humanities. We thank Prof. R. Bau of the University of Southern California for useful discussions.

Registry No. 1, 136457-90-4; **2**, 136457-91-5; **3**, 136358-03-7; **4**, 136358-05-9; **5**, 136358-07-1.

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[16] No H/D exchange of *n*-hexylamine was observed when it was exposed to D_2 under the same conditions (in the absence of the iridium complexes).

Origin of the Regioselectivity in the Photochemical Cycloaddition Reactions of Cyclic Enones with Alkenes: Chemical Trapping Evidence for the Structures, Mechanism of Formation, and Fates of 1,4-Biradical Intermediates[1]

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The cycloaddition of alkenes to the triplet excited state of cyclic enones is known to involve the intermediacy of triplet 1,4-biradical species which proceed to cyclobutane products in competition with reversion to the ground-state precursors (Scheme I).[2] For alkenes substituted by a polar group, the reaction exhibits some regioselectivity. Electron-rich alkenes such as ethyl vinyl ether yield the "head-to-tail" isomer **1** in preference to the "head-to-head" isomer **2**, whereas electron-poor alkenes such as acrylonitrile selectively yield the analogous head-to-head structure.[2,3] However, recent work has indicated that some electron-poor alkenes, such as α,β-unsaturated esters, do not always follow this rule.[4]

The regioselectivity is commonly explained in terms of the formation of a complex between the triplet excited state of the enone and the alkene in which the excited-state dipole is aligned with that of the ground-state alkene so as to maximize electrostatic attraction.[2] This oriented exciplex presumably would lead to preferential formation of those biradicals which generate the appropriate regioisomer. An alternative explanation has been suggested,[2d,5] namely, that the regiochemistry is determined by

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[1] Contribution number 442 from the Photochemistry Unit, University of Western Ontario.

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