the initially inferred C-19 chiralities of these compounds had to be reversed.[4]

From these indirect assignments, it was postulated that the "second hydroxylation" of **1a** proceeds with the elimination of the 19-*pro-R* hydrogen and that the formic acid retains the 19-*pro-S* hydrogen atom.[2,3]

Because of the biological importance of the estrogen formation process, we reinvestigated the problem and present direct proof for the assignment of the chemical shifts of the C-19 hydrogen atoms of the 19-acetate **1c**.

It has been conclusively established that the reduction of aldehydes by horse liver alcohol dehydrogenase (HLAD) and NADH involves the stereospecific transfer of a 4-*pro-R* hydrogen atom of NADH to the *re* face of the aldehyde.[5,6] It follows that the hydrogen atom originating from the NADH *is the 1-pro-R* hydrogen atom of the derived alcohol. Therefore, reduction of the 19-deuterioaldehyde (**6**) with HLADH and NADH should yield the 19S,19-^{2}H alcohol (**7a**). Previous attempts at reducing 19-aldehydes with HLAD-NADH failed. We have now succeeded, for the first time, in reducing **6** enzymatically and have obtained, presumably, optically pure **7b** in low yield (~0.3–0.8%). It is likely that the low yield of the enzymatic alcohol formation is due, at least in part, to the *very limited* solubility of the aldehyde in the aqueous medium.

The required **6** was obtained by LiAl^{2}H$_4$ reduction of methyl 17-ethylenedioxy-3β-methoxyandrost-5-ene-10β-carboxylate and oxidation of the resulting 19-d_2 alcohol (CrO$_3$–pyridine). The expanded NMR spectrum of the aldehyde **6** did not show a signal for an aldehydic hydrogen (~99% deuteration).

The deuterated aldehyde **6** (100 mg) was then diluted with a trace amount of 19-tritiated aldehyde **6** (~40 μg, 4.48 × 10^6 dpm of ^{3}H) and dissolved in ethylene glycol monoethyl ether acetate (5 mL). An aliquot of the aldehyde solution (~55 μL) was placed in a 25-mL Erlenmeyer flask containing water (5 mL) and Tween 80 (1 drop). The mixture was warmed to 50 °C and hand shaken. The obtained emulsion was cooled to 37 °C and then cyclohexanol (80 μL), phosphate carbonate buffer (0.02 M, pH 8.7, 3 mL), NAD (4 mg), and alcohol free HLAD (1.5 mg) were added sequentially. The mixture was incubated in the air for 20 h at 37 °C. A total of 90 incubations was carried out, using all of the aldehyde solution. The contents of the flasks were combined and continuously extracted with ethyl acetate for 24 h. The extract was washed, dried, and concentrated. The resulting residue was fractionated on TLC (silica gel, hexane–ethyl acetate (7:3)) and most of the aldehyde **6** was recovered (4.03 × 10^6 dpm of ^{3}H, 90% recovery). The product from the zone corresponding to the 19-alcohol 17-ketal **7a** (3.6 × 10^4 dpm of ^{3}H, 0.8% yield) was isolated and treated with 0.4 N aqueous methanolic HCl (5 mL, 50 °C, 15 min), and, following acetylation, the crude [19-^{2}H]-(19S)-19-acetoxy-3β-methoxyandrost-5-ene-17-one (**7b**) was obtained. The acetate was extensively purified by TLC and high pressure liquid chromatography (Partisil 10/20 column, eluted with isooctane-2-propanol (95:5), pressure 270 lb, flow rate 1 mL per minute). The resulting homogeneous **7b** (1.3 × 10^4 dpm of ^{3}H, 0.3% yield) was dissolved in CDCl$_3$ (100 μL) and its 90-MHz ^{1}H NMR spectrum was recorded (Bruker SXP instrument).

The spectrum of the **7b** showed a signal for the 19-*pro-R* hydrogen at δ 4.45 and was *devoid* of a signal at δ 3.95. It is evident that, *within the limits of the sensitivity of the NMR procedure,* the HLAD-NADH reduction was *completely* stereospecific. In view of the demonstrated stereospecificity of the reaction and in the absence of *any evidence* to the contrary, it may be assumed with considerable certainty that the reaction proceeded in the proven, conventional manner. Hence, it may be concluded that a hydrogen derived from 4-*pro-R* of NADH was added to the *re* face of the aldehyde **6** to yield 19S alcohol. Therefore, our results provide proof for the assignment

of the chemical shifts of the 19-*pro-R* and of the 19-*pro-S* (δ 3.95) hydrogen atoms of **7b**. It follows that the biosynthesis of estrogens by placental enzymes indeed involves the removal of the 19-*pro-R* hydrogen of **1** as water, and that the formic acid retains the 19-*pro-S* hydrogen, as previously proposed.[7]

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(7) This work was supported by NIH Grant GM 19882-12. The NMR spectra were recorded on the Worcester Consortium NMR facility instrument (Bruker SXP) purchased with funds from NSF Equipment Grant CHE77-09059.

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Synthesis of Transition Metal Complexes of Cycloheptatrienylidene

Sir:

For some years we have been interested in the chemistry of cycloheptatrienylidene, a reactive intermediate in which the vacant p orbital of the carbene is an integral component of an aromatic π system.[1]

The relatively recent widespread interest in the chemistry of transition metal complexes of carbenes and especially those not stabilized by heteroatoms[2] piqued our curiosity as to the physical and chemical properties of transition metal complexes of cycloheptatrienylidene and related carbenes. In this communication we report a synthetic method that may be general for preparing this type of complex.

Although the synthetic approach to carbene complexes of transition metals that has found the widest use (addition of RLi to a CO ligand)[3] had no potential for the synthesis of cycloheptatrienylidene complexes, there have been reported isolated methods[4–7] that appeared to have some chance of being useful for our purposes. Unfortunately, all attempts to apply known methods to the formation of cycloheptatrienylidene complexes failed. Reaction of either dichloro-, dibromo-, or 7,7-dimethoxycycloheptatriene with Na$_2$Cr(CO)$_5$ or Na$_2$Fe(CO)$_4$ gave only reduction of the tropyl ring,[8] as did reaction of tropylium salts with NaFe(CO)$_4$H. Reaction of heptafulvene with diphenylcarbene(pentacarbonyl)tungsten(0) gave no trace of 1,1-diphenylethylene and decomposition of the sodium salt of tropone tosylhydrazone in the presence of methylcyclopentadienyldicarbonyl(THF)manganese gave no sign of a carbene complex.

In view of the facile reduction of the tropyl cation, a synthetic approach was sought in which the carbon–metal bond is formed before the final unsaturation is introduced into the ring. Drawing on the well-known displacement of halides from transition metals by alkyl and aryl Grignard and lithium reagents[9] and a reported carbene synthesis by hydride abstraction,[10] the reaction sequence outlined in Scheme I was attempted.

Scheme I

(three isomers)   (three isomers)

1 (three isomers)

2

Scheme II

3

4

5
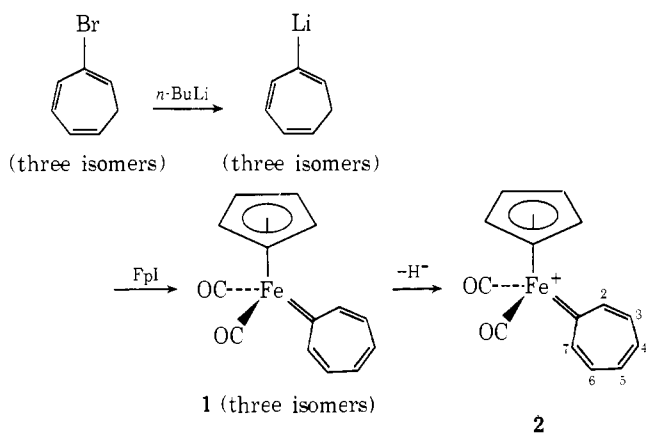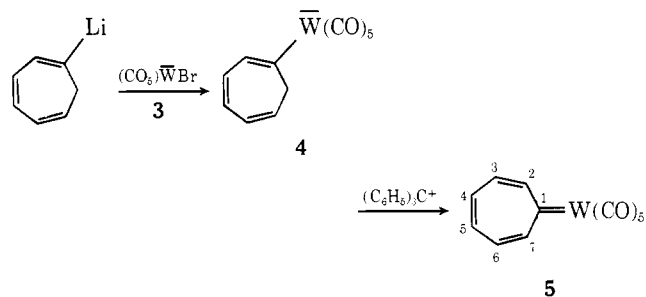
Reaction of a mixture of 1-, 2-, and 3-bromocyclohepta-trienes (from reduction of bromotropylium bromide)[11] with *n*-BuLi (−78 °C in THF) gave a mixture of 1-, 2-, and 3-cycloheptatrienyllithiums. Addition of the mixture to a solution of $C_5H_5(CO)_2FeI$ (FpI), at −78 °C, followed by column chromatography (pentane) on neutral alumina, gave a mixture of isomeric cycloheptatrienyliron complexes 1 (one shown).[12] Hydride abstraction from 1 (and its isomers) with triphenyl-methyl hexafluorophosphate (−78 °C, CH_2Cl_2) gave a scarlet red solution that was worked up by warming to room temper-ature and adding ethyl ether to precipitate the complex. This yielded a yellow-orange solid 2 in 90% yields (plates from CH_2Cl_2, mp 180–180.5 °C dec) that slowly decomposes in solution but is indefinitely stable in the solid form (when stored in a dark bottle). The ^1H NMR of the scarlet red solution of 2 (0 °C, acetone-d_6) showed resonances at δ 10.01 (2 H, d, J = 10.0 Hz, H-2, -7), 8.48–8.74 (2 H, m, H-4, -5), 7.94–8.3 (2 H, m, H-3, -6), and 5.50 (5 H, s, Cp). The decoupled ^{13}C spectrum of 2 (0 °C, acetone-d_6) showed resonances at δ (from Me4Si) 242.3 (C-1), 212.8 (CO), 170.0, 148.3, 138.2 (C-2, C-3, and C-4), and 88.3 (Cp). In the infrared the two CO stretches appear (CH_2Cl_2) at 2045 and 1996 cm^{-1}. In the UV–visible, maxima appear (acetonitrile) at λ_{max} 205 (log ε 4.41), 220 (sh), 270 (sh), 340 (sh), 405 (3.60). Anal. Calcd for $C_{14}H_{11}F_6FeO_2P$: C 40.81, H 2.69. Found: C 40.55, H 2.71.

Application of the same method to the synthesis of a neutral tungsten complex 5 is outlined in Scheme II. The cold solution of cycloheptatrienyllithiums was added to 0.5 equiv of tetra-butylammonium bromopentacarbonyltungstate (3)[13] in THF at −78 °C. Although 4 was not isolated as a pure material,[14] the ^1H NMR of 4 showed the presence of only the 1 isomer even though a mixture of bromocycloheptatrienes had been used. Consistent with this, bromocycloheptatrienes enriched in the 1 isomer (by chromatography on silica gel) gave the best yields of carbene complex.

Hydride abstraction from crude 4 (−78 °C, CH_2Cl_2) gave a deep purple colored solution that was worked up by washing with saturated $NaHCO_3$ (added cold), followed by rapid chromatography (pentane–ether) over silica gel. Sublimation

(0.01 Torr, 90–95 °C) gave ~15% (based on 3) 5. Recrystal-lization from CH_2Cl_2 gave purple needles, mp 115–116 °C dec. Anal. Calcd for $C_{12}H_6O_5W$: C 34.81, H 1.46. Found: C 34.65, H 1.49. The ^1H NMR spectrum of 5 (acetone-d_6) showed resonances at δ 9.96 (2 H, d, J = 10.0 Hz, H-2, -7), 8.1 (2 H, m, H-3, -6), 7.7 (2 H, m, H-4, -5). Low solubility in appro-priate solvents and long relaxation times has, to date, precluded ^{13}C spectra. The UV–visible (heptane) spectrum showed λ_{max} 548 (log ε 4.2), 285 (sh), 246 (sh), 227 (5.0).

The low field of the hydrogen resonances of 2 and 5 argue for substantial positive charge on the cycloheptatrienyl rings of the carbene complexes. This finds support in the chemical shift of cyclopentadienyl resonance of 2. It has been reported that the chemical shift of cyclopentadienyl resonances of $C_5H_5(CO)_2Fe$ complexes are sensitive to electron density on the metal with the forecast that increased density should lead to an upfield shift.[15] In fact, the Cp hydrogens of 6[2c] and 7[10]

6

7
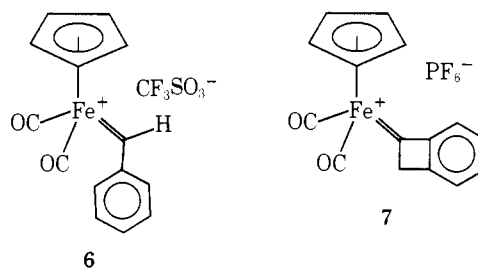
appear substantially lower field (δ 5.87 ppm and 5.9 ppm, re-spectively) than that of 2 (δ 5.50 ppm). On the other hand, the positive charge on the ring in 2 is probably more highly delo-calized than in 6 as evidenced by the ^{13}C chemical shift of the carbene carbons (242.3 and 342.4 ppm, respectively).

The IR spectra of both 2 and 5 also suggest substantial contribution from resonance forms represented by 8 and 9, respectively. Thus 2 shows absorptions at 2043 and 1996 cm^{-1}

8

9
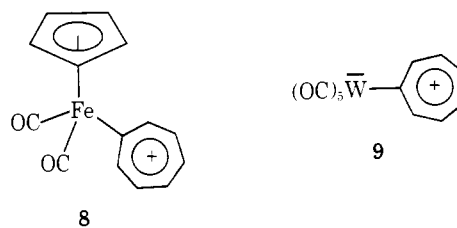
which are significantly lower frequently than the corresponding absorptions of 7 (2065 and 2020 cm^{-1})· A decrease in CO stretching frequency has been interpreted in terms of an in-crease in electron density on the metal (distributed into the CO ligands)[16] which, of course, in the case of 2 would mean a concomitant increase in positive on the cycloheptatrienylidene ligand. In the case of 5 the CO stretching frequencies are among the lowest of the pentacarbonyltungsten carbene complexes.[17] In addition, the cis and trans CO stretching force constants calculated by the Cotton–Kraihanzel method[18] are lower than compounds such as $(CO)_5WC(C_6H_5)_2$ (10) and $(CO)_5WC(OCH_3)C_6H_5$ (11)[2a,19] (by 0.53 and 0.36 and 0.37 and 0.18 mdyn/A, respectively). This indicates more negative charge on the $W(CO)_5$ moiety which, in turn, requires more positive charge on the ring.

The force constants for 5 are far greater than those of $(CO)_5^-WCH_2C_6H_4$-p-Me[13] and the differences between the cis and trans force constants (0.38 mdyn/A compared with 1.24 mdyn/A) is far less (even if differences in solvent are taken into account).[20] This suggests that there is still sub-stantial back-bonding from tungsten into the carbene ligand, although undoubtedly less than in carbene complexes 10 and 11. The most conclusive evidence for dipolar character of 5 is its large dipole moment of 7.7 ± 0.2 D[21] (C_6H_6, 25 °C). For

comparison, the dipole moments of **10** and **11** are 3.48 and 4.39 D, respectively.

Acknowledgment.

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(14) To date, all attempts to isolate the σ complex **4** as a pure material have failed. For example, workup as described by Casey¹³ for salts of methyl and phenyl pentacarbonyltungstate invariably gave a mixture of **4** and regenerated **3** (identified by IR). The ¹H NMR of the mixture showed resonances (acetone-d₆) at δ 2.76 (2 H, d, *J* = 7.0 Hz), 5.0–5.4 (1 H, m), 5.8–6.8 (4 H, m), ~0.8–2.0, and 3.1–3.6 (tetrabutylammonium, 20 × 100% too intense for pure **4**).
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(20) Complex **5** was measured in heptane and (CO)₅⁻WCH₂C₆H₄-*p*-Me in THF. In polar solvents, the force constants showed a tendency to become smaller.
(21) The uncertainty mainly arises from the low solubility of **5** in C₆H₆.

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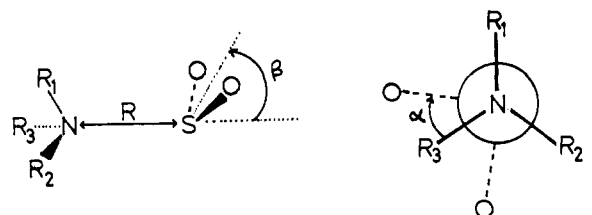*Gainesville, Florida 32611*

Trimethylamine–SO₂, the Prototype Strong Charge-Transfer Complex

Sir:

Of all the charge-transfer complexes in the literature, trimethylamine (TMA)–SO₂ is among the best characterized. It is one of the few where one has an available x-ray structure¹ and gas phase energy of complex formation (ΔE).² It has the additional advantage that it is small enough that one can directly apply theoretical ab initio molecular orbital methods to it.

Table I. Amine-SO₂ Interaction Energies, Geometries, and Energy Components

	complex[a]			
	NH₃-SO₂	MA-SO₂	DMA-SO₂	TMA-SO₂
Interaction energies and geometries				
$-\Delta E$, kcal/mol	11.7	13.9	14.5	15.0
R, Å[b]	2.63	2.45	2.40	2.36
β, deg[c]	85	85	(85)	(85)
α, deg[d]	0	60	(60)	(60)
Energy components[a,e]				
ΔE^f	−11.3	−13.7	−14.3	−14.8
$\Delta E_{es}{}^g$	−33.4	−33.1	−32.5	−31.8
$\Delta E_{pol}{}^h$	−3.4	−4.0	−4.5	−4.9
$\Delta E_{CT}{}^i$	−10.2	−12.3	−13.3	−14.1
$\Delta E_{ex}{}^j$	35.7	35.7	36.0	36.0

[a] The experimental monomer geometry for SO₂ and for the amines was used in the calculations, with the exception that all of the amines had tetrahedral RNR angles. A comparison of the ammonia-SO₂ results with θ(HNH) = 106.7° (experimental) and θ(HNH) = tetrahedral showed negligible difference with the difference in ΔE being 0.1 kcal/mol (NH₃-SO₂ with experimental NH₃ geometry had a $-\Delta E$ of 11.8 kcal/mol). In TMA, θ(CNC) = 108.7° experimentally. [b] $R = R$(N–S). [c] β is the tilt angle of the SO₂ off the N-S axis. [d] α is the dihedral angle of rotation of amine relative to the SO₂. In the Newman projection at the top of the page, for NH₃ (R₁ = R₂ = R₃ = H), MA (R₁ = Me; R₂ = R₃ = H), DMA (R₁ = R₂ = Me; R₃ = H), and TMA (R₁ = R₂ = R₃ = Me). [e] Energy components all evaluated at R = 2.45 Å, β = 85°, α = 180° in kilocalories/mole. [f] Total interaction energy. [g] Electrostatic interaction energy. [h] Polarization energy. [i] Charge-transfer energy. [j] Exchange repulsion energy.

In fact, a set of ab initio calculations on H₃N··SO₂ and TMA–SO₂ has appeared in this journal. Lucchese et al.³ found H₃N··SO₂ to be bound by 4.94 kcal/mol with R(N–S) = 2.86 Å and TMA–SO₂ bound by 4.06 kcal/mol with an identical R(N–S). These results are perhaps surprising when one realizes that the x-ray structure of TMA–SO₂ finds R(N–S) = 2.06 Å¹ and gas phase experiments find a $-\Delta E$ for TMA–SO₂ of 9.7 kcal/mol.² Lucchese et al. carried out more extended basis set calculations (double ζ) on H₃N–SO₂ and found that the interaction energy increased to 10.4 kcal/mol and R(N–S) decreased to 2.70 Å. They did not study TMA–SO₂ at the double ζ level.

These ab initio results are intriguing for a number of reasons. (1) Gas phase proton affinities of methyl substituted amines ($\Delta E \sim -200$ kcal/mol) follow the order TMA > DMA > MA > NH₃;⁴ gas phase Li⁺ affinities ($\Delta E \sim -40$ kcal/mol) are in the order DMA > TMA > MA > NH₃;⁵ thus it may be reasonable⁶ that, for the weaker Lewis acid SO₂, NH₃ is a stronger Lewis base than TMA. However, studies on the closely related Lewis acid I₂ in hydrocarbon solvents indicate the strength of interaction in the order H₃N < MA < DMA < TMA⁷. Is this latter a solvent effect and is it relevant to a gas phase study of amine–SO₂? What is the correct order of the Lewis basicity for amine–SO₂ interactions? (2) What is the reason for the extremely large difference of 0.8 Å¹ between the STO-3G calculated³ and experimental R(N–S)? It appears to be too great to be a crystal effect; yet STO-3G usually does well for structure predictions⁸ and almost always *underesti-*