

Figure 1. The 9.5-gHz spectra of (a) trans isomer **10** and (b) cis isomer **11** (1×10^{-4} M) in egg lecithin vesicles (60 mg/ml in 10 mM Tris buffer, pH 7.4) at 25 °C, scaled to the same total double integral.

converted into the mesylates **5**⁶ and thence into iodides⁷ **6** (74%, *m/e* 450.221) and **7** (16%, *m/e* 450.223) which were separable by silica gel chromatography (elution with CHCl_3). Following the procedure of Meyers,⁸ **6** and **7** separately were converted into oxazolines **8** and **9** and thence by quaternization and base hydrolysis⁸ into azethoxyl acids **10** (60%, *m/e* 382.332) and **11** (35%, *m/e* 382.332).

Evidence for the smaller steric size of an azethoxyl nitroxide as compared with a doxyl⁹ or proxyl nitroxide³ of similar chain length was obtained by trapping **10** in the cavity of a thiourea inclusion crystal.¹⁰ Neither the doxyl nor the proxyl nitroxides could be included in the thiourea crystals under similar conditions, presumably because they are sterically too large to fit into the cavity.

While the solution ESR spectra of **10**¹¹ and **11** were virtually identical, significant differences (over a temperature range of 25–45 °C) were observed in the spectra of the two isomers when diffused into egg lecithin vesicles (Figure 1). Computer simulation¹² of the ESR spectra led to an estimate of $50 \pm 3^\circ$ and $57 \pm 3^\circ$ for the angle between the nitroxide *Z* axis and the long axis of rotation of **10** and **11**, respectively. Simulations also revealed that the rotational motion experienced by cis isomer **11** was less than that of the trans isomer **10**.

A preliminary study of the relative rates of reduction of 12-doxylstearic acid, 14-proxylstearic acid¹³ and azethoxyl acid **10** indicate that the azethoxyl nitroxide is the most resistant toward reduction. In one series of experiments the nitroxides (1.1×10^{-4} M) were dissolved in 0.1 M phosphate buffer, pH 7.5, containing sucrose (0.25 M), EDTA (10^{-3} M), and sodium ascorbate (0.011 M).¹⁴ After 20 min only 3% of the original signal intensity remained for the doxyl nitroxide, whereas 90% remained for the proxyl nitroxide and 94% remained for the azethoxyl nitroxide.

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References and Notes

- (1) For a review see "Spin Labeling: Theory and Applications", L. J. Berliner, Ed., Academic Press, New York, N.Y., 1976.
- (2) It is convenient to name spin-labeled molecules as derivatives of their parent molecules. Thus, nitroxide **10** can be named as a *trans*-10-aza-9,11-ethano-*N*-oxyleicosanoic acid which is shortened to *trans*-10-azethoxyleicosanoic acid. This system has the advantage that it immediately locates the position of the label.
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- (10) T. B. Marriott, G. B. Birrell, and O. H. Griffith, *J. Am. Chem. Soc.*, **97**, 627 (1975). The diameter of the thiourea cavity is ~ 7 Å. To a lesser extent, isomer **11** can also be trapped in the cavity of thiourea inclusion crystals. Molecular models indicate that an approximately linear structure can be achieved by imposing a gauche conformation on each side of the pyrrolidine ring.
- (11) Isotropic *A* and *g* values for 2×10^{-4} M solutions of **10** are *A* = 14.1 G, *g* = 2.0062 in hexane and *A* = 16.3 G, *g* = 2.0054 in 0.1 M phosphate buffer (pH 7.5). The corresponding values for 14-proxylstearic acid are *A* = 14.5 G, *g* = 2.0058 (hexane) and *A* = 16.3 G, *g* = 2.0055 (H_2O); and for 12-doxylstearic acid *A* = 14.4 G, *g* = 2.0062 (hexane) and *A* = 16.0 G, *g* = 2.0056 (H_2O). Experimental errors are estimated to be ± 0.1 G for *A* and ± 0.0002 for *g*.
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Detection and Measurement of the Rate of 1,3 Iron Shift in Cycloheptatrieneiron Tricarbonyl

Sir:

Many fluxional organometallic systems are known in which a transition metal is bound to a fragment of a totally conjugated cyclic polyenyl or polyene system.¹ Examples include complexes containing the $(\eta^3\text{-C}_7\text{H}_7)\text{M}$,² $(\eta^5\text{-C}_7\text{H}_7)\text{M}$,³ $(\eta^4\text{-C}_8\text{H}_8)\text{M}$,⁴ $(\eta^6\text{-C}_8\text{H}_8)\text{M}$,⁵ and $(\eta^4\text{-C}_6\text{R}_6)\text{M}$ ⁶ moieties. In almost every case where the fluxional mechanism has been determined, the metal migrates around the ring via a series of 1,2 shifts with concomitant π -bond migration.^{1–8}

In similar cyclic polyene complexes, such as cycloheptatrieneiron tricarbonyl (I), cyclooctatrieneiron tricarbonyl (II), and cyclononatetraeneiron tricarbonyl (III) where the cyclic conjugation of the polyene system has been interrupted by a $(\text{-CH}_2\text{-})_n$ group, the facile 1,2 metal migration is precluded and the complex displays no fluxional behavior at moderate temperatures. For example, the ¹H NMR spectrum of I shows no line broadening up to temperatures of ~ 100 °C, where initial decomposition begins.⁹

Although 1,2 metal shifts are ruled out for complexes such as I, II, and III, degenerate isomerization by net 1,3 metal shifts is possible. Such formal 1,3 iron shifts have been observed by Takats and Li Shing Man for $(7\text{-exo-MMe}_3\text{C}_7\text{H}_7)\text{Fe}(\text{CO})_3$ (*M* = Si or Ge).¹⁰ In an effort to determine the activation energy for the 1,3 metal shift in the simplest unsubstituted non-conjugated polyene system and to contrast this with the energetics of 1,2 metal shifts, we have examined cycloheptatrieneiron tricarbonyl using the Forsén and Hoffman technique of spin saturation transfer.¹¹

In the spin saturation transfer (SST) experiment, the rate constant for exchange, *k*, in a two-site, equal-population system, $\text{A} \rightleftharpoons \text{B}$, is given by¹²

$$k = \frac{1}{T_{1A}} \left[\frac{M(0)}{M(\infty)} - 1 \right] \quad (1)$$

Table I. Spin Saturation Transfer Data, Rate Constants, and Free Energies of Activation

Complex	$T, ^\circ\text{C}$	$M(0)/M(\infty)$	T_1 of H_6^a	$k \times 10^2 \text{ s}^{-1}$	$\Delta G^\ddagger, \text{kcal mol}^{-1}$
I	61	1.27	14.5	1.90	22.2
	75	1.80	17.5	4.55	22.4
	86	2.52	10.7	14.2	22.5
	90	4.50	10.7	32.7	22.1
VI	80	1.12	7.7	1.56	23.6
	80	1.13	7.6	1.71	23.5
	95	1.20	7.9	2.53	24.3
	95	1.10	3.4	2.94	24.2
	105	1.36	4.1	8.77	24.0

^a Measured by the fast inversion recovery method: D. Canet and G. C. Levy, *J. Magn. Reson.*, **18**, 199 (1975).

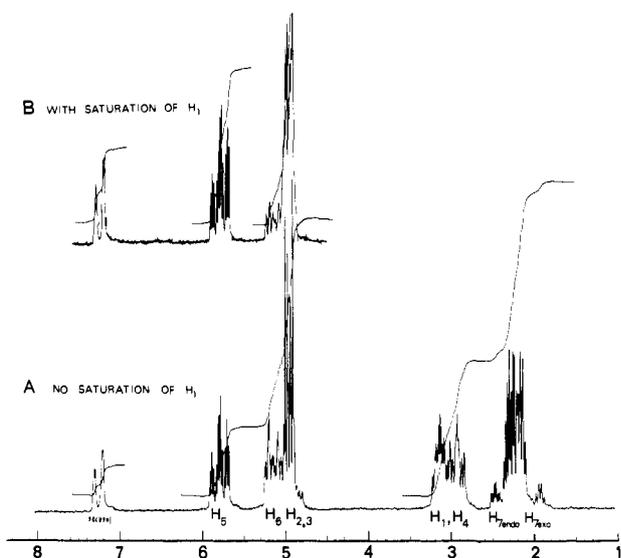
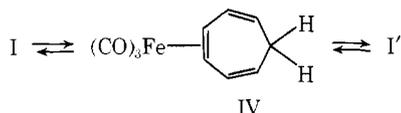
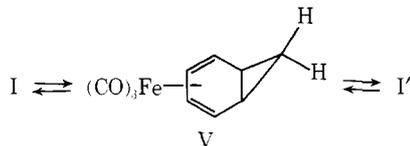


Figure 1. ^1H NMR spectra of cycloheptatrieneiron tricarbonyl at 90°C in toluene- d_8 : A, no saturation of H_1 ; B, with saturation of H_1 .

Scheme I

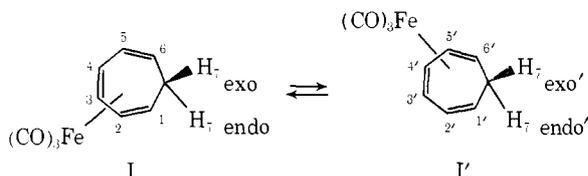


Scheme II



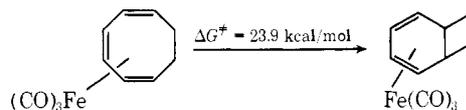
where T_{1A} is the spin-lattice relaxation time of the proton at site A, $M(0)$ is the normal equilibrium magnetization of the proton at A and $M(\infty)$ is the equilibrium magnetization of the proton at A after saturating the proton at site B.¹¹ Experimentally $M(0)/M(\infty)$ is determined by comparing the signal areas of proton A with and without saturation of proton B.

Through extensive decoupling experiments the ^1H resonances for complex I have been assigned as follows: δ 1.89 ($\text{H}_{7\text{-exo}}$), 2.12 ($\text{H}_{7\text{-endo}}$), 2.72 (H_4), 2.89 (H_1), 4.59–4.74 ($\text{H}_{2,3}$), 5.03 (H_6), and 5.68 (H_5).¹³ Degenerate 1,3 iron shifts interconvert H_1 with H_6 , H_2 with H_5 , and H_3 with H_4 . To test for



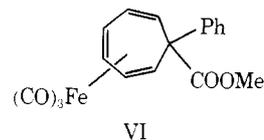
spin saturation transfer, it was experimentally most desirable to saturate H_1 and examine the H_6 signal since the resonances were well separated and irradiation of H_1 resulted in no nuclear Overhauser enhancement of the H_6 signal. Indeed, a reduction in intensity of the H_6 signal was observed upon saturation of H_1 at temperatures between 60 and 90°C . A typical set of spectra (taken at 90°C) is shown in Figure 1, in which the area of the H_6 resonance decreased by 78% upon saturation of H_1 . Data for $M(0)/M(\infty)$ are summarized in Table I along with T_1 values measured for H_6 . Also included are the rate constants calculated from eq 1 and the corresponding ΔG^\ddagger values for the 1,3 iron migration in I. The SST experiments clearly rule out any other averaging process such as hydrogen migration through a metal hydride intermediate since saturation of H_1 results only in reduction of intensity for H_6 ; similarly, saturation of H_6 results in reduction of intensity of H_1 .

Although the averaging process corresponds to a *net* 1,3 iron shift, two mechanisms for iron migration seem feasible: (1) a direct 1,3 shift involving dechelation of the 1,2 double bond to form the symmetrical η^2 -cycloheptatrieneiron tricarbonyl intermediate, IV, which can collapse to I', as shown in Scheme I; (2) two sequential 1,2 iron shifts involving a norcaradieneiron tricarbonyl intermediate, V, as shown in Scheme II. A norcaradiene intermediate is attractive in that only 1,2 metal shifts are involved, and also an analogous transformation of cyclooctatrieneiron tricarbonyl (II), to bicyclo[4.2.0]octa-2,4-dieneiron tricarbonyl has been observed.¹⁴



The substantially higher free energy of activation for the unsubstituted system ($\Delta G^\ddagger = 22.3 \text{ kcal/mol}$) as compared to the GeMe_3 substituted system of Takats ($\Delta G^\ddagger \approx 17.0 \text{ kcal/mol}$)¹⁰ is compatible with the norcaradiene intermediate in that a C_7 substituent would likely have a larger effect on the stability of the norcaradiene intermediate than on the transition state for a direct 1,3 iron shift.¹⁵

To gain additional information regarding the effect of C_7 substitution on the rate of degenerate isomerization, we examined 7-phenyl-7-carbomethoxycycloheptatrieneiron tricarbonyl (VI). The free ligand¹⁷ is known to exist as an $\sim 2:1$



ratio of norcaradiene to cycloheptatriene at 25°C .¹⁸ Even though the norcaradiene isomer predominates in the uncomplexed ligand, reaction with either $\text{Fe}(\text{CO})_5$ photolytically or benzylideneacetoneiron tricarbonyl thermally gave no norcaradiene complex, and only a single isomer of the triene

complex, VI, of unknown stereochemistry was isolated.¹⁹ Application of the SST technique to the measurement of the 1,3 iron shift in VI gave the results summarized in Table I. Surprisingly, ΔG^\ddagger (23.9 kcal/mol) for iron migration is slightly greater for this compound than for I. Although significant lowering of the ΔG^\ddagger might have been anticipated for VI relative to I if the norcaradiene mechanism obtains (Scheme II), we feel that these results do not necessarily rule out a possible norcaradiene intermediate for this fluxional process. If, for example, the phenyl group is exo to iron in VI, then steric interactions of the phenyl group with the cyclohexadiene unit in the norcaradiene-like transition state may offset any electronic stabilization of the transition state owing to the C₇ substituents.¹⁸

Although the detailed mechanism of the 1,3 iron shift cannot be precisely specified for I, it is clear from these results that activation energies for 1,3 iron shifts are higher than those for 1,2 iron shifts in cyclic polyene and polyenyl complexes. (ΔG^\ddagger s range from ~ 7 kcal for C₈H₈Fe(CO)₃²⁰ to ~ 15 kcal for (η^3 -C₇H₇)Fe(CO)(η^5 -C₅H₅).²) The results obtained in this study and those reported by Mann^{7c} demonstrate that spin saturation transfer is a very useful technique for studying relatively "slow" fluxional organometallic systems where thermal sensitivity of the complex precludes the use of standard line-broadening techniques at higher temperatures. Indeed, for these cycloheptatrieneiron tricarbonyl complexes, line broadening would have been observable by ¹H NMR only above 140 °C where decomposition is quite rapid.

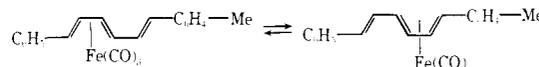
We are currently applying the spin saturation technique to other organometallic systems which are expected to exhibit fluxional processes with high activation energies.²¹

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Design of an Ion-Molecule Reaction Specific for Neutral Nitriles

Sir:

Only a few ion-molecule reactions have been observed which are so characteristic of a neutral functional group that the reaction may be used to identify the group. The classical examples of these are the reactions of ionized butadiene with olefins;¹ the metathesis of substituents between ionized and neutral olefins,² which may be used to locate double bonds;³ and the reactions of trihalomethyl cations with neutral carbonyl compounds.⁴ Reactions which distinguish between epimers because of their specificity for less hindered isomers⁵ are related to this category.

A reaction specific for nitriles was designed as follows. Transfer, not simple addition, pathways are more effective ion-molecule reactions at low pressures. Proton transfers are the best understood transfers. The proton affinity of acetonitrile is 5 kcal/mol greater than that of methanol,^{6,7} and, for reasons paralleling those adduced for series of nitrogen-containing⁸ and triply-bonded⁹ compounds, the proton affinities of nitriles with larger alkyl substituents are greater.^{6,7} Thus proton transfer from methanol to all nitriles should be observed, but of course proton transfer is not specific. Since methyl cation affinities have similar trends as proton affinities, with clear exceptions which bound the analogy,¹⁰ we examined other alkyl cations. While a positively charged atom is the primary reaction site in ion-molecule reactions, to create specific reactivity for a functional group, it is necessary to introduce another reaction site into the alkyl group. We chose a radical site. A radical site has little influence on electronic effects of alkyl groups, for the electronic effects of C₂H₅ and C₃H₇ are very similar to those of the analogous radicals from which a hydrogen atom has been removed, \cdot C₂H₄– and \cdot C₃H₅–, in at least one series of compounds.¹¹ The most desirable location of the radical site is adjacent to carbenium carbon, for this will permit four-center reactions with the nitrile group; rapid four-center reactions are common; and there is precedent for involvement of triply bonded atoms in a four-center reac-