comparable with those found for TC alone. Upon comparison of Figures 1A and 1D, a slight broadening for C_{12} is apparent in addition to upfield and downfield shifts for C_{11} and C_1, respectively. Thus if $Nd(NO_3)_3$ were added to a solution of TC·HCl which had been titrated to pH ~7, the observed effects on ^{13}C NMR signals, *when compared to those of TC·HCl prior to addition of* Nd^{3+}, could be interpreted as indicating binding at the C_{11}–C_{12} β-diketone moiety. However when the solution containing a 0.050 mole ratio of La^{3+}/TC is treated likewise with NaCl, these same effects on C_{12}, C_{11}, and C_1 are observed. Thus there are no selective *paramagnetic* effects when NaCl is present at a 1:1 mole ratio with TC.

The above observations account for the conclusions drawn by Asleson from carbon-13 NMR studies regarding the site of binding of several metals to TC·HCl.[4] Indeed, in a number of previous investigations of metal binding in tetracyclines utilizing various techniques such as potentiometric titration, uv, CD, ir, and fluorescence spectroscopy, either the HCl salt of the antibiotic was used or the free base was used in combination with a relatively high concentration of buffers or other electrolytes.[10-20]

The effect of added electrolyte was further examined by proton NMR in Me_2SO-d_6. As reported earlier, the amide proton resonances show pronounced selective broadening in the presence of Nd^{3+} and other paramagnetic ions.[1,2] Upon addition of NaCl to a solution of TC and $Nd(NO_3)_3$ the broadened amide resonance signals sharpen considerably, and the upfield component shifts to a higher field as is observed for TC in the presence of diamagnetic ions such as Ca^{2+} or La^{3+}.[1] These same effects are observed upon addition of $NaNO_3$ or $NaClO_4$, but no significant changes occur upon adding Et_4NNO_3 or Et_4NClO_4. Only slight signal narrowing occurs when Et_4NCl is added. Thus it would appear that Na^+ is primarily responsible for the effects observed here. Presumably Na^+ competes successfully for the ring A binding site of TC by a mass action effect.

In conclusion, these experiments demonstrate that the long-standing controversy over the site at which metal binding occurs in tetracycline antibiotics may result, at least in part, from the presence of various electrolytes in the media at high molar concentrations relative to the drugs. Small cations from the electrolytes saturate the ring A binding site, forcing out cations of lower concentration. No NMR evidence of binding at other sites, under the conditions employed here, has been found.

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Transition-Metal-Promoted Aldehyde–Alkene Addition Reactions

Sir:

The decarbonylation of aldehydes by chlorotris(triphenylphosphine)rhodium(I) (**1**) in solution under mild conditions (eq 1)[1] is one of many interesting and important examples of the utility of transition metal complexes in organic synthesis.

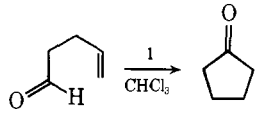
$$RCHO + \underset{\mathbf{1}}{RhCl(Ph_3P)_3} \rightarrow RH + RhCl(CO)(Ph_3P)_2 + PPh_3 \quad (1)$$

Although no evidence regarding the mechanism of this transformation has been reported, it has been suggested[1c] that the decarbonylation could proceed through an acylmetal hydride intermediate, i. The possible generation of metal

$$\underset{\mathbf{i}}{R{-}\overset{\overset{O}{\|}}{C}{-}Rh(H)(PPh_3)_2Cl}$$

complexes such as i via the oxidation additions of the aldehyde carbonyl carbon–hydrogen bonds to metal species is a fascinating concept. The potential utility of intermediates such as i in the synthesis of a variety of organocarbonyl compounds is great. Our continuing study of the role in catalysis of organotransition metal intermediates with unsaturated hydrocarbon ligands possessing C–M σ bonds[2] has led us to investigate the interaction of unsaturated aldehydes with transition metal compounds. We have sought to generate an acylmetal hydride intermediate and trap it, through the reaction of its M–C or M–H bond with an alkene ligand on the metal precursor, and also through reaction with unsaturation in the acyl ligand.

We wish to report that rhodium(I) complexes catalyze the addition of the aldehyde functional group in 4-pentenal to carbon–carbon double bonds to generate ketones. Both intermolecular and intramolecular reactions have been observed, the course of the reaction being dictated by the nature of the rhodium catalyst employed. Treatment of 4-pentenal with **1** in chloroform solution at room temperature afforded cyclopentanone (eq 2). When a 10:1 aldehyde:Rh mole ratio ([Rh] = 0.056 M) was employed, 32% of the

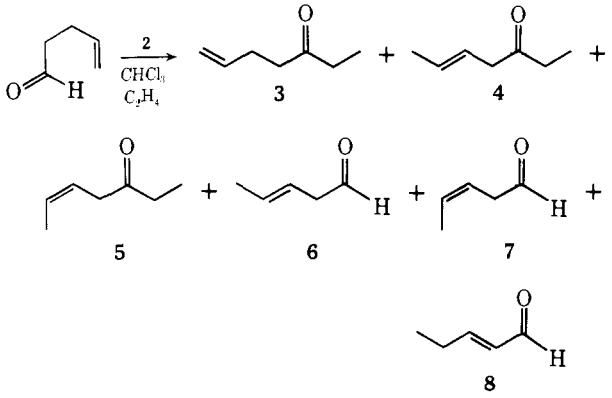


(2)

pentenal was converted to products and 43% of the reacted material was isomerized to cyclopentanone during 16 h. Higher yields of cyclopentanone could be achieved by the introduction of ethylene to the reaction mixtures. During 16 h, 65% of 4-pentenal was converted to products and a 78% yield of cyclopentanone was afforded when a 10:1 aldehyde:Rh ratio ([Rh] = 0.016 M) was employed in ethylene-saturated chloroform. After 88 h in ethylene-saturated chloroform, 96% of the 4-pentenal had been converted to products and a 72% yield of cyclopentanone was obtained.[3] Catalyst deactivation may occur by the competing decarbonylation reaction. Small quantities of chlorocarbonylbis(triphenylphosphine)rhodium(I) could be isolated from reaction mixtures in experiments carried to 96% conversion in ethylene-saturated chloroform. The infrared spectrum of the isolated rhodium compound proved to be identical with that of a literature preparation.[4] Very small amounts of a product with a GLC retention time identical with that of 1-butene were detected in the product mixtures.

The enhanced catalytic efficiency of **1** in the presence of added ethylene may indicate that alkene unsaturation preempts a metal coordination site that is required by the decarbonylation process.

Treatment of 4-pentenal with 2,4-pentanedionatobis(ethylene)rhodium(I) (**2**) (aldehyde:Rh = 10) in ethylene-saturated chloroform resulted in the catalytic generation of three heptenones, 6-hepten-3-one (**3**), *trans*-5-hepten-3-one (**4**), and *cis*-5-hepten-3-one (**5**), in 6, 39, and 2% yields, respectively, at 100% conversion during 16 h. Accompanying the formation of these ethylene–pentenal adducts were three double bond migration products, *trans*-3-pentenal (**6**), *cis*-3-pentenal (**7**), and *trans*-2-pentenal (**8**), afforded in 15, 1, and 3% yields, respectively (eq 3). A minor product with a GLC retention time identical with that of cyclopentanone was present in the product mixture. Its yield was determined to be ca. 1% by ^{1}H NMR analysis of its mixture with **4**, isolated by GLC.



(3)

When a chloroform solution of **2** was treated with 4-pentenal (aldehyde:Rh mole ratio = 10) in the absence of added ethylene, **3**, **4**, and **5** were formed in 1, 12, and 2% yields, respectively, and **6**, **7**, and **8** were afforded in 25, 4, and 8% yields at 100% conversion during 16 h.[5] The yields of heptenones indicates that 75% of the ethylene available in the **2** charged was consumed in the generation of **3**, **4**, and **5**.

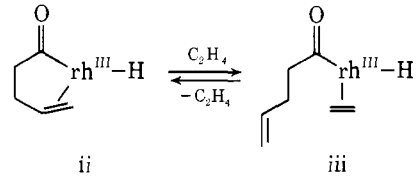
While the sum of the yields of **3**, **4**, and **5** in these experiments gives the total pentenal–ethylene addition product yield, the ratio of the 5-hepten-3-one derived from isomerization of **3**[7] to that generated by reaction of **6** and **7** with ethylene has not yet been determined.

The addition of hexanal to ethylene was not promoted by **1** or **2** at room temperature in ethylene-saturated chloroform.[8] Neither 3-octanone nor any other organic product derived from the aldehyde could be detected in the reaction mixture during 80 h when a 10:1 ratio of hexanal:**2** was employed. Treatment of hexanal with **1** in $CHCl_3$ or CH_2Cl_2 in the absence of ethylene led to the ca. stoichiometric decarbonylation according to eq 1. However, **2** did not promote the decarbonylation of hexanal under these same reaction conditions. When hexanal was treated with **1** in ethylene-saturated $CHCl_3$, decarbonylation occurred, but the loss of aldehyde was less than stoichiometric relative to rhodium during a 24-h period.

Many free-radical-promoted additions of aldehydes to alkenes are known.[10] Free-radical reactions of aldehydes with ethylene have afforded telomers as well as 1:1 adducts. Cyclopentanone is not a product in reported free-radical-induced decompositions of 4-pentenal.[11] Treatment of 4-pentenal with 5 mol % of benzoyl peroxide under our reaction conditions in $CHCl_3$ afforded no cyclopentanone during 65 h at 50°. An analogous experiment conducted in ethylene-saturated $CHCl_3$ did not produce any cyclopentanone, **3**, **4**, or **5** during 44 h at 50°.

These observations would indicate that the ketone products derived from 4-pentenal, on its treatment with **1** and **2**, do not come from direct attack of a pentenoyl free radical on alkene unsaturation. The fact that the intramolecular vs. intermolecular aspect of the addition reaction is governed by the nature of the rhodium complex employed emphasizes the intimate role of the transition metal in the transformations.

The ketone products are explained by the generation of intermediates such as ii and iii where rh^{III} represents the metal and its auxiliary ligands (eq 4).[12] The identity of



(4)

these ligands is determined by the nature of the metal complex, **1** or **2**, employed. The observed products could be formed by two modes of collapse of ii and iii: (a) C—Rh addition to coordinated alkene followed by reductive elimination via carbon–hydrogen coupling; (b) Rh–H addition to coordinated alkene followed by reductive elimination via carbon–carbon coupling.[13] Therefore, cyclopentanone would be generated from ii, and ketone **3** would come from an intermediate such as iii. Ketones **4** and **5** could derive from 3-pentenoyl isomers of iii. The mechanism(s) and synthetic scope of these reactions are being investigated.

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formed into each product. Yield and conversion data were determined by GLC on 20% Silicone GE XE-60 on 60/80 Chromosorb P and 20% 1,2,3-tris(2-cyanoethoxy)propane on 60/80 Chromosorb W columns. Standard mixtures of reactants and products were analyzed in order to determine the relationships between signal responses and molar ratios. The organic products were isolated by preparative GLC and were identified by their infrared, ^{1}H NMR, and mass spectra.

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Olefin Metathesis Reaction. III.[1] Mechanistic Considerations

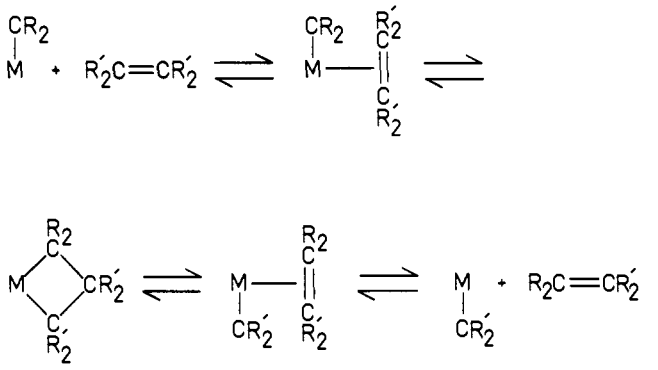
Sir:

After a period in which a plethora of reaction mechanisms were advanced for the remarkable catalytic olefin metathesis reaction,[2] there now appears to be a growing consensus that metal carbene and metallocyclobutane intermediates are involved in the reaction, at least for tungsten-based catalysts, as shown in Scheme I. The model tungsten carbene studies by Casey and Burkhardt,[3] the alkylidene exchange studies by Katz and McGinnis[4] and by Grubbs et al.,[5] and our[1] observations on the basic tungsten chemistry have strengthened the chain carbene concept originally advanced by Herisson and Chauvin.[6] Additionally, the recent *isolation* of a simple M–CH_2 carbene[7] demonstrates the plausibility of metal carbene intermediates that do not bear electronegative substituents on the carbene carbon atom. We report here some methylene transfer reactions that are consistent with this basic mechanistic concept, provide additional insight to the variability in the basic reaction with slight modifications in catalyst, and establish a stereochemical feature of these catalysts that must be fully explained in any mechanism proposed for olefin metathesis.

Metathesis catalysts based on WCl_6 reportedly do not metathesize terminal olefins.[2] From purely mechanistic considerations, we proposed[1] that terminal olefins do in fact metathesize in all catalytic systems but in a relatively selective and nonproductive (or degenerate) fashion so as to reform the original terminal olefin as in Scheme II. We have established that the catalyst derived from WCl_6 + C_2H_5OH + $4C_2H_5AlCl_2$ interacts more strongly with a terminal than with an internal olefin. The metathesis rate of *cis*-2-pentene with this catalyst system is sharply reduced on addition of 1-nonene (See Figure 1). This result is in full accord with the general finding that the association constants for olefin–metal complexes are larger for terminal than for internal olefins.[8] To determine if there would in fact be an interchange of terminal CH_2 and CD_2 groups in view of the incisive demonstration (Figure 1) of strong interaction of the terminal olefin with the catalyst, we decided to test our basic proposal[1] by following the fate of a terminal olefin mixture of 1-hexene and 1-heptene-*1,1*-d_2 (or 1-pentene-d_{10}) in the presence of catalysts prepared from the various WCl_6–R_xM recipes.[2]

The heterogeneous catalyst[9] derived from WCl_6 + 2*n*-C_4H_9Li[10] effected exchange of terminal CH_2 and CD_2 groups with 1-hexene and 1-heptene-*1,1*-d_2; 1-hexene-*1,1*-d_2 and 1-heptene were the only hydrocarbons other than the starting olefins and traces of productive metathesis products (vide infra) detected by GC mass spectral analysis. There was no evidence of H–D exchange via a carbon–hydrogen bond scission. An analogous CH_2–CD_2 exchange was ob-

Scheme I



Scheme II