The presence of a large nitrogen isotope effect indicates clearly that the carbon–nitrogen bond-breaking step is rate determining in the acylation of the enzyme.[11] In the case of chymotrypsin[5] we argued that the isotope effect observed is smaller than the actual isotope effect on the bond cleavage step because some prior step occurs at a rate similar to that of the cleavage step. The isotope effect varies with pH because of the variation in the relative rates of the two steps. In the case of papain, the isotope effect is so large that it is unlikely that such a reduction of isotope effect has occurred. Further, the isotope effect is larger than those observed in reactions of hydroxide ion with amides even in cases where carbon–nitrogen bond breaking is known to be rate determining.

The magnitude of the nitrogen isotope effect on the papain reaction indicates that the carbon–nitrogen bond is extensively broken at the transition state. This is consistent with the small solvent isotope effect ($k_{H_2O}/k_{D_2O} = 1.35$) observed in the same reaction.[8] Hydrogen isotope effects on proton transfers vary according to the position of the proton at the transition state,[12] the largest isotope effect being observed when the proton is half-way transferred, and smaller isotope effects being observed when the transition state is more asymmetric. The small solvent isotope effect here presumably occurs because the proton transfer is nearly complete at the transition state.

Thus, both nitrogen and hydrogen isotope effects indicate that the transition state in the papain-catalyzed hydrolysis of *N*-benzoyl-L-argininamide is characterized by extensive carbon–nitrogen bond breaking and concomitant nearly complete transfer of a proton from histidine to the departing nitrogen. We cannot deduce from these results whether or not a tetrahedral intermediate is involved in this reaction.

**Acknowledgment.** This research was supported by grants from the National Institutes of Health (NS-07657), the University of Wisconsin Graduate School, and the Research Corporation.

(10) K. G. Harbison, unpublished communication.

(11) However, the presence of this isotope effect gives no information about the relative rates of acylation and deacylation.

(12) W. H. Saunders, Jr., *Survey Progr. Chem.*, 3, 109 (1966); F. H. Westheimer, *Chem. Rev.*, 61, 265 (1961).

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## Alkyl Group Isomerization in the Oxidative Addition of Acyl Chlorides to Iridium(I) Complexes

*Sir:*

The oxidative addition of acyl and aroyl halides to the planar dinitrogen complex $IrCl(N_2)[P(C_6H_5)_3]_2$ has recently been shown to give initially five-coordinate acyl–iridium(III) complexes which then rearrange, probably *via* an alkyl or aryl group migration, to six-coordinate alkyl- or aryl–iridium(III) species (eq 1).[1,2]

$$IrCl(N_2)(PPh_3)_2 + RCOCl \xrightarrow{-N_2} IrCl_2(COR)(PPh_3)_2 \longrightarrow IrCl_2R(CO)(PPh_3)_2 \quad (1)$$

We have independently obtained a series of these compounds by addition of acyl halides to $IrCl[P(C_6H_5)_3]_3$ (**1**)[3] (eq 2) and find that if R in the acyl halide RCOCl is branched at the $\alpha$-carbon atom, the resulting alkyl–iridium(III) complex is exclusively the isomeric straight-chain derivative.

$$\underset{\mathbf{1}}{IrCl(PPh_3)_3} + RCOCl \xrightarrow{-PPh_3} \underset{\mathbf{2}}{\begin{matrix} & PPh_3 & \\ Cl & | & CO \\ & Ir & \\ Cl & | & R \\ & PPh_3 & \end{matrix}} \quad (2)$$

**a**, R = $CH_2CH_2CH_3$
**b**, R = $CH_2CH_2CH_2CH_3$
**c**, R = $CH_2CH_2CH_2CH_2CH_3$
**d**, R = $CH_2CH_2C_6H_5$

Thus, addition of 2-methylpropanoyl chloride, $(CH_3)_2CHCOCl$, to **1** in refluxing benzene gives the *n*-propyl complex (**2a**; R = $CH_2CH_2CH_3$) in 55% yield as colorless crystals: ir ($CH_2Cl_2$) 2030 [$\nu$(CO)], 305, 254 $cm^{-1}$ [$\nu$(IrCl)]; nmr ($CDCl_3$) $\delta$ 0.02 (t, 3, $CH_3$, $J(CH_2CH_3)$ = 7.5 Hz), 1.10 (m, 4, $CH_2CH_2$). An identical product is obtained in 80% yield from **1** and butanoyl chloride. Likewise, 2-methylbutanoyl chloride, 2-ethylbutanoyl chloride, and 2-phenylpropanoyl chloride react with **1** to give the *n*-butyl (**2b**), *n*-pentyl (**2c**), and 2-phenethyl iridium(III) complexes (**2d**), respectively, in 30–40% yield. The only other iridium-containing product isolated in the first two cases is the hydride $IrHCl_2[P(C_6H_5)_3]_3$, which may arise from traces of HCl impurity in the acyl chlorides; in the case of 2-phenylpropanoyl chloride, $IrCl(CO)[P(C_6H_5)_3]_2$ is also formed (32% yield), probably as a result of facile elimination of styrene and HCl from **2d** or its precursor.

We believe that the initial product of reaction of **1** with branched acyl chlorides is the appropriate *sec*-alkyl–iridium(III) complex and that this rapidly isomerizes to the *n*-alkyl *via* a hydrido–olefin intermediate,[4] *e.g.*

$$\begin{matrix} CH_3 & & CH_3 \\ & \diagdown\ \diagup & \\ & CH & \\ & | & \\ & Ir & \end{matrix} \longrightarrow \begin{matrix} CH_3CH{=}CH_2 \\ | \\ IrH \end{matrix} \longrightarrow \begin{matrix} CH_2CH_2CH_3 \\ | \\ Ir \end{matrix}$$

Molecular models suggest that the instability of the *sec*-alkyls with respect to the *n*-alkyls may be due to unfavorable steric interaction of the branched alkyl chain with the phenyl rings of the triphenylphosphine ligands. Support for this hypothesis is provided by a reexamination of the oxidative addition of acyl chlorides to the cyclooctene complex $[IrCl(CO)(C_8H_{14})]_2$ (**3**), which gives dimeric, octahedrally coordinated, chlorine-bridged alkyl–iridium(III) complexes (**4**).[5,6] In **4** there is no obvious steric hindrance to the formation of a *sec*-alkyl complex. As previously reported,[5] 2-

(1) M. Kubota and D. M. Blake, *J. Amer. Chem. Soc.*, *93*, *1368* (1971).

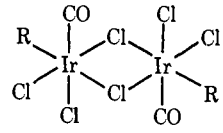
(2) M. Kubota, D. M. Blake, and S. A. Smith, *Inorg. Chem.*, 10, 1430 (1971).

(3) M. A. Bennett and D. L. Milner, *J. Amer. Chem. Soc.*, 91, 6983 (1969).

(4) There are many examples of reversible addition of a transition metal hydride to an olefin to give an alkyl [R. A. Schunn, *Inorg. Chem.*, 9, 2567 (1970), and references cited therein] and there is evidence in one case that this proceeds *via* a hydrido–olefin complex: J. Chatt, R. S. Coffey, A. Gough, and D. T. Thompson *J. Chem. Soc. A*, 190 (1968); A. J. Deeming, B. F. G. Johnson, and J. Lewis, *Chem Commun.*, 598 *(1970)*; *H. C.* Clark and H. Kurosawa, *ibid.*, *957 (1971)*.

(5) B. L. Shaw and E. Singleton, *J. Chem. Soc. A*, 1683 (1967).

(6) N. A. Bailey, C. J. Jones, B. L. Shaw, and E. Singleton, *Chem. Commun.*, 1051 (1967).



**4a**, R = $CH(CH_3)_2$
**b**, R = $CH_2CH_2CH_3$
**c**, R = $CH(CH_3)CH_2CH_3$
**d**, R = $CH_2CH_2CH_2CH_3$

methylpropanoyl chloride reacts with **3** in hot benzene to give the isopropyl complex (**4a**, R = $CH(CH_3)_2$) as white crystals: ir (Nujol) 2130, 2070 $cm^{-1}$ [$\nu$(CO)]; nmr ($CDCl_3$) $\delta$ 1.45 (d, 6, $CH_3$), 3.28 (septet, 1, CH, $J$ = 7.5 Hz), but after 90 min in refluxing benzene, the solution contains approximately equal amounts of the isopropyl and *n*-propyl complexes, as shown by nmr. The pure *n*-propyl complex **4b** is obtained as white crystals by treating **3** with butanoyl chloride {ir (Nujol) 2135, 2085 $cm^{-1}$ [$\nu$(CO)]; nmr ($CDCl_3$) $\delta$ 1.00 (t, 3, $CH_3$, $J$ = 8 Hz); 1.68 (sextet, 2, $CH_2CH_2$), 2.66 (m, 2, $CH_2CH_2$)}, but this also undergoes isomerization in refluxing benzene for 90 min to give the equilibrium mixture of isopropyl and *n*-propyl complexes. The *sec*-butyl complex **4c**, obtained from **3** and 2-methylbutanoyl chloride, isomerizes over a 3-hr period at ~30° to give an equilibrium mixture consisting almost entirely of the *n*-butyl complex **4d**. In both cases, isomerization is accompanied by formation of the insoluble hydride complex $[IrHCl_2(CO)_2]_n$,[5] which probably arises by competing decomposition of an intermediate hydrido–olefin complex.

Isomerization of $\pi$-$C_5H_5Fe(CO)_2CH_2CH_2CH_3$ to $\pi$-$C_5H_5Fe(CO)_2CH(CH_3)_2$ has been effected indirectly *via* an intermediate cationic propene complex $[\pi$-$C_5H_5Fe(CO)_2CH_2{=}CHCH_3]^+$ by successive $H^-$ abstraction and addition,[7] but so far as we are aware, the present work provides the first example of isomeric transition metal alkyls which are in thermal equilibrium. The observations may bear on the mechanisms proposed for reactions involving intermediate transition metal alkyls, such as hydroformylation, and particularly on the tendency of phosphine-modified cobalt–carbonyl catalysts to favor formation of straight-chain aldehydes in this reaction.[8]

(7) M. L. H. Green and P. L. I. Nagy, *J. Organometal. Chem.*, **1**, 58 (1963).
(8) L. H. Slaugh and R. D. Mullineaux, *ibid.*, **13**, 469 (1968).

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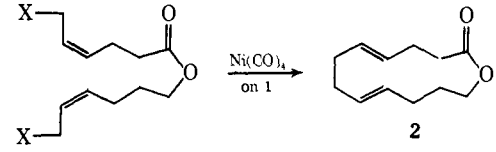
## A New Method for the Synthesis of Macrolides

*Sir:*

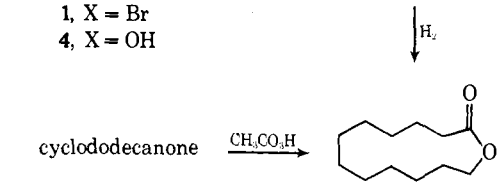
The cyclization of allylic dibromides by nickel carbonyl has previously been applied to the synthesis of carbocycles of 9–18 members, including the naturally occurring sesquiterpene humulene.[1–5] It has now been found that this procedure is also highly effective for the formation of macrocyclic lactones, an important class of organic substances (*e.g.*, in the antibiotic field) for which there exists only a very limited synthetic methodology.

Gradual addition (over 3.5 hr) of the dibromo ester **1**[6] (*Z,Z* isomer) to 6 equiv of nickel carbonyl in *N*-methylpyrrolidone[3,4] (*ca.* 0.2 *M* in $Ni(CO)_4$) with stirring at 50° under argon effected cyclization to the (*E,E*)-diene macrolide **2** as the major product.[7] Removal of excess nickel carbonyl[9] from the reaction by codistillation with ether, addition of water, extraction with pentane, concentration, and isolation by preparative layer chromatography (plc) on silica gel afforded **2**[6,7] (70–75% yield) having infrared max ($CCl_4$) due to C=O at 5.77 $\mu$ and due to *trans*-CH=CH at 10.33 $\mu$ and lacking absorption characteristic of *cis*-HC=CH at 14.2 $\mu$. Hydrogenation of the mixture of stereoisomeric lactones[7] in ethanol over palladium/charcoal catalyst produced $\omega$-hydroxydodecanoic acid lactone (**3**) as the sole product (by gas-chromatographic and thin-layer chromatographic analysis), identical with an authentic sample[10] prepared by the action of peroxyacetic acid–sulfuric acid on cyclododecanone.



1, X = Br
4, X = OH

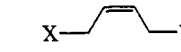
2

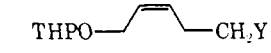


cyclododecanone

3

The dibromide **1** was prepared in 83% yield from the corresponding diol **4**[6a] by reaction with phosphorus tribromide in ether at 0° for 12 hr. The synthesis of **4** was carried out *via* the intermediates **5**–**12** as follows.





**5**, X = AcO; Y = OTs
**6**, X = AcO; Y = $CH(COOC_2H_5)_2$
**7**, X = HO; Y = $CH(COOC_2H_5)_2$
**8**, X = THPO; Y = $CH(COOC_2H_5)_2$
**9**, Y = $COOC_2H_5$
**10**, Y = COOH
**11**, Y = $CH_2OH$
**12**, Y = $CH_2I$

(5) For a synthesis of the divinylcyclohexane sesquiterpene elemol by this reaction, see E. J. Corey and E. A. Broger, *Tetrahedron Lett.*, 1779 (1969).
(6) Satisfactory (a) infrared and nuclear magnetic resonance data and (b) high-resolution mass spectral data were obtained for this liquid substance using samples which were homogeneous by thin-layer chromatographic analysis.
(7) In addition to **2**, two isomeric substances were produced (ratio 90:4:6) as ascertained by gas-chromatographic analysis (300 × 0.32 cm column of 5% diethylene glycol succinate on Chromosorb W at 190°). These by-products are considered to be stereoisomers of **2**, but their exact structures have not been determined. The predominating formation of the *E,E* product (even starting from the (*Z,Z*)-dibromide **1**) was expected on the basis of previous results[1,3,4,8] which show that the nickel carbonyl reaction results in the formation of the same stereoisomeric cyclization product(s) starting with (*E,E*)- or (*Z,Z*)-allylic dibromides.
(8) E. J. Corey, M. F. Semmelhack, and L. S. Hegedus, *J. Amer. Chem. Soc.*, **90**, 2416 (1968).
(9) All operations involving the toxic nickel carbonyl must be conducted in a well-ventilated hood.
(10) K. Kosswig, W. Stumpf, and W. Kirchhof, *Justus Liebigs Ann. Chem.*, **681**, 28 (1965).

(1) E. J. Corey and E. Hamanaka, *J. Amer. Chem. Soc.*, **86**, 1641 (1964).
(2) E. J. Corey and M. F. Semmelhack, *Tetrahedron Lett.*, 6237 (1966).
(3) E. J. Corey and E. K. W. Wat, *J. Amer. Chem. Soc.*, **89**, 2757 (1967).
(4) E. J. Corey and E. Hamanaka, *ibid.*, **89**, 2758 (1967).