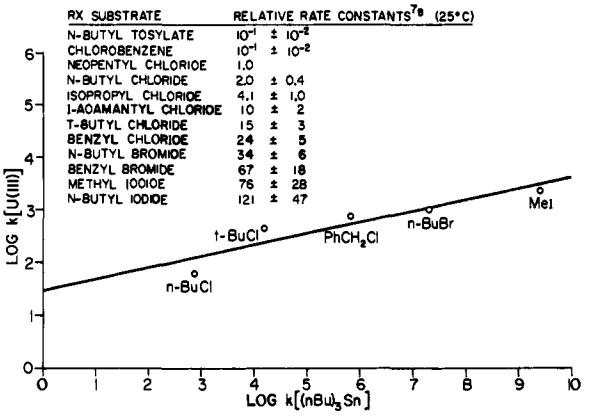


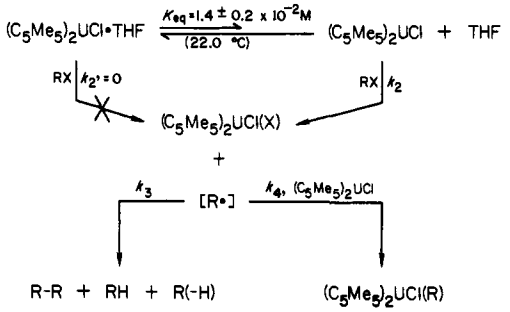
Figure 1.

benzene. The observed [THF] dependence is characteristic of a prior equilibrium, $(C_5Me_5)_2UCl{\cdot}THF \rightleftharpoons (C_5Me_5)_2UCl + THF$, where $K_{eq} \ll 1$ and where the relative reactivity is $(C_5Me_5)_2UCl \gg (C_5Me_5)_2UCl{\cdot}THF$. Derivation of the necessary kinetic equation[7] followed by the appropriate plot of the data shows that $1/k_2(obsd)$ vs. [THF] is linear with the slope = 2.1 ± 0.2 s and intercept = 0.031 ± 0.003 M s. The full rate law is consistent with the prior equilibrium and rate-determining step of Scheme I with[7a] $K_{eq} = 1.4 \pm 0.2 \times 10^{-2}$ M, $k_2 = 21 \pm 2$ M^{-1} s^{-1}, and $k_{2'} = 0$ for *n*-BuCl at 22.0 °C. The small K_{eq} for THF dissociation reflects the high oxygen affinity[5] of organoactinide reagents, and $k_2' = 0$ (within experimental error) suggests that coordinative unsaturation and the availability of an inner sphere process is a requirement for these facile oxidative-addition reactions.

The RX alkyl, structure-reactivity and halogen dependence was determined at 25 °C in benzene for 12 total RX, including X = I, Br, Cl, OTs, by pairwise competition experiments, monitoring the loss of RX in the ^1H NMR spectra. The results and the propagated error bars are tabulated in Figure 1 along with a log/log plot comparing the U(III) rates to those for one of the better studied organometallic atom abstractors,[8] $Bu_3Sn\cdot$. The relative RCl rates of benzyl ~ tertiary > secondary > primary > neopentyl and *n*-BuI > *n*-BuBr > *n*-BuCl are consistent with rate-determining formation of an R· intermediate with carbon-halogen bond cleavage in the transition state. The linear log/log correlation with the $Bu_3Sn\cdot$ data lends credence to both sets of data and suggests a similar rate-determining step for both the U(III) and $R_3Sn\cdot$ reagents.

An atom-abstraction mechanism (Scheme I) is consistent with all of our observations.[9]

Scheme I. Atom-Abstraction Mechanism of $(C_5Me)_2UCl$ Oxidative Addition of Alkyl Halides (Benzene)



To summarize, the results presented herein (1) provide evidence for an atom-abstraction RX oxidative-addition mechanism to $(C_5Me_5)_2UCl$; (2) quantify the reactivity of $(C_5Me_5)_2UCl$ in benzene as 10^4–10^7 faster than any known[10] isolable, transition-metal systems reacting by halogen atom abstraction, as only 42 times slower than the transient intermediate $Bu_3Sn\cdot$ in the case of alkyl chlorides, and as even 4.0 times faster than the S_N2 reagent[2a] $Fe(CO)_4^{2-}$; (3) quantify the relative rates of $(C_5Me_5)_2UCl/(C_5Me_5)_2UCl{\cdot}THF$ as 20:0 and suggest that this difference reflects primarily the difference in the degree of coordinative unsaturation[5,11] and thus the availability of an inner sphere pathway for the 7- and 8-coordinate U(III) species.

Further studies of organoactinide oxidative additions and the possible extension of this work to organolanthanides is currently under investigation.

Acknowledgment. Financial support through NSF Grant CHE 7811552 and a grant from Chevron Research is gratefully acknowledged.

(7) (a) The k_2 (obsd) given in Scheme I and used in the text includes a statistical factor, $(a + 2b)/(a + b)$, introduced by the reaction stoichiometry (and equal to 1.55 and 1.08 for *n*-butyl and neopentyl chlorides, respectively), k_2 (obsd) = $(a + 2b)/(a + b)$ $[K_{eq}k_2/([THF] + K_{eq})]$, when $k_2' = 0$. A plot of $1/k_2$(obsd) vs. [THF] will be linear if $k_2' = 0$ and will have slope = $1/[(a + 2b)/(a + b)]K_{eq}k_2$ and intercept = $1/[(a + 2b)/(a + b)]k_2$. From the observed slope and intercept, the values $K_{eq} = 1.4 \pm 0.2 \times 10^{-2}$ M and $k_2 = 21 \pm 2$ M^{-1} s^{-1} were obtained. (b) The relative rates in Figure 1 are relative k_2 (obsd)/$[(2a + b)/(a + b)]$, i.e., they do not include the statistical factor from the stoichiometry[7a] since the disappearance of RX was monitored, $-d[RX]/dt = k_2(obsd)/[(a + 2b)/(a + b)][U(III)]_T[RX]$.

(8) (a) Sakura; H. "Free Radicals"; Kochi, J. K., Ed.; John Wiley and Sons: New York, 1973; Vol. II, p 771. (b) See also ref 3b.

(9) (a) An alternate mechanism, common to reactions of this type,[3a] is the possibility of an outer sphere electron transfer,[9b-d] $(C_5Me_5)_2UCl + RX \rightleftharpoons (C_5Me_5)_2UCl^+ RX^-\cdot$, with equilibrium constant K_{eq}, rather than inner sphere atom abstraction. Several lines of evidence argue effectively against the electron-transfer mechanism: (1) first and foremost is the requirement of coordinative unsaturation in the U(III) oxidative additions, a feature readily understood in terms of an inner sphere but not in terms of an outer sphere process; (2) a second line of evidence is that the electron transfer appears to be nearly 1.5 V uphill and thus too endergonic to be facile. The cyclic voltammogram of $(C_5Me_5)_2UCl_2$ in THF gave[1] a $E_{1/2}$[U(IV)/U(III)] = −1.3 V vs. SCE. Using this $E_{1/2}$ value as a negative limit for the U(IV)/U(III) couple of $(C_5Me_5)_2UCl$ and from the Ep[9e] of *n*-BuCl ~ −2.8 V (SCE) (which includes kinetic effects but is probably[9f] $Ep \geq E_{1/2}$), one can estimate $E_{total} \leq -2.8 + 1.3 = -1.5$ V and thus $K_{eq} \leq 10^{-25}$ (25 °C) for $(C_5Me_5)_2UCl + BuCl \rightleftharpoons (C_5Me_5)_2UCl^+ + BuCl^-\cdot$. Although there is an interesting problem with calculations of this type in that several "unfavorable"[9c,d] electron transfers have suprisingly facile rates, we know of no electron transfers apparently uphill by ca. 1.5 V that have rates near our k_2(*n*-BuCl, 25 °C) = 20 M^{-1} s^{-1}. In fact, even though it has a more negative $E_{1/2}$ = −1.67 V (SCE) the radical anion of perylene, $Na^+C_{20}H_{12}^-\cdot$, reacts 586 times more slowly with *n*-BuBr, k_2 (obsd, 20 °C in THF)[9c] = $5.8 \pm 0.2 \times 10^{-1}$ M^{-1} s^{-1}; (3) a third line of evidence is derived from the relative RCl reactivities. When electron transfer takes place, one generally sees a correlation of log k with Ep[9c] and this is not what is observed from the following data: RX (relative rate, Ep (V, SCE) PhCl (10^{-1}–10^{-2}, −2.57)[9c], *n*-BuCl (2, −2.8)[9c], $(CH_3)_3CCl$ (15, −2.6)[9c], $PhCH_2Cl$ (24, −1.2).[9g] It is worth noting, however, that in addition to atom abstraction some alternate, slower pathway appears to exist since *n*-BuOTs does react with $(C_5Me_5)_2UCl{\cdot}THF$.[2p] (b) Bank, S.; Bank, J. F. *ACS Symp. Ser.* **1978**, *No. 69*, Chapter 21. (c) Bank, S.; Jucket, D. A. *J. Am. Chem. Soc.* **1976**, *98*, 7742. (d) Kochi, J. K. *Pure Appl. Chem.* **1980**, *52*, 571. (e) Lambert, F. L.; Ingall, G. B. *Tetrahedron Lett.* **1974**, 3231. (f) Nicholson, R. S.; Shain, I. *Anal. Chem.* **1964**, *36*, 707; see p 718. (g) Streitwieser, A., Jr.; Perrin, C. *J. Am. Chem. Soc.* **1964**, *86*, 4938. (h) Walling, C. *Ibid.* **1980**, *102*, 6854.

(10) (a) For example, k_2 ($PhCH_2Cl$, 25 °C, Co(II)$B_{12(s)}$ in $MeOH/H_2O$)[3g] = 1.0×10^{-2} M^{-1} s^{-1} while k_2($PhCH_2Cl$, 25 °C, $(C_5Me_5)_2UCl$ in benzene) = 2.4×10^2 M^{-1} s^{-1}; k_2 (*n*-BuBr, 25 °C, Cr(III)en_2^{2+} in DMF/H_2O)[3h] = 1.4×10^{-4} M^{-1} s^{-1} while k_2 (*n*-BuBr, 25 °C, $(C_5Me_5)_2UCl$ in benzene) = 3.4×10^2 M^{-1} s^{-1}; k_2 (*n*-$C_5H_{11}Cl$, 25 °C, Rh(I)$[C_2DOBF_2]$ in THF)[2o] = 6×10^{-6} M^{-1} s^{-1} while k_2 (*n*-BuCl, 22 °C, $(C_5Me_5)_2UCl$ in benzene) = 20 M^{-1} s^{-1}. (b) An interesting and probably better comparison under consideration is the system[4] Cp_2MCl (M = Ti, Zr, Hf) + RX. Cp_2ZrCl, with its more negative ca. −1.8 V vs. SCE Zr(IV)/Zr(III) couple,[10c] could be even more reactive than $(C_5Me_5)_2UCl$. (c) El Murr, N.; Chalyard, A.; Tirouflet, J. *J. Chem. Soc., Chem. Commun.* **1980**, 446.

(11) A detailed study of the magnetic and other properties of $(C_5Me_5)_2UCl$, its THF adduct, and the RX reactions of other actinide and transition-metal[10b] systems will be required to completely settle this point.

Stereochemistry of an Enzymatic Baeyer–Villiger Reaction. Application of Deuterium NMR

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Received December 12, 1980

Enzymatic conversion of ketones to esters is known to be a common feature in the microbial degradation of a wide variety

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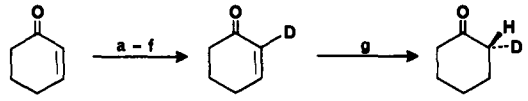
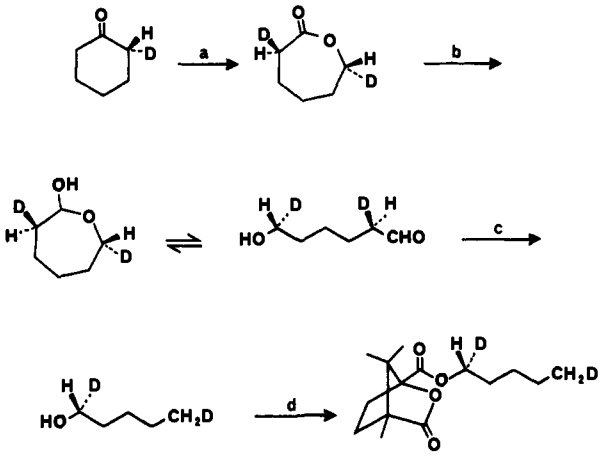
Scheme I



Scheme II



of organic compounds.[1] Limited enzymological data indicate that these enzyme systems are flavin-dependent monooxygenases,[1c-g,2] consuming one molecule each of ketone, molecular oxygen, and reduced pyridine nucleotide. The enzyme mechanisms are still a matter of much speculation, as are the mechanisms of action of a wide variety of flavin-dependent enzymes.[3] Nevertheless, there seems to be general agreement on the intermediacy of a flavin C-4a hydroperoxide (FlOOH) in flavin monooxygenase action.

Mechanistic proposals[4,5] have run the gamut from nucleophilic attack of $FlOO^-$ on substrate ketone[5a] to a nucleophilic attack by enolized ketone on the distal oxygen of FlOOH, a "carbonyl oxide" derivative of the flavin,[5b] or another variety of flavin-"O^+" donor.[5c] Bruice[3b] has, in fact, suggested that FlOOH may participate in formation of an enzymic peraspartic or perglutamic acid, leading to the accepted[6] mechanism for a nonenzymatic, Baeyer–Villiger[7] reaction.

"Biochemical Baeyer–Villiger" reactions proceed with retention of configuration in the case of certain steroid and bridged bicyclic

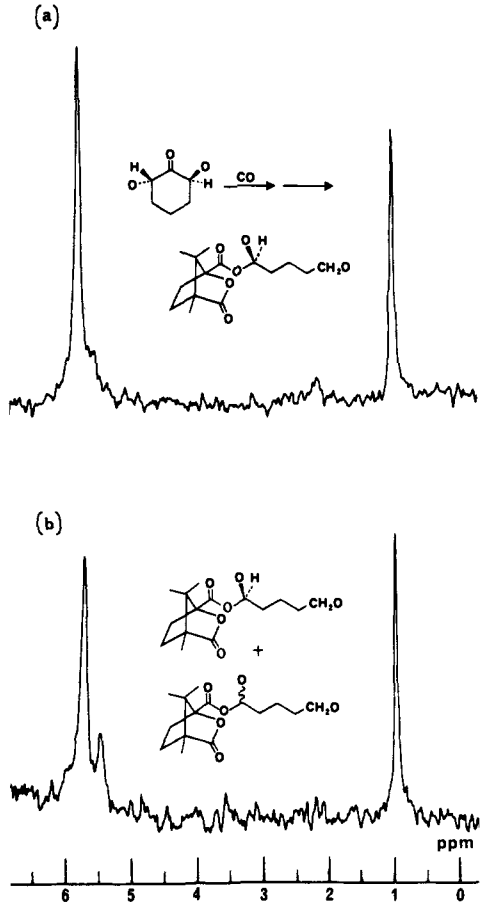


Figure 1. (a) $Eu(dpm)_3$-shifted 46-MHz deuterium NMR spectrum of pentyl camphanate from incubation of (2*S*,6*S*)-[2,6-$^2H_2$]cyclohexanone with cyclohexanone oxygenase, followed by degradation as shown in Scheme II. (b) As in (a), but with the addition of stereorandomly deuterated camphanate.

substrates.[2] However, these substrates are stereochemically biased,[8] and in an effort to shed light on the general mechanism, we have set out to determine unambiguously the stereochemical requirements of a system which utilizes an achiral molecule as substrate.

Cyclohexanone oxygenase (CO)[1e] catalyzes the conversion of cyclohexanone to ε-caprolactone (2-oxepanone). Study of the stereochemical mode of action requires the synthesis of cyclohexanone, chirally substituted with a hydrogen isotope at C-2, and a method for determining the chirality at C-6 of enzymatically produced caprolactone. Synthesis of (2*R*)-[2-$^2H_1$]cyclohexanone (Scheme I) was based upon the report by a French group[11] of the stereoselective reduction of a variety of conjugated enones by cultures of *Beauveria sulfurescens*. Accordingly, [2-$^2H_1$]cyclohex-2-enone was prepared by Smith's method,[12] and incubation of this material with *B. sulfurescens* led to isolation of a sample of deuterated cyclohexanone whose chirality at C-2 was deter-

(1) (a) Sih, C. J.; Rosazza, J. P. In "Applications of Biochemical Systems in Organic Chemistry"; Jones, J. B., Sih, C. J., Perlman, D., Eds.; Wiley: New York, 1976; Part II, pp 100–102. (b) Fonken, G. S.; Johnson, R. A. "Chemical Oxidations with Microorganisms"; Marcel Dekker: New York, 1972; pp 157–164. (c) Britton, L. N.; Brand, J. M.; Markovetz, A. J. *Biochim. Biophys. Acta* **1974**, *369*, 45–49. (d) Cripps, R. E. *Biochem. J.* **1975**, *152*, 233–241. (e) Donoghue, N. A.; Norris, D. B.; Trudgill, P. W. *Eur. J. Biochem.* **1976**, *63*, 175–192. (f) Griffin, M.; Trudgill, P. W. *Eur. J. Biochem.* **1976**, *63*, 199–209.

(2) (a) Trudgill, P. W.; DuBus, R.; Gunsalus, I. C. *J. Biol. Chem.* **1966**, *241*, 4288–4297. (b) Prarie, R. L.; Talalay, P. *Biochemistry* **1963**, *2*, 203–208. (c) Rahim, M. A.; Sih, C. J. *J. Biol. Chem.* **1966**, *241*, 3615–3623.

(3) (a) Massey, V.; Hemmerich, P. *Biochem. Soc. Trans.* **1980**, *8*, 246–256. (b) Bruice, T. C. *Prog. Bioorg. Chem.* **1976**, *4*, 1–87.

(4) Most published mechanistic proposals are for the aromatic hydroxylase class of monooxygenases; adaptation to the Baeyer–Villiger monooxygenases is straightforward. Attack of enol on flavin-O^+ donor suggests intermediacy of the enol epoxide, followed by ring expansion.

(5) (a) Walsh, C.; Jacobson, F.; Ryerson, C. C. In "Biomimetic Chemistry"; Dolphin, D., Ed.; American Chemical Society: Washington, 1980; pp 119–138. (b) Hamilton, G. A. *Prog. Bioorg. Chem.* **1971**, *1*, 83–157. (c) Orf, H. W.; Dolphin, D. *Proc. Natl. Acad. Sci. U.S.A.* **1974**, *71*, 2646–2650.

(6) Doering, W. von E.; Dorfman, E. *J. Am. Chem. Soc.* **1953**, *75*, 5595–5598.

(7) (a) Baeyer, A.; Villiger, V. *Ber.* **1899**, *32*, 3625–3633. (b) Baeyer, A.; Villiger, V. *Ibid.* **1900**, *33*, 858–864.

(8) The peracid-mediated (nonbiochemical) Baeyer–Villiger reaction was first shown to proceed with retention of configuration in two stereochemically biased molecules.[9] Mislow and Brenner[10] subsequently demonstrated elegantly the generality of the initial observations by using optically active 3-phenyl-2-butanone as substrate.

(9) (a) Turner, R. B. *J. Am. Chem. Soc.* **1950**, *72*, 878–882. (b) Gallagher, T. F.; Kritchevsky, T. H. *Ibid.* **1950**, *72*, 882–885.

(10) Mislow, K.; Brenner, J. *J. Am. Chem. Soc.* **1953**, *75*, 2318–2322.

(11) Kergomard, A.; Renard, M. F.; Veschambre, H. *Tetrahedron Lett.* **1978**, 5197–5200.

(12) Guaciaro, M. A.; Wovkulich, P. M.; Smith, A. B., III *Tetrahedron Lett.* **1978**, 4661–4664.

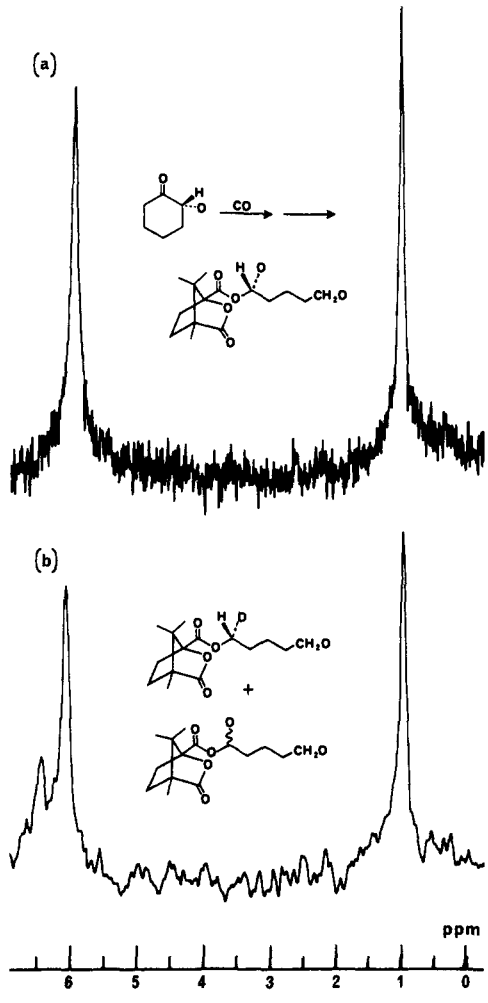


Figure 2. (a) Eu(dpm)$_3$-shifted 46 MHz deuterium NMR spectrum of pentyl camphanate from incubation of (2*R*)-[2-^{2}H$_1$]cyclohexanone with cyclohexanone oxygenase, followed by degradation as shown in Scheme II. (b) As in (a), but with the addition of stereorandomly deuterated camphanate.

mined by the route depicted in Scheme II. Baeyer–Villiger oxidation of chirally labeled ketone gave caprolactone, which was reduced to the corresponding lactol with diisobutylaluminum hydride. This hydroxy aldehyde was decarbonylated[13] using Wilkinson's catalyst, and the resulting 1-pentanol was converted,[14] without isolation, to its (−)-camphanic acid ester. Deuterium NMR analysis in the presence of Eu(dpm)$_3$ showed only a *single* downfield signal (5.83 ppm), plus the upfield methyl deuteron resonance. The proton NMR spectrum of the same sample showed the expected[15] pair of downfield multiplets, with the 5.83-ppm deuterium signal corresponding to the higher field proton resonance. Thus, on the basis of Gerlach's assignments,[14] the pentyl camphanate bore the *R* configuration at the labeled methylene position, and, perforce, its precursor cyclohexanone had the 2*R* configuration, with *no* indication of an enantiotopic deuteron. (2*S*,6*S*)-[2,6-^{2}H$_2$]cyclohexanone[16] was degraded and analyzed in a similar manner and proved to be of high stereochemical purity.[18]

Cyclohexanone oxygenase, purified from *Acinetobacter* NCIB 9871 through the DEAE-cellulose stage,[1e] was separately incubated with (2*R*)-[2-^{2}H$_1$]- and (2*S*,6*S*)-[2,6-^{2}H$_2$]cyclohexanone. The deuterium NMR analyses of pentyl camphanate samples derived from the enzyme-produced caprolactones are depicted in Figures 1 and 2. In Figure 1a, the Eu(dpm)$_3$-shifted spectrum of pentyl camphanate from incubation of (2*S*,6*S*)-ketone with CO shows a single downfield resonance. Addition of a small quantity of stereorandomly deuterated pentyl camphanate (from LiAl^{2}H$_4$ reduction of cyclohexene oxide followed by Jones oxidation and the usual degradation) (Figure 1b) established that the methylene signal in Figure 1a was the more downfield of the two possible resonances, indicating the presence of deuterium in the pro-*S* position of pentyl camphanate.[20] Figure 2 depicts the Eu(dpm)$_3$-shifted deuterium NMR spectra of pentyl camphanate from incubation of (2*R*)-[2-^{2}H$_1$]cyclohexanone with CO in the absence (Figure 2a) and presence (Figure 2b) of stereorandomly deuterium-labeled pentyl camphanate. Clearly, incubation of (2*R*)-[2-^{2}H$_1$]cyclohexanone with CO leads ultimately to ester-bearing deuterium in the pro-*R* position at pentyl C-1.

Cyclohexanone oxygenase catalyzes conversion of cyclohexanone to ϵ-caprolactone with complete *retention* of configuration. Thus the analogy between the microbial and chemical versions of the Baeyer–Villiger reaction is sustained, leaving open the possibility of mechanistic similarities. While it is not possible on the basis of these results to differentiate among the various proposed mechanisms, a control experiment involving incubation of [2,2,6,6-^{2}H$_4$]cyclohexanone[21] with CO followed by degradation of lactone to camphanate and proton NMR analysis did not show any substantial degree of label exchange. While this result suggests that enzymic enolization of substrate is not involved, the possibility of proton removal with severely limited access of solvent to the protonated enzyme base[22] remains. Experiments on this point as well as on regio- and enantioselectivity of CO interaction with unsymmetrically substituted substrates are in progress.[23]

Acknowledgment. I thank the following people for important contributions to these experiments: Dr. William Egan (FDA, Bureau of Biologics) for 46-MHz deuterium NMR spectra, Mr. Lawrence P. Thomas (New England Nuclear Corp.) for 200-MHz proton and 30.7-MHz deuterium NMR spectra, Professor Thomas H. Morton (Brandeis University) for a geneous gift of labeled cyclohexanone and several stimulating discussions, Professor P. W. Trudgill (University College of Wales) for samples of several CO-producing organisms, M. Renard and H. Veschambre (Université de Clermont) for details on microbiological enone reductions. Financial support was provided by NIH via Grant GM 27610-01.

(13) Ohno, K.; Tsuji, J. *J. Am. Chem. Soc.* **1968**, *90*, 99–107.
(14) Gerlach, H.; Zagalak, B. *J. Chem. Soc., Chem. Commun.* **1973**, 274–275.
(15) Owing to a lack of regioselectivity in the Baeyer–Villiger reaction, half of the label from [2-^{2}H$_1$]cyclohexanone went to C-2 and half to C-6 of caprolactone. In fact, the ^{2}H$_2$O used in the quench of the vinyl anion (Scheme I) was only 70% enriched, as judged by NMR analysis of [2-^{2}H$_1$]cyclohex-2-enone; hence the proton signals of interest were quite substantial, the diminution owing to deuterium substitution in the pro-*R* proton position being minor.
(16) (2*S*,6*S*)-[2,6-^{2}H$_2$]cyclohexanone, prepared by acetoacetate decarboxylase mediated exchange of [2,2,6,6-^{2}H$_4$]cyclohexanone,[17] was a generous gift of Professor Thomas Hellman Morton.
(17) Polavarapu, P. L.; Nafie, L. A.; Benner, S. A.; Morton, T. H. *J. Am. Chem. Soc.*, submitted for publication.
(18) A deuterium NMR spectrum of the camphanate ester taken in the presence of Eu(dpm)$_3$ showed no evidence of deuterium in the pro-*R* position. Nevertheless, the signal to noise ratio was not optimal, and Professor Morton has indicated that, on the basis of mass spectral analysis, the labeled cyclohexanone was 13% d_1, 80% d_2, 7% d_3. An independent degradative analysis[19] supports our assignment of the 2*S*,6*S* configuration to this ketone sample.
(19) Benner, S. A.; Rozzell, J. D., Jr.; Morton, T. H. *J. Am. Chem. Soc.* **1981**, *103*, 993–994.
(20) The upfield shoulder at 5.48 ppm in Figure 1a is likely of no special significance (see footnote 18).
(21) Merck and Co., Inc.
(22) Glyoxalase I has, for example, been shown to mediate a shielded proton transfer process. See: Hall, S. S.; Doweyko, A. M.; Jordan, F. *J. Am. Chem. Soc.* **1976**, *98*, 7460–7461.
(23) **Note Added in Proof**: Following submission of the manuscript, the author became aware of the very recent communication by Dauphin et al. (Dauphin, G.; Gramain, J. C.; Kergomard, A.; Renard, M. F.; Veschambre, H. *Tetrahedron Lett.* **1980**, *21*, 4275–4278) which describes a synthesis of (2*R*)-[2-^{2}H$_1$]cyclohexanone identical with that which is shown in Scheme I. The data presented in our communication validate the assumptions made by the French group regarding the absolute configuration and optical purity of their labeled ketone.