and has been reported in ion–molecule reactions (Li^+–CH_4) at moderate pressures.[10]

With the exception of $CH_3Li_2^+$, which has been reported[2,11] to be the base peak in some unpublished work of G. D. Stucky and co-workers on the decomposition mass spectrum of $LiB(CH_3)_4$, all of the carbocations in the table were first observed in this laboratory. $CH_3Li_2^+$ is also found to be the base peak in the high-resolution spectrum of methyllithium.[12]

A further collaborative study[13] is planned to ascertain whether these five-coordinate carbocations are produced by ion–molecule reaction or by ionization of neutral species. Further, the ionization potentials and other thermodynamic data of these interesting species will be measured.

Schleyer, Pople, and co-workers have recently produced an optimistic forecast for the prospects of stability of hypervalent neutrals such as $C(Li)_n$ (n = 5,6) and similar mixed hydrogen–lithium species.[14] Experimental conformation of these predictions would be both surprising and important.

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Bifunctional Chiral Synthons via Biochemical Methods. 3. Optical Purity Enhancement in Enzymic Asymmetric Catalysis[1]

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Microorganisms and enzymes are becoming increasingly recognized as valuable chiral catalysts for asymmetric syntheses, and many examples of their synthetic utilities have been documented.[2] The hydrolytic enzymes have been particularly widely investigated because many of them are capable of transforming diesters into chiral monoesters via enantiotopic group differentiation.[3] While these enzymes generally have relaxed substrate specificities toward unnatural compounds, suitable enzyme systems with high stereochemical specificity are often not readily accessible. Herein we describe a concept that allows one to prepare monoesters of high optical purity using esterases of low to moderate stereoselectivity for the enantioselective hydrolysis of diesters.

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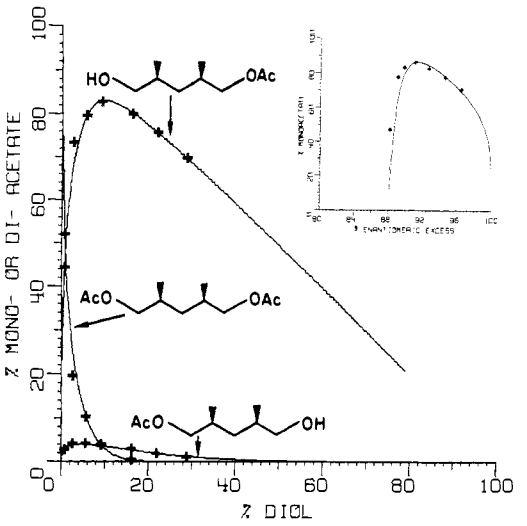
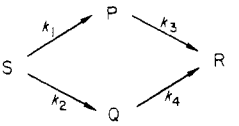


Figure 1. Plot of percent diacetate or monoacetate as a function of percent diol. The curves were computer generated (eq 1, 2, and 3) by using the following: α = 15.6, E_1 = 0.036, and E_2 = 0.18. (#) Experimentally determined values. Insert: Percent monoacetate as a function of percent enantiomeric excess.

Suppose that S is an achiral diester with a plane of symmetry, which is converted by an esterase yielding the two enantiomeric monoesters P (fast forming) and Q (slow forming); in turn, they are further hydrolyzed by the same enzyme to afford R.



When the substrate is a dicarboxylic ester, the reaction generally terminates at the monoester stage with most carboxyesterases.[4] Thus, the ratio of the rates of formation of P and Q is dictated by the constant $\alpha = k_1/k_2$, and the optical purity of the monoester fraction is simply defined by $\beta = (\alpha - 1)/(\alpha + 1)$. On the other hand, when the substrate is a diacetoxy ester, the resulting monoesters (P and Q) usually undergo further concomitant cleavage to yield the diol, R. If the same stereochemical preference is maintained, one would expect the relative rate constants of hydrolysis to follow the order $k_1 > k_2$ and $k_4 > k_3$.[5] Hence, in such cases, this combined procedure (enantioselective hydrolysis followed by kinetic resolution) provides a convenient method of enhancing the optical purity of the monoester fraction.

Since the hydrolytic reaction is virtually irreversible and product inhibition is generally noticeable only at very late stages of the reaction, one may derive quantitative expressions[6] to calculate the concentrations of S, P, Q, and R at any extent of conversion. Definition of the kinetic parameters α, E_1, and E_2 allows the

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(5) k_1, k_2, k_3, and k_4 (apparent first-order rate constants) can be related to the kinetic constants of the enzyme as $k_1 + k_2 = k_{cat(S)}/K_S$, $k_3 = k_{cat(P)}/K_P$, and $k_4 = k_{cat(Q)}/K_Q$, where $k_{cat(S)}$, $k_{cat(P)}$, and $k_{cat(Q)}$ are turnover numbers and K_S, K_P, and K_Q are their respective Michaelis constants.
(6) Quantitative expressions:

$$P = \frac{\alpha S_o}{(\alpha + 1)(1 - E_1)}\left[\left(\frac{S}{S_o}\right)^{E_1} - \left(\frac{S}{S_o}\right)\right] \quad (1)$$

$$Q = \frac{S_o}{(\alpha + 1)(1 - E_2)}\left[\left(\frac{S}{S_o}\right)^{E_2} - \left(\frac{S}{S_o}\right)\right] \quad (2)$$

$$R = S_o - S - P - Q \quad (3)$$

where $E_1 = k_3/(k_1 + k_2)$ and $E_2 = k_4/(k_1 + k_2)$. See supplementary material for (a) derivation of equations, (b) determination of α, E_1, and E_2, and (c) analytical methods.

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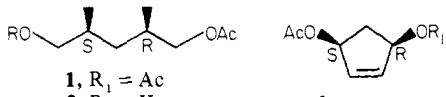
prediction of the enantiomeric excess (ee) of the monoester fraction and the optimization of optical and chemical yields.

To confirm the validity of our theoretical considerations, we selected two meso esters, 1,5-diacetoxy-*cis*-2,4-dimethylpentane[7a] (**1**) and *cis*-3,5-diacetoxycyclopent-1-ene[7b] (**3**), as model substrates for incubation with two different enzymes, pig pancreatic lipase (PPL) and pig liver esterase (PLE).[3]



1, R_1 = Ac
2, R_1 = H

3, R_1 = Ac
4, R_1 = H

A solution of **1** (1.08 g) in 0.1 M phosphate buffer, pH 7.0 (150 mL), was incubated with PPL (200000 units, Sigma Type VI S) at 25 °C with stirring. At various intervals, the extent of conversion and the ee of the monoacetate fraction were determined.[6] A sample of the monoacetate, **2**, $[\alpha]^{25}_D$ −9.5° (89.7% ee), was transformed into the known (2*S*,4*R*)-2,4-dimethylvalerolactone, $[\alpha]^{25}_D$ +36.9° [lit.[1a] (2*R*,4*S*) −41.1°], indicating that the *pro-S* acetoxy group of **1** was preferentially cleaved by PPL. When eq 1 and 2 were used, the kinetic constants for the hydrolysis of **1** were calculated to be $\alpha = 15.6 \pm 0.5$, $E_1 = 0.036 \pm 0.002$, and $E_2 = 0.18 \pm 0.01$. As can be seen from Figure 1, the experimental data are in good agreement with the computer-generated curves for these kinetic constants. On the other hand, PLE preferentially hydrolyzed the *pro-R* acetoxy group of **1** and afforded kinetic constants of $\alpha = 2.47 \pm 0.36$, $E_1 = 0.22 \pm 0.05$, and $E_2 = 0.60 \pm 0.10$ (ee = 0.80, 36% yield; ee = 0.95, 15% yield).

In a similar experiment, **3** (920 mg) was exposed to PLE (1500 units) in 150 mL of 0.1 M phosphate buffer, pH 7.0. The resulting monoacetate, **4**, $[\alpha]^{25}_D$ −56.3° (80.3% ee), was established[8] to be 3(*S*)-acetoxy-5(*R*)-hydroxycyclopent-1-ene, confirming that the *pro-R* acetoxy group of **3** was preferentially attacked by PLE. The kinetic constants for the hydrolysis of **3** were $\alpha = 8.44 \pm 0.56$, $E_1 = 0.06 \pm 0.01$, and $E_2 = 0.12 \pm 0.02$.[9] On the basis of the computer-generated graph (not shown), the maximal recovery obtainable of the monoacetate fraction was 83% with an ee of 81%. Recrystallization of the monoacetate fraction (ee = 81.5%) from benzene–Skelly B (1:5) afforded **4** (ee >96%).

The essential feature of this approach lies in the recognition of the importance of the inherent consecutive kinetic resolution step in enhancing the optical purity of the chiral species during enantioselective hydrolysis of diesters. It is noteworthy that even though the α-value for the initial enantioselective hydrolysis step may be low, high optical purity of the desired chiral intermediate may still be obtained in fair yield. In principle, this concept is of general applicability to biochemical processes involving enantiotopic group differentiation. Consequently, this strategy provides synthetic chemists with considerably more flexibility in the selection of enzyme systems for asymmetric syntheses.

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Supplementary Material Available: Derivations of equations, determination of kinetic parameters, and description of analytical methods (4 pages). Ordering information is given on any current masthead page.

(7) (a) Compound **1** was prepared by LAH reduction of dimethyl *cis*-2,4-dimethylglutarate[1a] followed by acetylation (Ac_2O/Pyr). (b) Compound **3** was prepared by acetylation of *cis*-3,5-dihydroxycyclopent-1-ene, kindly provided by Professor Josef Fried.

(8) The monoacetate **4**, was transformed to the known (+)-3(*S*)-hydroxy-5(*R*)-(tetrahydropyranoxy)cyclopent-1-ene, $[\alpha]^{23}_D$ +17.8°. See: Nara, M.; Terashima, S.; Yamuda, S. *Tetrahedron* **1980**, *36*, 3161.

(9) Although conventional preparations of PLE were shown to be heterogenerous (Ferb, D.; Jencks, W. P. *Arch. Biochem. Biophys.* **1980**, *203*, 214), the experimental data were in accord with the predictions of eq 1 and 2.

Reactivities of Activated Metal Carbonyl Clusters. Ligand Substitution Kinetics of the Methoxycarbonyl Adduct $Ru_3(CO)_{11}(CO_2CH_3)^-$

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Investigations in this laboratory have been concerned with the activation of coordinated carbon monoxide by oxygen containing nucleophiles in context of the mechanistic details of the base-catalyzed water gas shift reaction.[1] In the course of these studies with trinuclear group 8 metal carbonyls, it was noted that reactions with methoxide to give methoxycarbonyl adducts $M-CO_2CH_3^-$ also activated the cluster to ligand substitution both by ligands in solution and by coordinated ligands capable of shifting from a monodentate to a bidentate coordination mode.[2] Reported here is a kinetics investigation showing the methoxycarbonyl adduct $Ru_3(CO)_{11}(CO_2CH_3)^-$ to be orders of magnitude more labile than the parent compound $Ru_3(CO)_{12}$. Such quantitative information is of considerable interest given that methoxycarbonyl adducts are proposed as intermediates in several catalytic cycles[3] and that ligand substitution is a key feature of homogeneous catalysis mechanisms.

When $NaOCH_3$ is added to a solution of $Ru_3(CO)_{12}$ under CO, a stable methoxycarbonyl adduct (A) is formed (eq 1), which can be isolated as the PPN^+ salt, $[PPN][Ru_3(CO)_{11}(CO_2CH_3)]$[4a] ($PPN^+$ = bis(triphenylphosphine)iminium).

$$Ru_3(CO)_{12} + OCH_3^- \rightleftharpoons \underset{A}{Ru_3(CO)_{11}(CO_2CH_3)^-} \quad (1)$$

Reactions of A with trimethyl phosphite in solution under CO results in the formation of the neutral products $Ru_3(CO)_{11}P(OCH_3)_3$ (eq 2) or $Ru_3(CO)_{10}(P(OCH_3)_3)_2$, depending upon the

$$Ru_3(CO)_{11}(CO_2CH_3)^- + P(OCH_3)_3 \rightarrow Ru_3(CO)_{11}(P(OCH_3)_3) + OCH_3^- + CO \quad (2)$$

conditions. In 10/90 THF/CH_3OH (v/v), addition of excess $P(OCH_3)_3$ gave $Ru_3(CO)_{11}P(OCH_3)_3$ (eq 2) as evidenced by infrared and electronic spectral changes. Stopped flow kinetics[4b] of this reaction showed that for $[P(OCH_3)_3] >> [Ru_3]$, plots of $\ln(Abs - Abs_\infty)$ vs. time were linear, indicating the rate law to be first order with respect to the cluster concentration. Plots of k_{obsd} vs. $[P(OCH_3)_3]$ were nonlinear, but k_{obsd}^{-1} vs. $[P(OCH_3)_3]^{-1}$ plots were linear with nonzero intercepts (Figure 1). Such plots at different CO pressures displayed different slopes but identical

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(4) (a) Elemental Analysis of $[PPN][Ru_3(CO)_{11}(CO_2CH_3)]$ calcd: Ru, 25.1; C, 48.67; H, 2.73; N, 1.16; P, 5.13. Found: Ru, 24.95; C, 48.56; H, 2.79; N, 1.18; P, 5.23. (b) $[Ru_3] = 2.6 \times 10^{-4}$ M, $[NaOCH_3] = 5.2 \times 10^{-3}$ M, THF and CH_3OH solvents were freshly distilled, freeze degassed, and then saturated with the appropriate gas. $[P(OCH_3)_3]$ ranged from 3×10^{-3} to 0.1 M.

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