The data in Table I can be used to estimate the enthalpy of a number of interesting potential $Cp^*(PMe_3)Ir$ oxidative addition reactions; these are presented in Table II. The following conclusions can be drawn from the trends in this table: (1) C-C insertion into dicyclohexyl is mildly exothermic and into biphenyl is strongly exothermic; thus these reactions are inhibited by kinetic rather than thermodynamic barriers. (2) In spite of the fact that dihalogen bond energies decrease on moving down the periodic series, Ir-halogen bond energies decrease more (in contrast to the trend for M-C bonds)—thus the $M + X_2$ insertions become progressively less exothermic. (3) The almost identical exothermicities of the H-X insertions support Bercaw and Bryndza's correlation[11] of M-X with H-X bond energies, at least for electronegative X groups.

One of the most striking results of this work is the high strength of the Ir-phenyl bond. To our knowledge this is the first example of a solution-phase M-C bond stronger than an M-H bond in the same series. Further thermodynamic investigations are in progress aimed at determining the physical basis of this phenomenon.

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Origin of Rate Accelerations in an Enzyme Model: The *p*-Nitrophenyl Ester Syndrome

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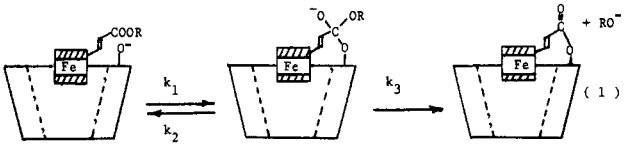
Laboratories the world over are designing, synthesizing, and examining organic systems that in some way "mimic" or "model" enzyme activity. For example, the digestive enzyme, chymotrypsin, has been modeled by groups in Strasbourg,[1] New York,[2] Los Angeles,[3] Evanston,[4] Fukuoka,[5,6] and Atlanta[7] to name a few. Impressive rate accelerations, even surpassing those of chymotrypsin, have been achieved. Yet these chymotrypsin models are deficient in at least one respect: they all use *p*-nitrophenyl esters as substrates.[8] Chymotrypsin "in real life" is, of course, *not* an esterase. Its primary function is to hydrolyze amides (substrates that are far less reactive than *p*-nitrophenyl esters). The question therefore arises as to why chemists persist in working with such artificial substrates. Favorable reaction time is ostensibly one explanation. But amides should, seemingly, present no serious rate problem when a mimic attains enzyme-like accelerations. A second explanation for the prevalence of *p*-nitrophenyl esters relates to convenience (their hydrolyses being easily followed spectrophotometrically). There appears, however, no reason why hydrolyses of "natural" substrates cannot be monitored by the same procedures commonly used with actual enzymes.[9] Is there perhaps a more fundamental reason for the popularity of *p*-nitrophenyl esters? In answering this question, we not only disclose the etiology of the "*p*-nitrophenyl ester syndrome", we uncover an important principle governing mimic behavior.

Our experiments were motivated by the remarkable 3.3×10^5 acceleration in hydrolysis rate, observed by Breslow et al.,[2,10] when *p*-nitrophenyl 3-ferrocenylacrylate binds fully to β-cyclodextrin (eq 1). Thus, the substrate–cyclodextrin complex in 60% (v/v) Me_2SO/H_2O at 30.0 °C and pH_{app} 10 has a half-life of only 7.4 s. In Table I, we compile rate data for complexes between β-cyclodextrin and several additional esters of 3-ferrocenylacrylic acid. Consider first the ethyl ester which is only 56 times less reactive than the *p*-nitrophenyl ester toward basic hydrolysis.[11] One might anticipate, therefore, that ethyl 3-ferrocenylacrylate should, when complexed with β-cyclodextrin, react with a half-life of a few minutes (i.e., 56×7.4 s). In actual fact, we found that the ethyl ester remains >99% unreacted after 10 days under the conditions of Breslow et al.[2,10] The half-life of bound ester is not a few minutes but at least 2 years.[12] Whatever the source of the 3.3×10^5 acceleration with the *p*-nitrophenyl ester, it vanishes totally with the ethyl ester. Little wonder that ethyl esters (not to mention amides) are seldom used to test the efficacy of chymotrypsin mimics.



Absence of significant rate accelerations with the ethyl ester could, possibly, be caused by insufficient binding. To investigate this point, we determined spectrophotometrically the association constant between the ethyl ester and β-cyclodextrin. It was found that $K_{assoc} = 24 \pm 7$ M^{-1} as compared to 133 M^{-1} reported for

Table I. Rate Data for the Hydrolysis of Ferrocenylacrylate Esters (*F*CH=CHCOOR) as Complexes with β-Cyclodextrin ($k_{complex}$) and as Free Substrates (k_{un}).

R	pK_a of ROH	$10^8 k_{un}$, s^{-1}	$t_{1/2}$	$k_{complex}/k_{un}$
ethyl	15.9	0.5[c]	>2 year[a,b]	<2
benzyl	15.2	0.7	>1 year	<2
p-nitrobenzyl	14.6	0.9	>1 year	<2
phenyl	9.9	7.9	18 h	140
m-chlorophenyl	9.1	12	3.9 min	0.26×10^5
p-cyanophenyl	8.0	20	37 s	0.95×10^5
p-nitrophenyl[d]	7.2	28	7.4 s	3.3×10^5

[a] Half-lives for ester disappearance ($t_{1/2}$) were determined by using 6.4×10^{-2} M β-cyclodextrin in 60% (v/v) Me_2SO at 30.0 °C with a phosphate buffer of $pH_{app}10$. Quantitative isolation experiments along with the equation in ref 12 allowed the calculation of $t_{1/2}$ values. In addition, the $t_{1/2}$ for the *p*-cyano compound was measured spectrophotometrically and found to agree with that from the isolation method. [b] The ratio of β-cyclodextrin to ester always exceeded 100. Esters were >60% bound to β-cyclodextrin (as determined spectrophotometrically or by solubility measurements). [c] Observed rates for uncatalyzed hydrolyses (k_{un}) were calculated for reactions under the same conditions as mentioned above but without β-cyclodextrin (see ref 2 and 11). Buffer corrections were neglected. [d] Data from ref 2.

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(11) Rates of hydroxide-catalyzed hydrolyses were calculated from the data in ref 2 and from those of: Bender, M. L.; Zerner, B. *J. Am. Chem. Soc.* **1962**, *84*, 2550. It was assumed that cinnamate esters have the same relative rates as 3-ferrocenylacrylate esters.
(12) Estimated from the quantitative recovery of ester, with an uncertainty <1%, and from ln [100/(% unreacted ester)] = kt where t = 10 days.

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the *p*-nitrophenyl ester. Although the ethyl ester has a somewhat smaller K_{assoc}, we compensated for this by using higher β-cyclodextrin concentrations than did Breslow et al.[2,10] (6.4×10^{-2} M vs. 1.0×10^{-2} M). Under these circumstances, all esters in Table I, including the ethyl ester, are >60% bound. Consequently, the inertness of the ethyl ester cannot be attributed to lack of complex.

If the complexes of the *p*-nitrophenyl and ethyl esters possessed substantially different structures, then their reactivities might also differ.[13] Two factors render this unlikely. (a) Breslow et al.[2,10] argued that the ferrocenyl moiety seats itself within the β-cyclodextrin cavity (eq 1), so that the geometry of the complex is dictated by the ferrocene unit and not by its ester appendage. (b) The *p*-nitro*benzyl* ester, although only 31 times less reactive toward OH^- than the *p*-nitrophenyl ester, is stable for 10 days as a complex under conditions where the *p*-nitrophenyl ester reacts in a few seconds (Table I). Since the two esters differ in structure by only a methylene, the absence of a 3.3×10^5 acceleration with the *p*-nitrobenzyl ester has likely nothing to do with dissimilar binding.

A clue to the etiology of the "*p*-nitrophenyl ester syndrome" is provided by the series of phenyl esters in Table I. It is seen that the acceleration, $k_{complex}/k_{un}$, begins to manifest itself when the pK_a of the leaving group drops to that of phenol (9.9). A 10^4–10^5 acceleration is reached only with leaving groups whose pK_a's are 9 or less. How might this be explained? In the case of *p*-nitrophenyl ester, for example, the tetrahedral intermediate in eq 1 partitions almost exclusively toward product, so that $k_{obsd} = k_1$. With the ethyl and benzyl esters, partitioning favors reactants, so that k_{obsd} now equals $k_1(k_3/k_2)$ where $k_3/k_2 \ll 1$. The phenyl ester lies in a borderline region where neither step in eq 1 is rate-determining. Surprisingly, the preferential movement of tetrahedral intermediate toward product requires phenols of $pK_a < 9$ (more than 3 units *below* the pK_a of the reactive β-cyclodextrin hydroxyl[14]). The β-cyclodextrin oxyanion behaves, therefore, as a much better leaving group than one might expect from its pK_a. The reason for this is critical to the understanding of the "*p*-nitrophenyl ester syndrome". Acylated β-cyclodextrin possesses a high-energy s-cis configuration[15,16] (eq 1) that need not form in simple ester interchanges or hydrolyses. As a result, the tetrahedral intermediate in eq 1 tends to eject the β-cyclodextrin oxyanion and revert to unreacted complex. Clearly, chymotrypsin modelling has disguised its inadequacies by employing substrates whose leaving groups have pK_a values below 9; partitioning toward product then occurs despite the deleterious s-cis effect and despite the absence of electrophilic assistance to the departing entity.

An additional explanation for the data in Table I (consistent with our "spatiotemporal hypothesis"[17]) must be mentioned. Assume that (a) all ester complexes have an identical HO/C=O distance and (b) the "critical distance"[17] for carbonyl addition is smaller for less reactive esters. Therefore, the HO/C=O distance within the complex can be productive for the *p*-nitrophenyl ester but not for the ethyl ester.

Correcting the above shortcomings via more advantageous positioning of the hydroxyl, in order to catalyze the hydrolysis of authentic substrates, presents a challenge that nature, but not organic chemistry, has already met.

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Supplementary Material Available: Analytical, melting point, and spectroscopic data on the new compounds in Table I (second through sixth entries) (4 pages). Ordering information is given on any current masthead page.

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The First Hydrocarbyl Trinuclear and Tetranuclear Clusters of Tungsten: $W_3O(CH_2Ph)(O\text{-}i\text{-}Pr)_9$ and $W_3O(R)_2(O\text{-}i\text{-}Pr)_8$ Where R = CH_2Ph, Ph, and $W_4(p\text{-tolyl})_2(O\text{-}i\text{-}Pr)_{10}$

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Examples of transition-metal clusters containing alkyl[1] and σ-aryl[2] ligands have been known since the early 1970's but as a class of compounds there are relatively few well-characterized members. Indeed the first structural characterization of an alkyl cluster supported by carbonyl ligands was only just reported.[3] We describe here the synthesis and characterization of the first tungsten clusters bearing hydrocarbyl ligands. These compounds are of particular interest with respect to the development of cluster chemistry supported by alkoxide ligands.[4]

Addition of *i*-PrOH (5 equiv) to hexane solutions of $W_2(p\text{-tolyl})_2(NMe_2)_4$[5] at 0 °C affords the green, tetranuclear cluster $W_4(p\text{-tolyl})_2(O\text{-}i\text{-}Pr)_{10}$ (**1**) in ca. 40% isolated crystalline yield according to eq 1.[6] The ^1H and $^{13}C\{^1H\}$ NMR data[6] for **1** are

$$W_2(p\text{-tolyl})_2(NMe_2)_4 + 5i\text{-PrOH} \rightarrow {}^1/_2W_4(p\text{-tolyl})_2(O\text{-}i\text{-}Pr)_{10} + C_6H_5Me + 4\ HNMe_2 \quad (1)$$

consistent with a static, tetranuclear cluster containing two inequivalent aryl groups and 10 inequivalent O-*i*-Pr ligands, each having diastereotopic methyl groups. The formation of $W_4(p\text{-tolyl})_2(O\text{-}i\text{-}Pr)_{10}$ in eq 1 may be understood in terms of coupling two $W_2(p\text{-tolyl})(O\text{-}i\text{-}Pr)_5(M{\equiv}M)$ compounds in a related manner to the dimerization of two $W_2(O\text{-}i\text{-}Pr)_6(M{\equiv}M)$ species which yields $W_4(O\text{-}i\text{-}Pr)_{12}$.[7] The molecular structure of **1**[8] is shown in Figure 1 and provides an unprecedented structural type for a 12-electron M_4 cluster.[9] On the basis of M–M distances, one

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