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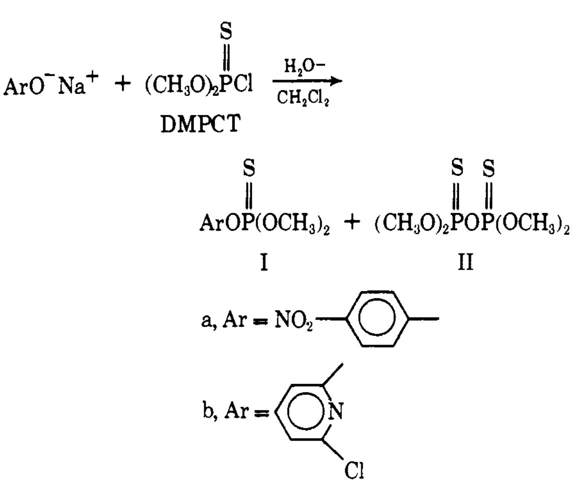
Received October 20, 1975

Cocatalysis of Phenolate Phosphorylation in Biphasic Media

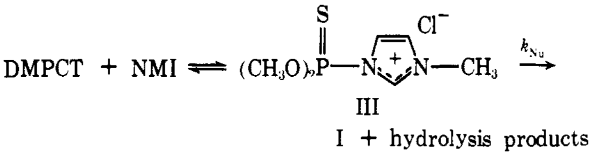
Sir:

Acyl transfer reactions between a basic, anionic nucleophile in aqueous medium and a hydrolyzable acyl compound in a nonpolar solvent are inhibited by the mutual insolubilities of the reagents as well as the sensitivity of the acyl compound to the alkaline aqueous environment. In particular, thiophosphorylation of moderately nucleophilic phenolates or pyridinates by dialkylthiophosphoryl chlorides in such a biphasic medium is a slow and inefficient process in which the major products may be those of hydrolysis rather than esterification (eq 1). We now present data on several approaches to catalysis of this process including: (1) activation of the acylating agent (nucleophilic catalysis),[1] (2) activation of the nucleophile (phase transfer catalysis)[2] (PTC), and (3) a combination of (1) and (2) in which both rates and product selectivity are enhanced by the unique interaction of intermediates generated from both reactants.


(1)

We initially investigated the formation of methyl parathion (Ia) by rapidly stirring a refluxing 0.15 M solution of dimethylphosphorochloridothionate (DMPCT) in methylene chloride with an excess of aqueous sodium *p*-nitrophenolate.[3] That this uncatalyzed reaction has negligible synthetic utility is shown by its slow rate ($t_{1/2}$ ~30 h) and final product distribution of 40% Ia and 60% of DMPCT hydrolysis products, mainly tetramethylthiopyrophosphate(II).

The addition of 1% (1.5×10^{-3} M) of the nucleophilic catalyst, N-methylimidazole (NMI), greatly increased the reaction rate ($t_{1/2}$ ~1.5 h) but considerable hydrolysis (20%) was still evident. This rate increase clearly implicates the formation of the reactive intermediate III,[4] which is partitioned between the two nucleophiles (eq 2). This reaction is very sensitive to stirring rate and, as with a similar nucleophilic catalysis reaction in a biphasic system,[5] may be largely interfacial in nature.


(2)

Catalysis can also be accomplished with organosoluble quaternary ammonium (Q^+) salts, the first example of PTC applied to phosphorylation. Addition of 1% of tetra-*n*-butylammonium bisulfate (TBAB) gives 91% of ester Ia with $t_{1/2}$ of ~4 h. Unlike the NMI catalyzed process, but as generally found for PTC reactions,[6] the rate is insensitive to stirring beyond ~100 rpm.

Combining both catalysts, 1% each of NMI and TBAB, provides a unique cocatalytic effect in which the rate enhancement of the nucleophilic catalyst and the product specificity of the phase transfer catalyst are both combined and even surpassed ($t_{1/2}$ ~ 1.2 h, % I = 95). The most plausible explanation for this previously unobserved phenomenon is that an additional mechanistic pathway has been made available; the activated electrophilic intermediate III can now react directly with the activated nucleophile, the quaternary ammonium phenate IV, as it is extracted into the organic layer (eq 3). The rate constant for such a reac-

$$\underset{(aq)}{ArO^-Na^+} + \underset{(aq)}{Q^+HSO_4^-} \rightleftharpoons \underset{\substack{(org)\\ \text{IV}}}{ArO^-Q^+} + \underset{(aq)}{NaHSO_4}$$

$$(Q^+ = n\text{-}Bu_4N^+)$$

$$\underset{(org)}{\text{III} + \text{IV}} \xrightarrow{k_{cocat}} \text{I} + \text{NMI} + Q^+Cl^- \qquad (3)$$

Table I. Pseudo-First-order Rate Constants (k_{obsd}) for Uncatalyzed, Individually Catalyzed, and Cocatalyzed Aqueous 0.8 M Sodium 2-(6-chloropyridinolate) and 0.2 M DMPCT in CH_2Cl_2 at 25° and 500 rpm.

	$k_{obsd} \times 10^4$, s^{-1} [a]						
	Catalyst[b]		Cocatalyst				
[Cat], M	TBAB	NMI	[TBAB] = [NMI]	[TBAB] (0.01 M NMI)	[TBAB] (0.02 M NMI)	[NMI] (0.01 M TBAB)	[NMI] (0.02 M TBAB)
0.000	0.046	0.046	0.046	3.0	6.3	0.6	1.0
0.002	—	—	0.7	—	—	—	—
0.005	—	—	1.8	3.3	—	2.5	—
0.010	0.6	3.0	4.5	4.5	7.8	4.5	4.8
0.020	1.0	6.3	10.1	4.8	10.1	7.8	10.1
0.030	1.2	8.7	22	6.7	—	—	—

[a] All ±10%. [b] Individual catalysts.

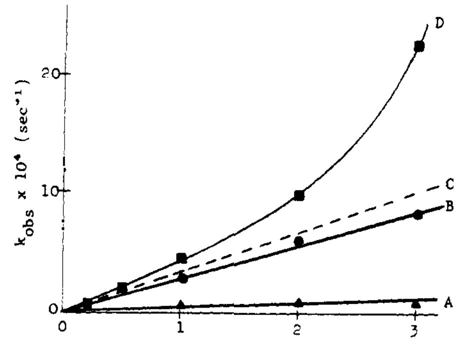


Figure 1. Effect of catalyst concentration on rate of reaction (1) using data of Table I. Catalysts are: (A) TBAB; (B) NMI; (C) TBAB + NMI, equimolar, calculated assuming additivity of A and B; (D) TBAB + NMI, equimolar, found.

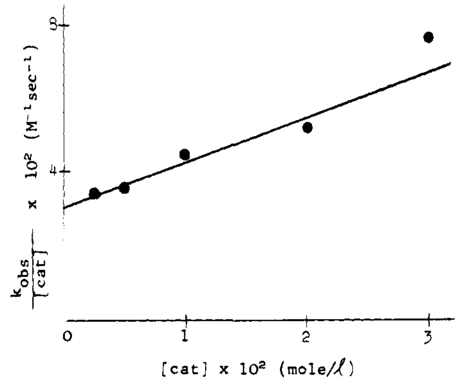


Figure 2. Plot of $k_{obsd}/[cat]$ vs. [cat] for data of curve D, Figure 1.

tion (k_{cocat}) would be predicted to be very large, but at low catalyst levels its contribution to the overall process would be severely mediated by its bimolecular nature. To obtain definitive information on the extent of this cocatalysis we undertook a kinetic study of the formation of Ib utilizing the more water soluble nucleophile, sodium 2-(6-chloropyridinolate).

The observed pseudo-first-order rate constants (k_{obsd}) are summarized in Table I for the uncatalyzed, NMI or TBAB catalyzed, and cocatalyzed reactions.[7] The dependence of k_{obsd} on catalyst concentration is shown in Figure 1. Individually, the rate constants for both the phase transfer (curve A) and amine (curve B) catalyzed reaction give the expected first-order behavior. However, k_{obsd} for the combined catalysts (curve D) fits the calculated, additive curve C only at low concentrations, the sharply upward deviation at concentrations greater than 0.01 M indicating the presence of an additional, higher order component in k_{obsd}.

The overall rate (neglecting an insignificant contribution from the uncatalyzed reaction) for the binary catalysis process may be written as shown in eq 4 and 5.

$$\frac{-d(\mathrm{DMPCT})}{dt} = k_{PTC}[\mathrm{TBAB}][\mathrm{DMPCT}] + k_{Nu}[\mathrm{NMI}][\mathrm{DMPCT}] + k_{cocat}[\mathrm{TBAB}][\mathrm{NMI}][\mathrm{DMPCT}] \quad (4)$$

and

$$k_{obsd} = k_{PTC}[\mathrm{TBAB}] + k_{Nu}[\mathrm{NMI}] + k_{cocat}[\mathrm{TBAB}][\mathrm{NMI}] \quad (5)$$

From these rate equations and the data of Table I, all the pertinent rate constants may be evaluated. For equivalent concentrations of the two catalysts the data may be plotted as in Figure 2, the slope yielding $k_{cocat} = 1.3 \pm 0.3$ l.^{2} mol^{-2} s^{-1} and the intercept = $k_{PTC} + k_{Nu} = 3 \times 10^{-2}$ l. mol^{-1} s^{-1}. Plots of [TBAB] vs. k_{obsd} for three different NMI concentrations and of [NMI] vs. k_{obsd} for differing [TBAB] give straight lines whose slopes increase with increasing [NMI] in the former and [TBAB] in the latter. This result requires that the overall catalytic effect of one catalyst is increased in proportion to the concentration of the other; i.e., *a cocatalytic effect has been demonstrated.*

From the slopes and intercepts of k_{obsd} vs. [cat] for nonequivalent catalyst concentrations, additional rate data may be obtained[8] which agree well with each other but differ somewhat from those evaluated from Figure 2. The average (±10%) values, calculated as pseudo-first-order rate constants for 1.0 M catalysts are: $k_{PTC} = 45$, $k_{Nu} = 290$, and $k_{cocat} = 8500$ s^{-1}. Using these k's we calculate that at the 0.02 M catalyst level, 33% of the total reaction proceeds via eq 3.

Finally, we can again demonstrate that the optimum features of the individual catalysts are incorporated in cocatalysis: using equivalent amounts of 0.2 M pyridinolate and DMPCT with 0.02 M catalysts the rate of the cocatalyzed process is 1.5 times that of the sum of the individually catalyzed reactions while still maintaining the PTC-catalyzed selectivity ratio of 9:1 (ester:hydrolysis) rather than the NMI-catalyzed selectivity of 1:1. The full implication of these results, particularly for bioorganic applications, remains to be explored.[9]

Acknowledgment. The authors are grateful to D. E. Golan and R. A. Dubois for experimental contributions and to Professors W. P. Jencks and C. P. Lillya for critical discussions.

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Received December 12, 1975

Electrochemical Synthesis and Structural Characterization of the Iron-Sulfur Cluster Cation[1] $[(\eta\text{-}C_5H_5)_2Fe_2(S_2)(SC_2H_5)_2]^+$

Sir:

The synthesis and structural analysis[2] of $[Cp_2Fe_2(S_2)(SC_2H_5)_2]$ (**1**) (Cp = η-C_5H_5) have expanded the growing list of crystallographically determined mole-