When the reaction was carried out in CCl_4 instead of $CDCl_3$, the yellow precipitate of $(Ph_3P)_2PdCl_2$ began to appear immediately after the reactants were mixed and reaction was complete after 30 min. In this case examination by nmr showed only the resonances for α-(pentamethylcyclopentadienyl)styrene and no high-field hydride signal. When the solvent was distilled (to remove the styrene and triphenylphosphine) $CHCl_3$ was clearly observed in the nmr spectrum.

The reaction of **6** with 2 equiv of triphenylphosphine in $CDCl_3$ under argon gave an orange yellow solution, the nmr of which (taken immediately after mixing) showed the presence of only the styrene and an acetylacetonate which was not further characterized. Yield of the styrene was quantitative.

$C_5Me_5CHPhCH_2Pd(PPh_3)Cl$ (**13**).[32] This complex could be obtained, albeit somewhat impure owing to the rapidity with which it decomposed, by reaction of triphenylphosphine (220 mg) and the complex **1** (160 mg) in 25 ml of chloroform. When the reaction was rapidly quenched by adding hexane (50 ml), it gave a yellow solid, mp 104° dec, which could not be purified owing to decomposition. *Anal.* Calcd for $C_{36}H_{38}ClPPd$: C, 67.19; H, 5.95; Cl, 5.51; P, 4.81. Found: C, 67.21; H, 5.70; Cl, 6.28; P, 5.36.

The decomposition was also evident from the nmr spectrum; however, broad peaks in the methyl region at δ 0.86, 1.76, 1.86, 1.98, 2.06, and 2.29 as well as small broad multiplets at 2.7 and 3.7, and complex resonances at 7.33 and 7.68 (phenyl) owing to **13** were observed. The spectrum at −60° showed further splitting and indicated that some exchange process was occurring.

(32) We are indebted to Dr. K. L. Kaiser for preparing and characterizing this complex.

Acknowledgment. We thank the National Research Council of Canada for supporting this work and Johnson Matthey and Mallory for the loan of palladium salts.

Anion-Catalyzed Ester Aminolyses in a Hydrocarbon Solvent

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Abstract: Tetra-*n*-hexylammonium benzoate hemihydrate (THAB) catalyzes the reaction between piperidine and *p*-nitrophenyl acetate in toluene. For example, 0.054 *M* THAB increases the rate more than 1200-fold. The acceleration arises from removal of a proton residing on the nitrogen of a tetrahedral intermediate; the intermediate can then collapse to products without first forming an N-protonated amide. In toluene, benzoate is a 10^3 better proton acceptor than piperidine (corresponding to a 10^{10} reversal in basicity relative to that in water). THAB displays an even greater catalysis in the aminolysis of *p*-nitrophenyl acetate by imidazole. Thus, the half-life of the ester in toluene at 25.0° with 0.0104 *M* imidazole and no THAB is about 25 hr. Addition of 0.059 *M* THAB decreases the half-life to 7.5 sec! A plot of k_{obsd} *vs.* [THAB] curves downward with the rate becoming independent of the [THAB] above 0.1 *M*. We conclude that THAB induces a change in rate-determining step. The behavior at high [THAB], where formation of intermediate is rate limiting, permits the first determination of the rate constant for addition of imidazole to an ester carbonyl in an aprotic solvent. This rate is 29 times *faster* than the corresponding rate in water. Therefore, the slowness of ester aminolyses in aprotic solvents can be ascribed solely to an unfavorable partitioning of a tetrahedral intermediate to products.

Enzymes might activate their ionic catalytic groups by holding them in hydrophobic portions of the active sites.[2-4] This idea has appeal because impaired ion solvation often leads to huge rate and equilibrium enhancements. Thus, the equilibrium constant for heterolysis of trityl chloride in ether increases 7×10^9-fold upon addition of 5.05 *M* $LiClO_4$.[5] Chloride ion reacts with methyl iodide 2×10^6 times faster in acetonitrile than in methanol.[6] We now report a study of the effect of carboxylate anion on ester aminolyses in toluene. The work was stimulated in particular by the observation that chymotrypsin has its Asp-102 carboxylate buried in a nonpolar region[7] where it can accept a proton from the adjacent catalytically important imidazole.[8] Only one previous publication relates directly to our model investigations. Haake and coworkers[9] reacted *p*-nitrophenyl acetate with imidazole in acetonitrile in the presence of tetramethylammonium benzoate. Benzoate causes a catalysis, although of much smaller magnitude than the ones described below. Moreover, in the present paper we interpret our results in terms of recent mechanistic thought, namely, that collapse of a tetrahedral intermediate is rate limiting with aprotic aminolyses.[10] This is not a technicality; we will show that carboxylate anion in an aprotic solvent can change the nature of the rate-determining step.

Experimental Section

Materials. Spectrograde toluene was distilled over calcium hydride through a 30-cm Vigreux column. No water could be detected by glc. Piperidine (Aldrich) was also distilled over calcium hydride and then stored under N_2. Imidazole, *p*-nitrophenyl acetate, and 2,4-dinitrophenyl acetate (all Eastman) were crystal-

(1) Recipient of a Camille and Henry Dreyfus Foundation Teacher-Scholar grant and a National Institutes of Health Career Development Award.

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(3) W. N. Lipscomb, *Chem. Soc. Rev.*, 1, 319 (1972).

(4) D. Semenow-Garwood, *J. Org. Chem.*, 37, 3797 (1972).

(5) Y. Pocker and R. F. Buchholz, *J. Amer. Chem. Soc.*, 92, 2075 (1970).

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(7) T. A. Steitz, R. Henderson, and D. M. Blow, *J. Mol. Biol.*, 46, 337 (1969).

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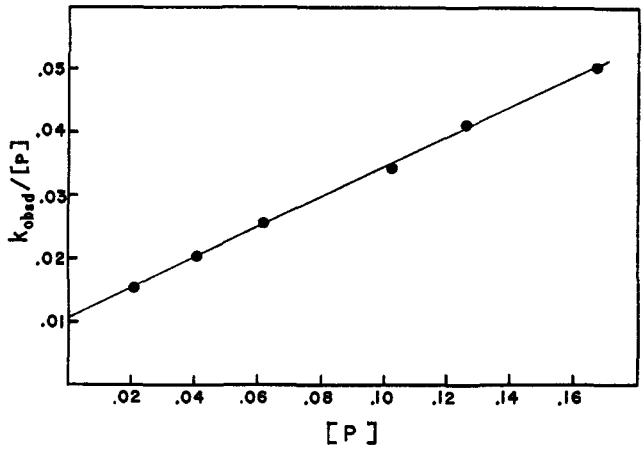


Figure 1. Plot of k_{obsd}/[piperidine] *vs.* [piperidine] for the reaction between piperidine and *p*-nitrophenyl acetate in toluene at 25.0°. The units of k_{obsd} are sec^{-1}. This plot is used to determine that $k_1 = 0.011\ M^{-1}\ sec^{-1}$ and $k_2 = 0.24\ M^{-2}\ sec^{-1}$ (see eq 2).

lized twice from benzene–hexane. Octadecylammonium benzoate was prepared according to a published method,[11] crystallized from petroleum ether, and dried under reduced pressure over calcium sulfate, mp 64.0–65.5° (lit.[11] mp 64.0–65.5°).

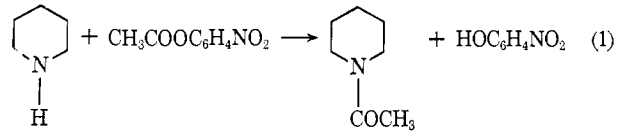
Tetra-*n*-hexylammonium benzoate hemihydrate (THAB) was prepared using the method of Swain, *et al.*[12] The starting material, Eastman tetrahexylammonium iodide, was crystallized several times from acetone–ether until it was colorless. The product, a liquid salt, was dried in a vacuum desiccator at 10^{-2} mm over P_2O_5, stored over P_2O_5, and transferred when needed in a glove bag under N_2. *Anal.* Calcd for $C_{31}H_{57}NO_2 \cdot 0.5H_2O$: C, 76.80; H, 12.06. Found: C, 76.68; H, 12.03.

Kinetics. A typical kinetic run was carried out as follows. A stoppered cuvette containing 3.00 ml of a freshly made toluene solution of piperidine (0.0112 *M*) and THAB (0.0108 *M*) was equilibrated at 25.0 ± 0.1° for 20 min within the thermostated cell compartment of a Cary 14 or Acta II spectrophotometer. A small amount (25 μl) of a toluene solution of *p*-nitrophenyl acetate was then added to the cuvette (by means of a stirring rod flattened at one end) such that the initial concentration of ester in the cuvette was 2.53×10^{-5} *M*. The increase in absorbance at 430 nm was then traced as a function of time until the reaction was over (greater than 8 half-lives). Reactions between imidazole and 2,4-dinitrophenyl acetate were monitored at 340 nm. Absorbance–time data were processed with the aid of an RCA Spectra 70 computer to secure the pseudo-first-order rate constants.

Rate constants from systems without THAB were reproducible to ±3%. On the other hand, repeat runs involving THAB gave observed rate constants which varied by as much as twofold depending on the particular batch of THAB. Undoubtedly, this was caused by small variations in the water content of the liquid salt. Two points must be made with regard to this complication. First, all rate constants reported in this paper involve a *single* batch of THAB used within 2 weeks of preparation; reproducibility under these circumstances was good. Second, a batch-to-batch variation of twofold is trivial compared to the large rate accelerations caused by the THAB. No mechanistic conclusion of ours is based on small rate changes.

Results and Discussion

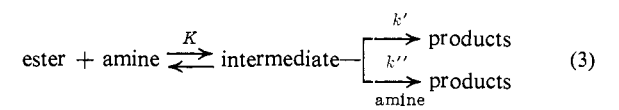
We determined the kinetics governing the aminolysis of *p*-nitrophenyl acetate by piperidine in toluene (eq 1). The reaction obeys a two-term rate law



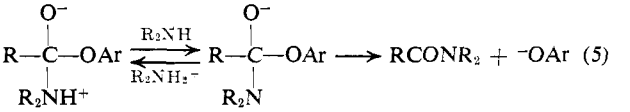
(eq 2) when carried out under pseudo-first-order conditions. By plotting k_{obsd}/[amine] *vs.* [amine] and measuring the intercept and slope of the straight line (Figure 1), we evaluated the parameters k_1 and k_2: $k_1 = 0.011\ M^{-1}\ sec^{-1}$ and $k_2 = 0.24\ M^{-2}\ sec^{-1}$ at 25.0.

$$k_{obsd} = k_1[\text{amine}] + k_2[\text{amine}]^2 \qquad (2)$$

There exists strong evidence that eq 2 is best explained by a reversible formation of a tetrahedral addition intermediate followed by rate-determining collapse of the intermediate (eq 3).[10,13] The intermediate in eq 3 forms products with and without the aid of a second amine molecule, leading to a rate expression (eq 4) which is kinetically equivalent to eq 2. We surmise that the second amine molecule in the k_2 step functions by removing a proton from the tetrahedral intermediate, thereby avoiding formation of a high-energy N-protonated amide when the intermediate collapses (eq 5).



$$k_{obsd} = k'K[\text{amine}] + k''K[\text{amine}]^2 \qquad (4)$$



Addition of small quantities of tetra-*n*-hexylammonium benzoate (THAB) to the aminolysis mixtures leads to large rate enhancements (Table I). For example, 0.054 *M* THAB increases the rate by more than three orders of magnitude. One reason for the increase, albeit a minor reason, stems from the fact that THAB itself reacts with *p*-nitrophenyl acetate in toluene (Table II). Either the ester acylates the benzoate moiety to form a mixed anhydride, or else the ester is attacked by a water molecule bound to the benzoate (with the benzoate acting as a general base). We did not investigate the details of this THAB reaction be-

Table I. Observed Rate Constants for the Reaction of Piperidine with *p*-Nitrophenyl Acetate in Toluene at 25.0° in the Presence of Tetra-*n*-hexylammonium Benzoate (THAB)

[Piperidine], *M*	[THAB], *M*	k_{obsd}, sec^{-1}
5.60×10^{-3}	0.000	6.90×10^{-5} [a]
5.60×10^{-3}	0.0108	1.94×10^{-2}
5.60×10^{-3}	0.0216	3.92×10^{-2}
5.60×10^{-3}	0.0216	3.79×10^{-2}
5.60×10^{-3}	0.0324	4.41×10^{-2}
5.60×10^{-3}	0.0324	4.35×10^{-2}
5.60×10^{-3}	0.0540	8.77×10^{-2}
5.60×10^{-3}	0.108	1.41×10^{-1}
1.12×10^{-2}	0.000	1.50×10^{-4} [a]
1.12×10^{-2}	0.0108	4.47×10^{-2}
1.12×10^{-2}	0.0216	7.85×10^{-2}
1.12×10^{-2}	0.0324	1.17×10^{-1}
1.12×10^{-2}	0.0540	1.84×10^{-1}

[a] Calculated from eq 2.

(11) A. Kitahara, *Bull. Chem. Soc. Jap.*, **30**, 586 (1957).

(12) C. G. Swain, A. Ohno, D. K. Roe, R. Brown, and T. Maugh, *J. Amer. Chem. Soc.*, **89**, 2648 (1967).

(13) The validity of eq 3 is supported by the observation that aminolyses of aryl benzoates in aprotic solvents are much more sensitive to substituents on the leaving group of the esters (ρ = 4–6) than to the substituents on the acyl portion of the esters (ρ = 1–2).[10]

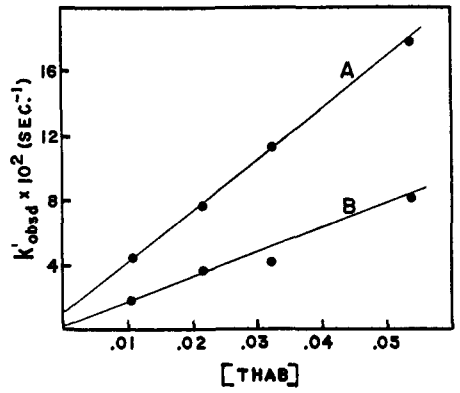


Figure 2. Plot of corrected observed rate constants *vs.* [THAB] for the THAB-catalyzed aminolysis of *p*-nitrophenyl acetate by piperidine in toluene at 25.0°. Piperidine concentration is 1.12×10^{-2} *M* (line A) and 5.60×10^{-3} *M* (line B). Data are taken from Table I.

Table II. Observed Rate Constants for the Reaction of Tetra-*n*-hexylammonium Benzoate (THAB) with *p*-Nitrophenyl Acetate in Toluene at 25.0°

[THAB], *M*	$k_{obsd} \times 10^3$, sec^{-1}
0.0216	1.45
0.0432	4.07
0.0845	8.63
0.118	12.4
0.169	19.6

cause we were primarily interested in the properties of THAB as a catalyst. Moreover, we found that the reaction was particularly sensitive to protic impurities. In the following analysis of the effect of THAB on ester aminolyses, the rate of the "THAB plus ester" reaction is always subtracted from the observed rate constants to give corrected parameters symbolized by k'_{obsd}. The corrections necessitated by the side reaction are small. Thus, the third entry in Table I had to be reduced by only 4.7%.

The accelerative effect of THAB on the aminolyses, apparent in Table I, is derived mainly from the appearance of a third term in the overall rate expression (compare eq 2 and 6). Plots of k'_{obsd} *vs.* [THAB] at

$$k'_{obsd} = k_1[\text{amine}] + k_2[\text{amine}]^2 + k_3[\text{amine}][\text{THAB}] \quad (6)$$

constant [amine] are linear (Figure 2), as demanded by eq 6. The intercepts of the plots are small, indicating that the k_1 and k_2 terms of eq 6 are negligible relative to the THAB-catalyzed process. We calculate from the slopes of Figure 2 that $k_3 = 280\ M^{-2}\ sec^{-1}$ which is more than 10^3 times larger than the $k_2 = 0.24\ M^{-2}\ sec^{-1}$ secured from Figure 1. Stated in another way, benzoate accepts a proton from the tetrahedral intermediate (eq 5) three orders of magnitude more effectively than does piperidine. Since in aqueous solutions piperidine is 10^7 more basic than benzoate, our results correspond to a 10^{10} reversal in basicity from water to toluene. The magnitude of this value seems all the more imposing when it is considered that we are dealing with a hemihydrate of THAB. A "bare" carboxylate in toluene would, no doubt, have manifested an even greater reactivity.

Is catalysis by THAB perhaps a nonspecific ion solvation effect? The following experiment answers this question. Addition of 0.100 *M* octadecylammonium benzoate to a toluene solution of 0.0500 *M* piperidine increases the aminolysis rate only 2.4 times. Therefore, presence of ions in the hydrocarbon solvent is in itself not sufficient to promote the aminolysis significantly.

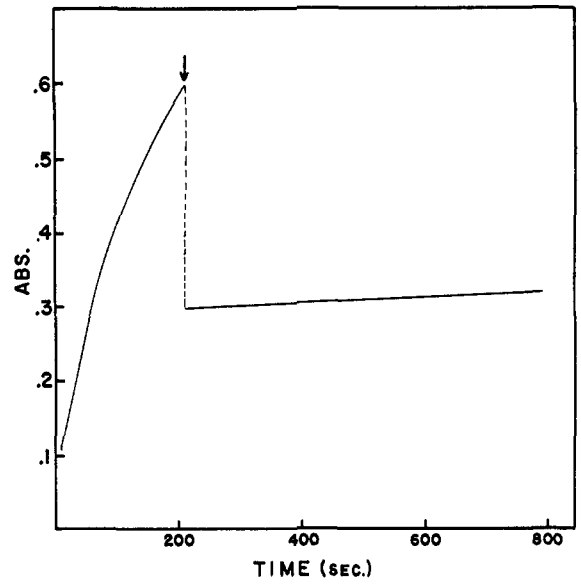


Figure 3. Absorbance *vs.* time tracing at 430 nm for a reaction between piperidine (1.13×10^{-3} *M*), *p*-nitrophenyl acetate (2.53×10^{-5} *M*), and THAB (4.55×10^{-2} *M*) in 3.00 ml of toluene at 25.0°. The arrow indicates the point at which 25 μl of methanol was added to the solution.

Hydroxylic additives can effectively quench THAB catalysis. Figure 3 shows an absorbance *vs.* time tracing of a reaction between 1.13×10^{-3} *M* piperidine, 2.53×10^{-5} *M p*-nitrophenyl acetate, and 4.55×10^{-2} *M* THAB in toluene. The arrow in Figure 3 indicates the point at which we added 25 μl of methanol to the cuvette, giving a 0.20 *M* methanol solution. The methanol causes an immediate twofold drop in absorbance as well as a 16-fold decrease in reaction rate. Solvation of *p*-nitrophenolate diminishes the absorbance,[14] whereas hydrogen bonding of methanol to the benzoate impairs the catalysis. An 11-fold molar excess of methanol over THAB was found to terminate the catalysis altogether.

The importance of histidine to enzyme action led us to wonder how THAB would perturb the reaction between imidazole and *p*-nitrophenyl acetate in toluene. In the absence of THAB, imidazole and the ester react extremely slowly even when the imidazole concentration nears its solubility limits in toluene (0.02 *M*). More specifically, the half-life with 0.0104 *M* imidazole (and no THAB) is about 25 hr (Table III). On the other hand, in the presence of 0.059 *M* THAB, the half-life decreases to 7.5 sec. Since direct reaction between THAB and ester can account for only 6% of the latter rate, we must be observing a remarkably effective THAB catalysis. A plot of k'_{obsd} *vs.* [THAB] at constant [imidazole] displays convex curvature (Figure 4) with k'_{obsd} becoming *independent* of the [THAB] above 0.1 *M*. Such a change in behavior, from a strong dependence at low catalyst concentrations

(14) H. Baba, A. Matsuyama, and H. Kokubun, *Spectrochim. Acta, Part A*, **25**, 1709 (1969).

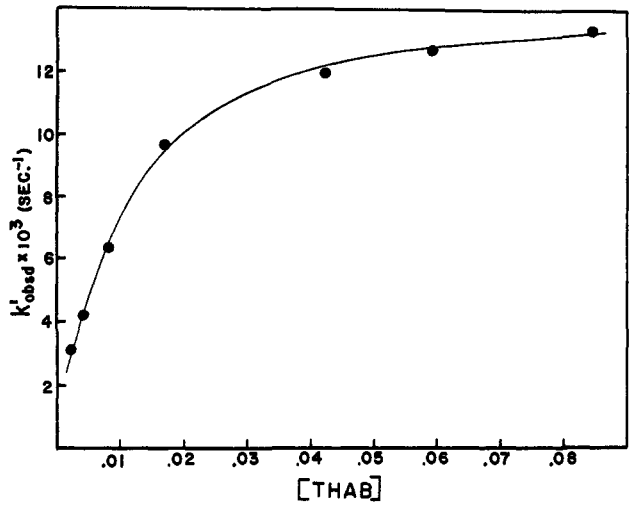


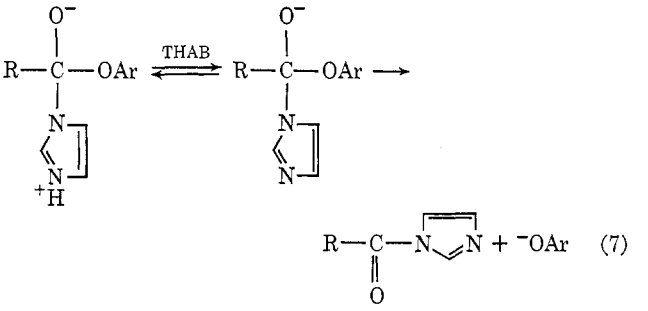
Figure 4. Plot of corrected observed rate constants *vs.* [THAB] for the THAB-catalyzed aminolysis of *p*-nitrophenyl acetate by imidazole in toluene at 25.0°. Imidazole concentration is 1.01×10^{-3} *M*. Data are taken from Table III.

Table III. Observed Rate Constants for the Reaction of Imidazole with *p*-Nitrophenyl Acetate in Toluene at 25.0° in the Presence of Tetra-*n*-hexylammonium Benzoate (THAB)

[Imidazole], *M*	[THAB], *M*	k_{obsd}, sec^{-1}
1.04×10^{-2}	0.00	7.80×10^{-6}
1.01×10^{-3}	2.12×10^{-3}	3.20×10^{-3}
1.01×10^{-3}	4.23×10^{-3}	4.22×10^{-3}
1.01×10^{-3}	8.45×10^{-3}	6.31×10^{-3}
1.01×10^{-3}	1.69×10^{-2}	9.83×10^{-3}
1.01×10^{-3}	4.23×10^{-2}	1.50×10^{-2}
1.01×10^{-3}	5.90×10^{-2}	1.79×10^{-2}
1.01×10^{-3}	8.45×10^{-2}	2.19×10^{-2}
1.04×10^{-2}	2.12×10^{-3}	4.52×10^{-3}
1.04×10^{-2}	4.23×10^{-3}	9.56×10^{-3}
1.04×10^{-2}	8.45×10^{-3}	2.33×10^{-2}
1.04×10^{-2}	1.69×10^{-2}	4.75×10^{-2}
1.04×10^{-2}	4.23×10^{-2}	8.11×10^{-2}
1.04×10^{-2}	5.90×10^{-2}	9.22×10^{-2}
1.04×10^{-2}	8.45×10^{-2}	1.09×10^{-1}

to no dependence at high concentrations, constitutes evidence for (1) catalysis in the decomposition of a tetrahedral intermediate and (2) a change in rate-determining step.[15,16] Thus, the following mechanistic picture emerges. In the absence of THAB, product formation from a tetrahedral intermediate is rate limiting (just as it is with aliphatic aminolyses in aprotic solvents[10]). THAB effects catalysis by removing a proton from the cationic imidazole component of the intermediate (eq 7), permitting collapse to an unprotonated acylimidazole product. Ultimately, decomposition to product becomes so fast that it no longer limits the rate.

Since THAB undoubtedly aggregates in toluene,[17,18] the curvature in Figure 4 could conceivably be related to ion association. Although we cannot exclude this possibility, one should bear in mind that curvature was *not* found in the THAB-catalyzed aminolysis by piperidine (Figure 2). Moreover, the rate of reaction between THAB and *p*-nitrophenyl acetate is *linearly* related to the THAB concentration (Table II). These observations suggest that neither the basicity nor the nucleophilicity of the benzoate anion is greatly affected by the aggregation state of THAB. By virtue of comparison, therefore, the marked curvature in Figure 4 seems mechanistically significant.



We have collected independent evidence that product formation in the uncatalyzed imidazole aminolysis is rate limiting. Imidazole (0.0104 *M* in toluene) was found to react 980 times faster with 2,4-dinitrophenyl acetate than with *p*-nitrophenyl acetate. If formation of an addition intermediate were rate limiting, aminolysis by imidazole would not be so sensitive to a second nitro substituent on the leaving group of the ester.[10]

The details of tetrahedral intermediate formation are not yet clear because imidazole forms linear complexes in aprotic solvents.[19] The nucleophilic agent could be monomeric imidazole, associated imidazole, or both.[20] This uncertainty does not affect the above analysis.

Reaction between imidazole and an ester in toluene may be described more mathematically by means of eq 8. The mechanism leads to the steady state rate

$$\text{imidazole} + \text{ester} \underset{k_b}{\overset{k_a}{\rightleftharpoons}} \text{intermediate} \xrightarrow[k_c]{\text{THAB}} \text{products} \qquad (8)$$

expression given in eq 9. When the [THAB] is small,

$$k'_{obsd} = \frac{k_a k_c[\text{Im}][\text{THAB}]}{k_b + k_c[\text{THAB}]} \qquad (9)$$

collapse of the intermediate is rate limiting ($k_b \gg k_c$[THAB]), and $k'_{obsd} = (k_a k_c/k_b)$[Im][THAB]. At high [THAB], formation of the tetrahedral intermediate becomes rate determining (k_c[THAB] $\gg k_b$), and $k'_{obsd} = k_a$[Im]. From Figure 4 we see that at [Im] $= 1.01 \times 10^{-3}$ *M* the limiting value of k'_{obsd} is 14×10^{-3} sec^{-1}. Hence $k_a = 14$ *M*$^{-1}$ sec^{-1}, a large number considering that the value for the identical reaction in water is only 0.48 *M*$^{-1}$ sec^{-1}.[21] Two important conclusions arise from this comparison. (1) The slowness of ester aminolyses in aprotic solvents can be ascribed solely to an unfavorable partitioning of an intermediate to products. (2) Charge creation in toluene during the k_a step must be more than compensated by a diminished need to desolvate the reactants prior to bonding.

Acknowledgment. This work was supported in part by the National Science Foundation.

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(19) D. M. W. Anderson, J. L. Duncan, and F. J. C. Rossotti, *J. Chem. Soc.*, 2165 (1961).
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(21) M. L. Bender, *Chem. Rev.*, **60**, 53 (1960).