Nucleophilic Reactivities Toward Substituted Aryl Trimethylacetates: Conflicting Steric Effects of Ground-State Activation and Transition-State Crowding

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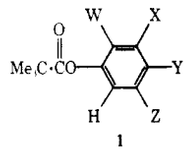
The hydroxide ion and imidazole catalyzed hydrolyses of a series of leaving-group-substitued aryl trimethylacetates have been studied at 25 °C in 10% (v/v) acetonitrile–water. The ρ value for hydroxide ion catalysis (*vs.* σ) is 0.99, with a low correlation coefficient (r = 0.962). The Brønsted plot for dependence of log k_{HO^-} on the pK_a of the conjugate acid (slope, β_{LG}) indicates that 2,3-dimethylphenyl trimethylacetate is some 25-fold less reactive than predicted; 2-chloro-4-nitro- and 2,4-dinitrophenyl esters are 3.5- and 5-fold inhibited, respectively. These deviations are ascribed to steric hindrance. Imidazole catalysis is nucleophilic even for esters with ortho substituents and the β_{LG} value was −1.16, indicating a high dependence on leaving group pK_a. The transition state for imidazole catalysis is suggested to incorporate some degree of bond cleavage between the acyl and leaving groups. The unusually high reactivity of trimethylacetylimidazole toward imidazole is suggested to be caused by steric destruction of resonance in the ground state.

Yeast carboxypeptidase Y, a protease which sequentially cleaves amino acid residues from the C terminus of proteins and peptides, has recently been shown to possess esterase activity toward aryl trimethylacetates.[1b-3] During a study of this reactivity, it became essential to obtain rate data for attack on these esters by nucleophilic species to serve as standards of reference for the enzymatic reactions. To this end, we have prepared a series of aryl-substituted trimethylacetates covering a wide range of reactivity, **1a–i** in Table I, and have studied their hydrolyses catalyzed by hydroxide ion, imidazole, and some other species. The results have led to a dissection of the steric effects which the bulky trimethylacetyl



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group can exert in the reactions of the title esters. A recent communication[4] has appeared discussing the effect of substituent variation in bridged and non-bridged trialkyl acetate 4-nitrophenyl esters.

Results

Solvolysis Catalyzed By Hydroxide Ion. Reactions of all esters studied were first order in hydroxide ion concentration so that slopes of k_{obsd} (the observed pseudo-first-order rate constant when [HO⁻] ≫ [ester]) vs. stoichiometric hydroxide ion concentration yielded values of the second-order rate constant k_{HO^-} (recorded in Table II). Values of ifk_{HO^-} for monosubstituted meta and para derivatives obeyed a Hammett relationship with Hammett σ values (eq 1, Figure 1). The relatively low correlation coefficient for this equation is characteristic of such reactions (cf. phenyl acetates,[5] phenyl benzoates[6,16]).

$$\log k_{HO^-} = 0.99\ (\pm 0.10)\ \sigma - 0.92\ (\pm 0.05) \qquad (r = 0.962) \qquad (1)$$

When k_{HO^-} values were analyzed in terms of a Brønsted-type relationship for leaving-group dependence (by plotting log k_{HO^-} vs. the pK_a of the conjugate acid of the leaving group), esters with ortho substituents were found to be considerably less reactive than meta and para derivatives (see eq 2). 2,3-Dimethylphenyl trimethylacetate is some 25-fold less reactive than the Brønsted plot (Figure 2) predicts, while the (2-chloro, 4-nitro) and 2,4-dinitro esters are 3.5- and 5-fold less labile. The slope of the Brønsted (leaving group) plot for meta and para derivatives is −0.36.

$$\log k_{HO^-} = 2.64 - 0.36\ pK_{LG} \qquad (r = 0.969) \qquad (2)$$

Solvolysis in Imidazole Buffers. Repetitive scanning of the reaction during imidazole-catalyzed solvolysis of 4-nitrophenyl trimethylacetate [imidazole buffer containing 90% free base (0.0763 M) and 10% (v/v) acetonitrile at an ionic strength of 0.1] provided evidence of a two-stage reaction course, as the isosbestic point for the initial part of reaction was 249 nm, but was 241 nm by the end of the reaction. For the 4-nitrophenyl esters, the variation of k_{obsd} with $[Im]_{tot}$ for a series of buffer ratios at constant ionic strength indicates (Figure 3) that the free base form of imidazole is catalytically active and that the reaction is first order in imidazole. Plotting these data as $(k_{obsd} - k_{intercept})/[Im]_{tot}$ vs. the mole fraction of buffer present as free base (Figure 4) indicates that there is no contribution to the observed rate from terms in $[ImH^+]$ or the kinetic equivalent because at 25 °C and ionic strength 1.0 and in the presence of 10% acetonitrile $k_{Im} = 2.68 \pm 0.49 \times 10^{-3}\ M^{-1}\ s^{-1}$ and k_{ImH^+} is calculated to be zero within experimental error.

The value of the intercept on the k_{obsd} axis for 4-nitrophenyl trimethylacetate in 90% free base imidazole buffer [10% (v/v) acetonitrile, ionic strength 0.1] when k_{obsd} is plotted vs. $[Im]_{free}$ is $6.43 \pm 1.32 \times 10^{-4}\ s^{-1}$. At this pH (8.00) and under these conditions, this intercept must describe the spontaneous, water-catalyzed rate, as k_{HO^-} is only 0.92 $M^{-1}\ s^{-1}$ for this ester.

Values of k_{Im} were determined for the series of aryl trimethylacetates from the slopes of plots of k_{obsd} vs. $[Im_{free}]$ at 90% base, ionic strength 0.1 (with NaCl as supporting electrolyte) in the presence of 10% (v/v) acetonitrile at 25 °C. Results are collected in Table II and plotted as a Brønsted leaving-group plot in Figure 5. If all the points are fitted to a Brønsted relationship, eq 3 is obtained.

The order of magnitude difference in the value of k_{Im} for 2,5-dinitro and (2-chloro, 4-nitro) esters probably indicates that strong steric factors dominate these imidazole-catalyzed reactions. The kinetic solvent deuterium isotope effects for the imidazole reactions of these latter esters are $(k_{Im})^{H_2O}/(k_{Im})^{D_2O} = 1.17$ and 0.93, respectively.

$$\log k_{Im} = 9.95 - 1.16\ pK_{LG} \qquad (r = 0.982) \qquad (3)$$

The second-order rate constant for the attack of 2,4,6-trimethylpyridine on 2,5-dinitrophenyl trimethylacetate at 25 °C [μ = 0.4, 10% (v/v) acetonitrile] is $3.38 \times 10^{-4}\ M^{-1}\ s^{-1}$.

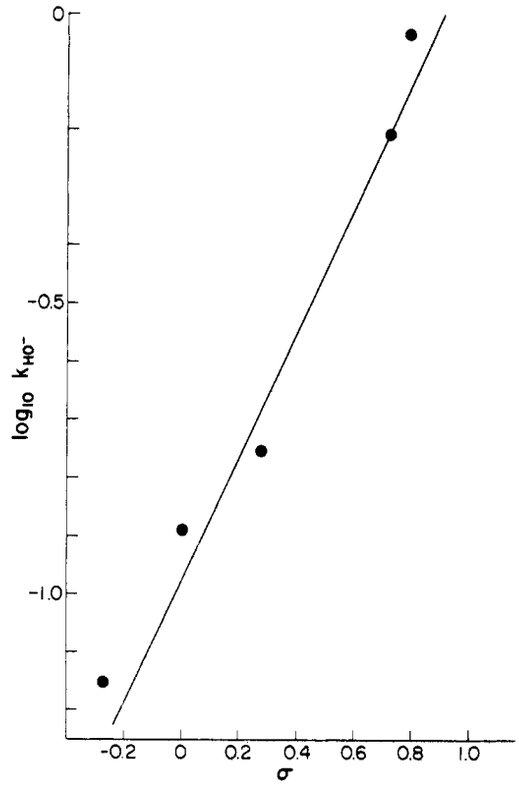


Figure 1. Dependence on σ of the rate constants for the alkaline hydrolysis or aryl-substituted trimethylacetates: values are from G. B. Barlin and D. D. Perrin, *Q. Rev., Chem. Soc.*, **20**, 75 (1966), and rate data are from Table II; line is theoretical (eq 1).

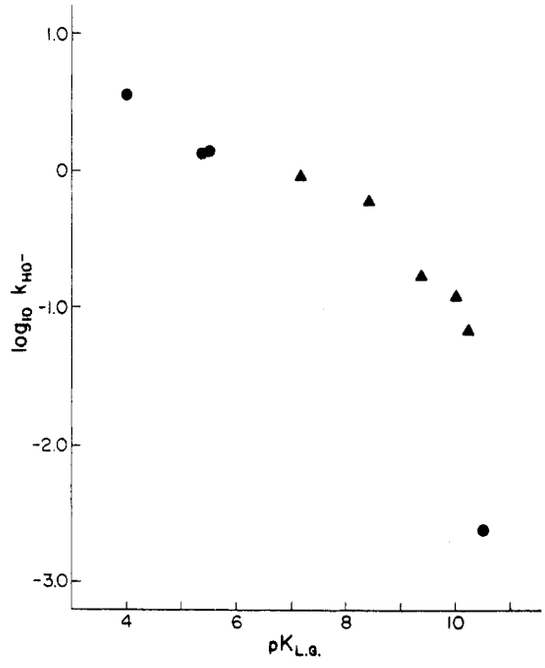


Figure 2. Dependence on the pK_a of the conjugate acid of the leaving group (pK_{LG}) of the rate constants for alkaline hydrolysis of aryl-substituted trimethylacetates: (●) esters with ortho substituents in the leaving group, (▲) esters with only meta or para substitution.

Discussion

Fife[7] has suggested on the basis of a near-unity kinetic solvent isotope effect $(k_{Im})^{H_2O} = 1.15\ (k_{Im})^{D_2O}$ that the imidazole-catalyzed hydrolysis of 4-nitrophenyl trimethylacetate is nucleophilic by analogy with the well-known nucleophilic catalysis observed for 4-nitrophenyl acetate $(k_{Im})^{H_2O} = (k_{Im})^{D_2O}$.[8] However, the best evidence for nucleophilic as opposed to general-base catalysis undoubtedly involves direct detection of the acylimidazole. Thus, the present study in which an intermediate, most likely trimethylacetylimidazole,[9] has been detected by a shift in the apparent isosbestic point during the course of reaction, along with the previous data of Fife,[7] argues strongly for nucleophilic catalysis by imidazole of 4-nitrophenyl trimethylacetate hydrolysis. Indeed, the near-unity kinetic solvent isotope effects observed in imidazole buffers for the ortho-substituted esters 2-chloro-4-nitrophenyl and 2,5-dinitrophenyl trimethylacetates (Table II) imply nucleophilic catalysis even for these "crowded" derivatives. The 1000-fold greater nucleophilic reactivity of imidazole than 2,4,6-trimethylpyridine toward the last-named ester further supports this view.[10] At this point a sharp contrast may be drawn between the steric control of mechanism rife in phosphorus(V) chemistry and the relative insensitivity of mechanistic route to steric influences shown by carboxyl substrates. Diphenyl phosphinates are subject to general base (imidazole) catalyzed attack of water. Steric hindrance by bulky groups in the substrate of direct nucleophilic attack by imidazole, offered as an explanation,[5] seems likely, as imidazole catalyzes the cleavage of the less-hindered aryl dimethylphosphinate analogues by a nucleophilic pathway.[11]

Table I

	W	X	Y	Z
a	NO_2	H	NO_2	H
b	NO_2	H	H	NO_2
c	Cl	H	NO_2	H
d	H	H	NO_2	H
e	H	NO_2	H	H
f	H	H	Br	H
g	H	H	H	H
h	H	H	MeO	H
i	CH_3	CH_3	H	H

Table II. Kinetic Parameters for Hydroxide Ion and Imidazole Catalyzed Hydrolyses of Aryl-Substituted Trimethylacetates[a]

Ester 1	Registry no.	pK_{phenol}	$10^2\ k_{HO^-}$ ($M^{-1}\ s^{-1}$)	$10^5\ k_{Im}$[b] ($M^{-1}\ s^{-1}$)
a	57025-45-3	3.96[f]	359.6 ± 6.0[c]	70 005 ± 389
b	63549-53-1	5.32	133.9 ± 7.5[c]	27 330 ± 510[d]
c	57025-46-4	5.45[g]	137.2 ± 2.0	2820 ± 49.9
d	4195-17-9	7.15	92.3 ± 1.6[e]	304.3 ± 17.9
e	63549-54-2	8.38	62.1 ± 5.3	38.8 ± 0.49
f	63549-55-3	9.34	17.7 ± 0.4	2.45 ± 0.08
g	4920-92-7	9.94	13.0 ± 1.6	
h	19820-47-4	10.20	7.8 ± 0.24	
i	63588-60-3	10.50	0.250 ± 0.012	

[a] Ionic strength 0.1 (NaCl support electrolyte), 10% acetonitrile (v/v) at 25.0 °C. Except where noted, pK values are taken from "Dissociation of Organic Acids", by G. Kortum, W. Vogel, and K. Andrussow, Butterworth, London, 1961. [b] In 90% free-base form imidazole buffer. [c] Checks on the stopped-flow results over periods of several weeks showed reproducibility of 6% or better for **1a** and **1b**. [d] In imidazole–D_2O buffer, k_{Im} was 0.2335 ± 0.00272 $M^{-1}\ s^{-1}$ and $k_{collidine}$ was 3.375 ± 0.485 × 10^{-4} $M^{-1}\ s^{-1}$ at 25 °C, ionic strength 0.4 in 60% free-base collidine buffer (10% (v/v) acetonitrile). [e] The value quoted in the table was measured by conventional spectrophotometry, the value from stopped-flow measurements was 1.20 ± 0.02 $M^{-1}\ s^{-1}$. [f] The pK value for 2,4-dinitrophenol was taken from: "Handbook of Chemistry and Physics", 51st ed, Chemical Rubber Co., Cleveland, Ohio, 1970. [g] The pK value for 2-chloro-4-nitrophenol was taken from: V. E. Bower and R. A. Robinson, *J. Phys. Chem.*, **64**, 1078 (1960).

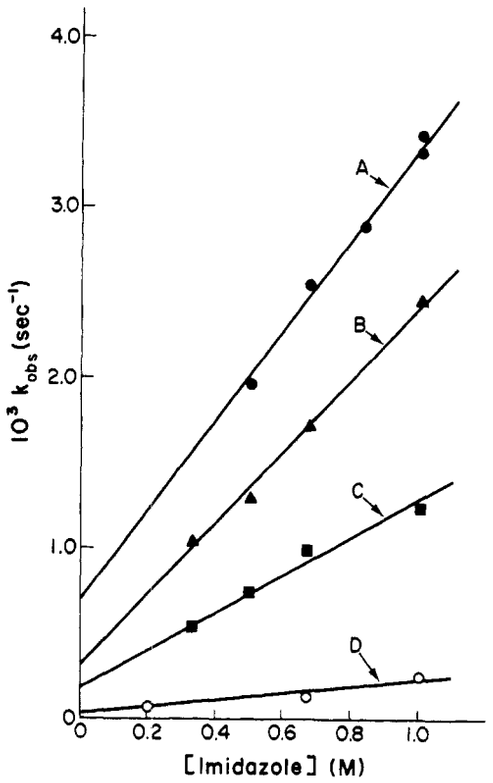


Figure 3. Dependence on imidazole concentration of observed rate constants (k_{obsd}) for imidazole-catalyzed hydrolysis of 4-nitrophenyl trimethylacetates at 25 °C in the presence of 10% (v/v) acetonitrile. Curve A (●) refers to an imidazole buffer series containing 90% free base, pH_{app} 8.06, *with an ionic strength of 0.1*. Curves B (▲), C (■), and D (○) refer to imidazole buffer series containing 80, 50, and 10% of free base, with pH_{app} values of 7.40, 7.30, and 6.21, respectively. For B, C, and D the ionic strength was 1.0.

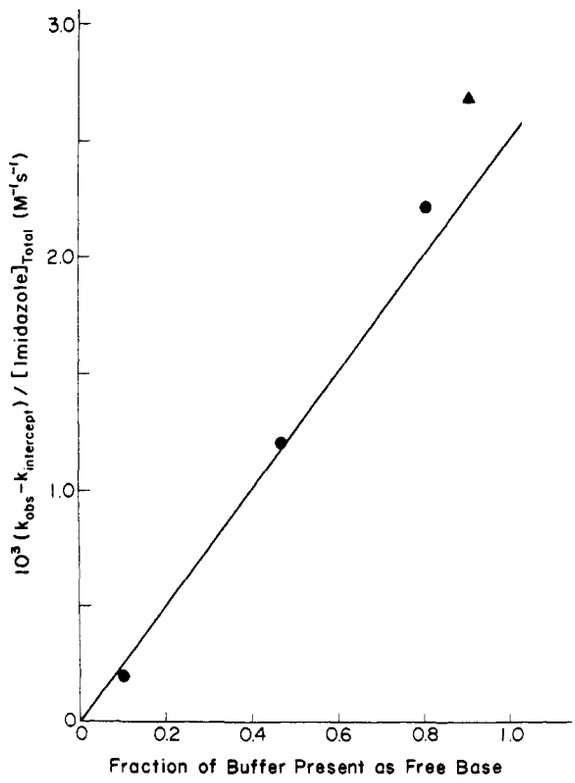
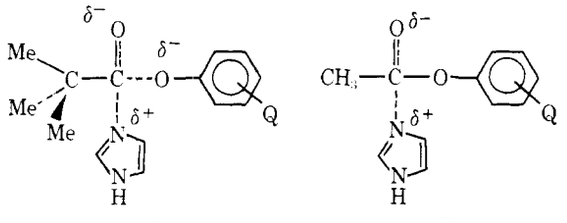


Figure 4. Separation of contributions to imidazole catalysis of 4-nitrophenyl trimethylacetate (25 °C, 10% acetonitrile, v/v) by acidic (imidazolium) and basic (imidazole) forms of the buffer. The values used on the ordinate are the slopes of plots, at a given buffer ratio, of k_{obsd} vs. $[Imidazole]_{total}$. Except for the point (▲) at 0.90 fractional free base, for which the ionic strength was 0.1, the data were obtained at an ionic strength of 1.0.

Further indication of a mechanistic shift from a nucleophilic to a general-base pathway because of steric effects comes from work on the sterically crowded bis(*p*-nitrophenyl) methylphosphonate.[12] The role of steric effects in the nucleophile is well documented for P(V) chemistry.[11-13] However, at the carboxyl level, even the highly hindered trimethylacetic esters with *o*-nitro- or *o*-chloro-substituted leaving groups react by a nucleophilic mechanism. Presumably the difference lies in the lower coordination number of trigonal carbon compared to tetrahedral phosphorus(V).

The ρ value for hydroxide ion catalysis for trimethylacetates (1.08) is comparable with that for phenyl acetates (0.8)[5,14] and substituted aryl benzoates (1.28).[6,15] However, if we calculate an apparent ρ value for imidazole catalysis of aryl trimethylacetate decomposition from the β_{LG} value of −1.04 using only data for monosubstituted esters (or −1.16 using all data), we obtain a value of $\rho_{Im} \simeq 2.4$ for leaving-group change, a very high value compared to that for imidazole-catalyzed hydrolysis of phenyl acetates (ρ_{Im} = 0.8)[5] or aryl-substituted benzoates (ρ_{Im} = 0.7),[15] presumably indicating some degree of bond cleavage in the transition state in order to relieve the considerable steric demands of such a nucleophilic transition state **2** (cf. **3**).



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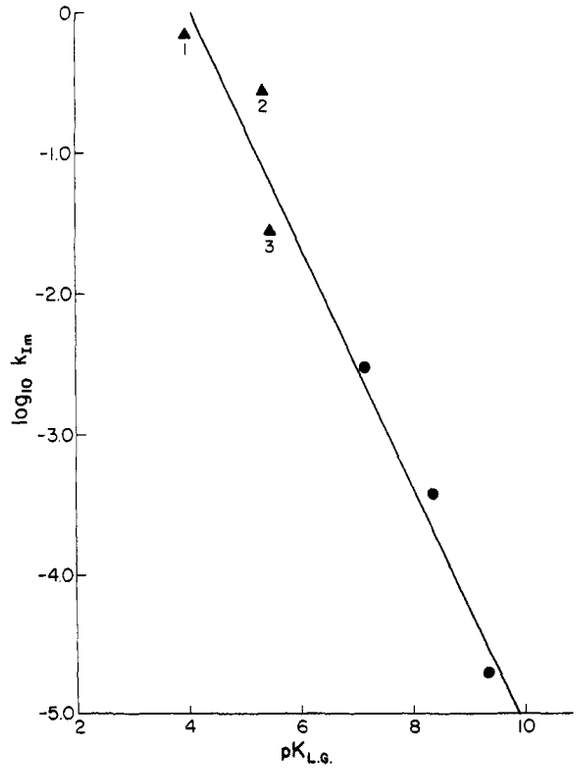


Figure 5. Dependence on the pK_a of the conjugate acid of the leaving group (pK_{LG}) of the rate constants for imidazole catalysis of the hydrolysis of substituted aryl trimethylacetates. Line is theoretical (log k_{Im} = 9.95 − 1.16 pK_{LG}; r = 0.982) for esters with meta or para substitution (●); esters with ortho substituents (▲) are designated as follows: (1) 2,4-dinitro; (2) 2,5-dinitro; and (3) 2-chloro-4-nitro.

Table III. Steric Effects on Hydroxide and Imidazole Catalyzed Hydrolyses of Some Acyl Derivatives

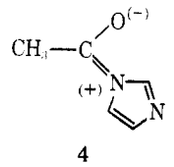
Compound	k_{HO^-} (M^{-1} s^{-1})	10^3 k_{Im} (M^{-1} s^{-1})	Reference
$CH_3CO{\cdot}OC_6H_4$-pNO_2[a]	53.7[a]	590	17
$(CH_3)_3C{\cdot}CO{\cdot}OC_6H_4$-$pNO_2$[b]	0.92	3.04	This work
$CH_3CO{\cdot}Im$[c]	317	2.33	18 (HO^-), 7 (Im)
$(CH_3)_3C{\cdot}COIm$[d]	534	6.50	18 (HO^-), 7 (Im)

[a] At 25 °C, ionic strength 1.0. [b] At 25 °C, ionic strength 0.1. [c] At 25 °C, ionic strength 0.2. [d] At 30 °C, ionic strength 1.0.

Further support for this conclusion lies in the considerably greater rate constant for the imidazole catalysis of 4-nitrophenyl trimethylacetate decomposition than for that of the 3-nitro ester (~80-fold difference), probably implying a correlation with Hammett σ^- rather than σ values[16] ($\Delta\sigma^- = 0.56$, $\Delta\sigma = 0.07$). Such a rate difference indicates extra stabilization of the leaving group, presumably mesomeric, in a phenolate-ion-resembling transition state.

Some values of k_{HO^-} and k_{Im} for esters and acyl imidazoles are collected in Table III. By comparing rate constants in this table it is obvious that for RCOIm, substitution of R = CH_3– by R = $(CH_3)_3C$– causes slight increases in both k_{HO^-} and k_{Im}. The pK_a values for 4-nitrophenol and imidazole are comparable and, other things being equal, one would expect similar rates of hydroxide catalysis for acylimidazoles and the corresponding 4-nitrophenyl esters. This is indeed so for 4-nitrophenyl acetate and acetylimidazole, the difference being only some sixfold. However, trimethylacetylimidazole hydrolyzes 580 times as fast in base as 4-nitrophenyl trimethylacetate. The most likely explanation will lie either in an abnormally high rate of hydrolysis for trimethylacetylimidazole or an abnormally low rate for 4-nitrophenyl trimethylacetate.

Kristol et al.[4] have recently reported that values of k_{HO^-} for a series of trialkylacetate 4-nitrophenyl esters can be correlated well with Charton's constants and a modified Taft equation, showing no unusual behavior for 4-nitrophenyl trimethylacetate.[19] The rate of hydroxide-ion-catalyzed cleavage of trimethylacetylimidazole is *faster* than the corresponding rates for acetyl- and *n*-butyrylimidazole and equal to that for propionylimidazole.[7] Thus, the answer appears to lie in an unexpectedly high reactivity toward hydroxide ion for trimethylacetylimidazole, which is probably caused by steric destruction by the bulky *tert*-butyl group of contributions such as **4** to the ground-state stabilization of trimethylacetylimidazole; little such stabilization is likely for *p*-nitrophenyl esters.



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A comparable explanation (resonance destruction) was advanced by Staab[20] to account for the faster rates of "neutral" hydrolysis of *N*-acylimidazoles as branching in the acyl moiety increased, although he suggested an acylium ion mechanism in that case.

We have demonstrated the abnormal steric effect on substitution of a trimethyl group in the acyl portion of 4-nitrophenyl carboxylic esters and a steric acceleration of the base hydrolysis of trimethylacetylimidazole. Figure 2 shows that ortho groups in the leaving group can also exert a considerable retarding effect, especially on hydroxide catalysis. 2,3-Dimethylphenyl trimethylacetate reacts some 25-fold less readily than predicted, while the effects of 2-nitro or 2-chloro groups are to decrease the rates of hydroxide catalysis some fourfold.

Table IV. Properties and Spectral Characteristics of Substrates

Ester 1	λ_{HO^-}[a] (nm)	λ_{Im}[b] (nm)	mp or bp,[f] °C/Torr
a	410	410	66.5–67.5
b	400	400	117–119
c	410	400	79–80
d	400	400[c]	94.8–96[g]
e	340	340	82–83
f	295	275	58.5–60.5
g	295		240–245/760.2
h	305[d]		270–280/760.3
i	290[e]		*h*

[a] Wavelength at which kinetics were studied in hydroxide ion solution. [b] Wavelength at which kinetics were studied in imidazole buffers. [c] Isosbestic wavelength changes from 249 to 241 nm as reaction proceeds. [d] Isosbestic wavelengths are 282 and 260.5 nm throughout the reaction. [e] Isosbestic wavelength is 309 nm throughout the reaction. [f] Melting points are uncorrected; satisfactory data (±0.3% for C, H,N) were reported for **1a–c** and **1e–i**. [g] Lit. mp 94–95 °C. C. E. McDonald and A. K. Balls, *J. Biol. Chem.*, **227**, 727 (1957). [h] Not recorded.

If one considers the effects of leaving-group substitution on the rates of imidazole catalysis, the situation is much more complex. Equation 3 shows that rate constants for imidazole catalysis obey a Brønsted (leaving-group) relationship with a reasonable correlation coefficient, $r = 0.982$. However, this relationship may well be fortuitous, especially in view of the results for the 2,5-dinitro- and 2-chloro-4-nitro-substituted esters which react with rate constants differing by an order of magnitude, although their pK_{LG} values are closely similar. It is not possible at this point to decide whether the observed difference is caused by the difference in substitution patterns (2,5- as opposed to 2,4-) or by the change from an *o*-nitro to an *o*-chloro substituent.

In summary, then, this work presents the interesting situation wherein the reactivity patterns of a given group of compounds may exhibit a steric acceleration caused by increased steric bulk blocking resonance stabilization of the molecular ground state or a steric retardation arising from ortho substitution in the leaving group, noted especially for hydroxide catalysis.

Experimental Section

Materials. Aryl trimethylacetates were prepared from trimethylacetyl chloride (Aldrich Chemical Co.) by the following, nonaqueous, Schotten–Baumann procedure, described for the 2-chloro-4-nitrophenyl ester. To a solution of trimethylacetyl chloride (1.21 g, 0.01 mol) in dry dichloromethane (50 mL) was added a mixture of redistilled triethylamine (1.01 g, 0.01 mol) and 2-chloro-4-nitrophenol (1.74 g, 0.01 mol) in dichloromethane (50 mL). The reaction mixture was stirred at ambient temperature overnight, the solvent was removed and the residue was suspended in dry ether, cooled, and filtered; solvent was removed from the filtrate to give brown crystals which were recrystallized twice from ethanol, yielding white crystals, mp 79–80 °C. Liquid esters were purified by distillation immediately prior to use. Analytical data for the esters are presented in Table IV.

Imidazole perchlorate and sodium perchlorate were each recrystallized twice from methanol before use in buffer solutions. Deuterioimidazole was prepared by dissolving imidazole in deuterium oxide and removing the solvent under vacuum. Imidazole was recrystallized from benzene before use in buffer solutions. Acetonitrile was redistilled, "Gold label" spectroscopic grade from Aldrich, or if Reagent Grade, was fractionally distilled off phosphorus pentoxide for purification. Collidine was freshly distilled before use. Water was distilled

and deionized for these studies. Deuterium oxide was from Columbia Organic Chemicals Co. Inc., and deuterium chloride was supplied by Merck, Sharp and Dohme of Canada, Ltd. as a 38% solution in D_2O and was standardized before use by titration against sodium hydroxide solution.

Methods. Rates of hydrolysis of the esters were determined spectrophotometrically at 25.0 ± 0.1 °C in 10% (v/v) acetonitrile solution containing buffer or sodium hydroxide as appropriate. Ionic strengths were maintained at 1.0 using sodium perchlorate or at 0.1 with sodium chloride as supporting electrolyte.

Spectral scanning experiments on a Cary Model 15 spectrophotometer during the course of reaction indicated the best wavelength for determining kinetic parameters and also provided evidence on the nature of the reaction course. Spectral data are recorded in Table IV. Rates were routinely determined on either a Cary Model 15 or Gilford Model 222 recording spectrophotometer. A typical procedure involved addition of 25 or 50 μL of ester solution in acetonitrile to 3.00 mL of appropriate buffer in a cuvette by plunging in a Teflon rod with a flattened tip. Commencement of recording could be accomplished within 7 s of addition. When velocities were too high for such conventional procedures, reactions were studied usiong a Durrum-Gibson stopped-flow instrument equipped with a logarithmic converter and differential amplifier enabling results to be obtained directly in absorbance units. In typical stopped-flow studies, one syringe was filled with an aqueous acetonitrile solution of the substrate and the other with an acetonitrile–hydroxide ion solution. These solutions were allowed to equilibrate to 25.0 °C. Reaction was initiated by rapid mixing of equal volumes of the contents of these syringes. Experimental traces of phenolate ion production were recorded and retained on the screen of a storage oscilloscope and then photographed, several runs under any given experimental condition being superimposable.

Rate constants were obtained under pseudo-first-order conditions (buffer concentration was also at least 100 times that of the ester), usually from plots of log $(A_\infty - A_t)$ vs. t, where A_∞ and A_t are the changes in absorbance by the end of reaction and by time t, respectively. Final absorbance values (A_∞) were measured directly for sufficiently rapid reactions and calculated in other cases from the exponential time record of the reaction.[21] Random checks showed that measured and calculated final absorbance values were identical. Very slow reactions were studied by the method of initial rates using A_∞ values obtained by allowing specimen runs to proceed to completion.

pH measurements were carried out before and after the reaction using a Beckman Research Model pH meter standardized against appropriate Fisher Sicentific Co. certified buffer solutions. Calculations and least-squares analyses were performed on a Hewlett-Packard Model 9100-A programmable calculator.

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References and Notes

(1) (a) Department of Chemistry, Duquesne University, Pittsburgh, Pa. 15219 (b) Y. Nakagawa and E. T. Kaiser, *Biochem. Biophys. Res. Commun.*, **61,** 730 (1974).
(2) K. T. Douglas, Y. Nakagawa, and E. T. Kaiser, *J. Chem. Soc., Chem. Commun.*, 429 (1975).
(3) K. T. Douglas, Y. Nakagawa, and E. T. Kaiser, *J. Am. Chem. Soc.*, **98,** 8231 (1976).
(4) D. C. Kristol, R. C. Parker, H. D. Perlmutter, K.-C. H. Chen, D. H. Hawes, and G. H. Wahl, Jr., *J. Org. Chem.*, **41,** 3205 (1976).
(5) A. Williams and R. A. Naylor, *J. Chem. Soc. B*, 1967 (1971).
(6) A. A. Humffray and J. J. Ryan, *J. Chem. Soc.*, 468 (1967).
(7) T. H. Fife, *J. Am. Chem. Soc.*, **87,** 4597 (1965).
(8) M. L. Bender, E. J. Pollack, and M. C. Neveu, *J. Am. Chem. Soc.*, **84,** 595 (1962).
(9) Fife[7] has shown that k_{Im} for the general-base-promoted breakdown of trimethylacetylimidazole (30 °C, ionic strength 1.0) is 0.39 M^{-1} min^{-1} and that k_{Im} for nucleophilic attack of imidazole on 4-nitrophenyl trimethylacetate is 0.55 M^{-1} min^{-1}. As the rates of formation and breakdown of trimethylacetylimidazole are comparable, it is impossible to obtain the spectrum of the intermediate using 4-nitrophenyl trimethylacetate. Should such a spectrum be required, it should be readily measured by means of **1a.**
(10) S. L. Johnson, *Adv. Phys. Org. Chem.*, **5,** 237 (1967).
(11) K. T. Douglas and A. Williams, *J. Chem. Soc., Perkin Trans. 2*, 515 (1976).
(12) H. J. Brass and M. L. Bender, *J. Am. Chem. Soc.*, **94,** 7421 (1972).
(13) (a) G. O. Dudek and F. H. Westheimer, *J. Am. Chem. Soc.*, **81,** 2641 (1959); (b) J. Epstein, P. L. Cannon, Jr., and J. R. Sowa, *ibid.*, **92,** 7390 (1970); (c) M. Kilpatrick and M. L. Kilpatrick, *J. Phys. Chem.*, **53,** 137 (1949); (d) M. A. Weinberger, R. Greenhalgh, and P. M. Lutley, *Can. J. Chem.*, **48,** 1358 (1970).
(14) T. C. Bruice and G. L. Schmir, *J. Am. Chem. Soc.*, **86,** 418 (1964).
(15) Unpublished observations of K. T. Douglas and A. Williams. K. T. Douglas, Ph.D. Thesis, University of Kent at Canterbury (1973).
(16) All σ and σ^- values used herein are taken from the review by G. B. Barlin and D. D. Perrin, *Q. Rev., Chem. Soc.* **20,** 75 (1966).
(17) J. F. Kirsch and W. P. Jencks, *J. Am. Chem. Soc.*, **86,** 837 (1964).
(18) W. P. Jencks and J. Carriuolo, *J. Biol. Chem.*, **234,** 1272, 1280 (1959).
(19) These data were obtained in 1:1 acetonitrile:0.05 M aqueous Tris buffer, pH 9.0 by the method of initial rates. It is unclear whether the Tris buffer effect which would be expected (cf. k_{Im} for 4-nitrophenyl trimethylacetate) was allowed for in each of the cases studied, nor was it apparent how the hydroxide ion concentration present in the reaction medium was estimated at the single pH_{app} used. Although the absolute values of the second-order hydroxide ion rate constants remain to be established, the relative order of hydroxide ion reactivities is probably reflected in the values reported.
(20) H. A. Staab, *Chem. Ber.*, **89,** 1927, 2088 (1956).
(21) A. Williams and K. T. Douglas, *J. Chem. Soc., Perkin Trans. 2*, 1454 (1972).