220–222° (sealed tube), in 96% yield. Tosylate **5c** was prepared by the treatment of the lithium salt of the corresponding alcohol with *p*-toluenesulfonyl chloride. Tosylates **2c–4c** were prepared by the conversion of the alcohols to the sulfinate esters[11] and oxidation by *m*-chloroperbenzoic acid[12] or ruthenium tetroxide.

The latter oxidation method, which can be applied at low temperature (<−20°) in nonpolar aprotic media (*i.e.*, halocarbon solvents), was particularly useful for the preparation of the more reactive tosylates **2c** and **4c**. This leads us to suggest the ruthenium tetroxide oxidation of sulfinate esters as a generally useful extension of the method of Coates and Chen[12] for the preparation of hindered or very reactive tosylates.

Samples of authentic acetates were prepared by treatment of the carbinols with ketene in chloroform containing a trace of sulfuric acid, characterized by nmr and ir spectroscopy, and compared with the reaction products by establishing identity using glpc–mass spectrometry.

The tremendous accelerations expected[1-6] for ionizations of cyclopropylcarbinyl or allyl tosylates are absent in **3c** and **5c**. Their acetolyses (45°) are actually *slower* than those of model compound **2c** (or **4c**) by *ca.* 10^2 and 10^4, respectively. Clearly the conjugative stabilization of a carbonium ion center by an adjacent perpendicular cyclopropyl ring or vinyl group is insignificantly small.

The deceleration seen for **3c** and **5c** could be attributed to (a) steric inhibition of solvation (shown to be unimportant by the fast acetolysis of **4c**, which has the even bulkier *gem*-dimethyl at C-2), (b) increased transition state angle strain for sp^2 hybridization at C-2 compared with the sp^3 hybridization of **2c** and **4c** (the angle at C-2 is compressed toward 90° in the cation), or (c) inductive transition-state destabilization by the more electronegative cyclopropyl or vinyl group at C-2. Explanation b may contribute to the difference between **3c** and **2c** but can hardly be significant in the comparison of **3c** and **5c**, both of which have essentially sp^2 hybridization at C-2. Explanation c is favored by the observation of a rough correlation of rates with the σ^* values[13] appropriate for the α substituents in **2c–5c**.

It is interesting to note that the 3-kcal/mol $\Delta\Delta H^{\pm}$ between **3c** and **5c** is of the same sign and approximate magnitude as the comparable difference seen[14] for model compounds lacking the geometric restraints of **3c** and **5c**. This suggests that the resonance stabilizations of planar allyl and bisected cyclopropylcarbinyl cations are nearly equal, despite calculations[15] (EHT) of a 3-kcal/mol larger barrier to rotation for cyclopropylcarbinyl than for allyl cation.

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(11) J. W. Wilt, R. G. Stein, and W. J. Wagner, *J. Org. Chem.*, **32**, 2097 (1967).
(12) R. M. Coates and J. P. Chen, *Tetrahedron Letters*, in press.
(13) T. L. Brown, *J. Amer. Chem. Soc.*, **80**, 6489 (1958); R. W. Taft, Jr., in "Steric Effects in Organic Chemistry," M. S. Newman, Ed., John Wiley & Sons, Inc., New York, N. Y., 1956.
(14) T. Tsuji, I. Moritani, and S. Nishida, *Bull. Chem. Soc. Jap.*, **40**, 2338 (1967).
(15) R. Hoffmann, *J. Chem. Phys.*, **40**, 2480 (1964).

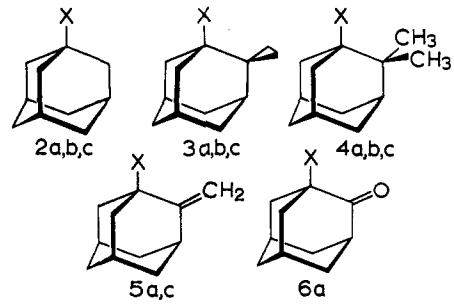

Figure 1. Compounds studied (**a**, X = OH; **b**, X = *p*-toluenesulfinyl; **c**, X = *p*-toluenesulfonyl).

(16) P. von R. Schleyer and V. Buss, *J. Amer. Chem. Soc.*, **91**, 5880 (1969).

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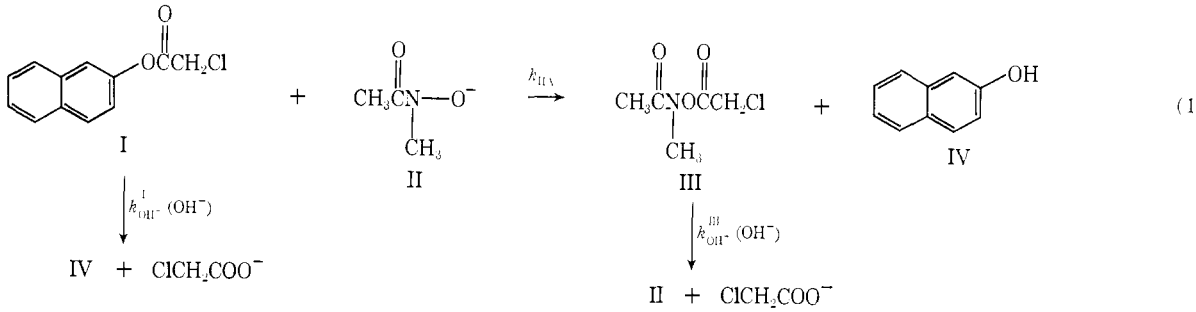
N-Methylacetohydroxamic Acid Catalyzed Ester Hydrolysis[1]

Sir:

Related to our efforts to develop intracomplex nucleophilic catalysts[2] for ester hydrolysis, it was essential to find intermolecular nucleophilic catalysts of high efficiency and relatively simple chemistry. An efficient nucleophilic catalyst for ester hydrolysis must combine the properties of high nucleophilicity toward ester substrates with exceptional lability of all intermediates on the pathway leading to the formation of products and regeneration of the catalyst.[3] Toward labile esters, the best nucleophiles known with pK_a's in the neutral pH range are functional groups exhibiting the α effect,[4] such as hydroxamate ion and hydroxylamine. However, the acyl intermediates formed by most such nucleophiles are either stable to hydrolysis or undergo decomposition reactions which do not regenerate the original nucleophile.[5] This is the case with hydroxamate ions since acylhydroxamates readily undergo the Lossen rearrangement to form isocyanates.[6] We sought to remedy this deficiency by alkyl substitution on the hydroxamic acid nitrogen, since with this modification the Lossen rearrangement cannot occur and deacylation must regenerate the hydroxamate ion. Furthermore, acyl derivatives of N-alkylhydroxamic acids are exceptionally labile in aqueous solution; for example, the hydrolysis rate of N,O-diacetyl-N-methylhydroxylamine is comparable to that of *p*-nitrophenyl acetate.[7]

(1) This work has been supported by Grant No. HE 05726-08 from the National Institutes of Health.
(2) M. L. Bender, *Trans. N. Y. Acad. Sci.*, **29**, 301 (1967).
(3) For a comprehensive discussion of ester hydrolysis catalyzed by nucleophiles such as imidazole, see T. C. Bruice and S. J. Benkovic, "Bioorganic Mechanisms," Vol. 1, W. A. Benjamin, Inc., New York, N. Y., 1966, Chapter 1.
(4) For a discussion of the α affect, see W. P. Jencks, "Catalysis in Chemistry and Enzymology," McGraw-Hill Book Co., Inc., New York, N. Y., 1969, pp 107–111.
(5) For example, see W. P. Jencks, *J. Amer. Chem. Soc.*, **80**, 4581 (1958), and A. L. Green and B. Saville, *J. Chem. Soc.*, 3887 (1956).
(6) D. G. Hoare, A. Olson, and D. E. Koshland, Jr., *J. Amer. Chem. Soc.*, **90**, 1638 (1968).
(7) J. F. Kirsch and W. P. Jencks, *ibid.*, **86**, 837 (1964).



(1)

In light of these considerations we have investigated the hydrolysis of β-naphthyl chloroacetate[8] (I) in the presence of N-methylacetohydroxamate anion (II). β-Naphthyl chloroacetate was chosen as substrate because of the large $\Delta\epsilon$ between substrate I and the product, β-naphthol (IV), and the expected facile hydrolysis of the presumed chloroacetyl intermediate III.

When N-methylacetohydroxamic acid[9] is allowed to react[10] with a threefold excess of ester I at pH 7.35, the appearance of β-naphthol, followed spectrophotometrically at 336 nm, adheres strictly to pseudo-first-order kinetics for at least 90% of hydrolysis with $k_{obsd} = 1.58 \times 10^{-4}$ sec^{-1}. Under the same conditions in the absence of hydroxamate II, the hydrolysis rate is 0.36×10^{-4} sec^{-1}. Thus the hydrolysis of I is catalyzed 4.4-fold by II under these turnover conditions.

General-acid, general-base, and nucleophilic catalysis are the most reasonable mechanisms by which this catalysis could occur. The following data establish that the nucleophilic mechanism is operative. (a) The pH–rate profile for the hydrolysis of I catalyzed by hydroxamate anion (II) under turnover conditions is a sigmoid[11] dependent on the ionization of a base of $pK_{app} = 9.53$. The pK_a of N-methylacetohydroxamic acid determined spectrophotometrically at 260 nm in 32.2% CH_3CN, $\mu = 0.2$ M, is 9.52 ± 0.02. (b) From the above pH–rate profile, the second-order rate constant, k_{HA}, for the reaction of I with II is 26.1 M^{-1} sec^{-1}. When determined at pH 9.08 with hydroxamate II in great excess[12] of substrate I, k_{HA} is 29.3 ± 5 M^{-1} sec^{-1}, within experimental error the same value as obtained for k_{HA} under turnover conditions. (c) The second-order rate constant,[13] $k^{III}_{OH^-}$, for the reaction of chloroacetyl N-methylacetohydroxamate (III) with hydroxide ion is 7.29×10^3 M^{-1} sec^{-1}. (d) For the reaction of I with II under turnover conditions using deuterium oxide as solvent,[14] $k^{H_2O}_{HA}/k^{D_2O}_{HA} = 1.05 \pm 0.1$.

From a and b above, the rate constant for the hydrolysis of ester I in the presence of hydroxamate anion II can be described by eq 2, where $(II)_T$ is the analytical

$$k_{obsd} = k^{I}_{OH^-}(OH^-) + k_{HA}(II)_T\alpha_{II} \qquad (2)$$

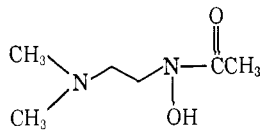
concentration of the hydroxamic acid and α_{II} is the fraction of II ionized. Equation 2 is consistent with general-base or specific-base–general-acid catalysis. It is also consistent with nucleophilic catalysis, since from the rate constants in a and c, $k^{III}_{OH^-}(OH^-) > k_{HA}(II)$. Therefore, intermediate III would not accumulate, if it is on the reaction pathway, and the concentration of II would remain constant throughout the reaction. The crucial experiment in deciding between general-base, specific-base–general-acid, and nucleophilic catalysis is the effect of deuterium oxide solvent on the reaction rate.[15] The absence of a kinetic solvent deuterium isotope effect supports the nucleophilic mechanism given in eq 1.

According to eq 2 the 4.4-fold catalysis previously observed may be enhanced simply by increasing the catalyst concentration. However, at very high catalyst concentrations, there will be a limit to the observed catalysis, namely, the hydrolysis rate of intermediate III. Therefore, the ratio of the hydrolysis rate of intermediate III to that of ester I is the theoretical limit of the catalytic efficiency. At pH 7.35 the pseudo-first-order rate constants for the hydrolysis of I and III are 3.6×10^{-5} sec^{-1} and 2.8×10^{-3} sec^{-1}, respectively. Under these conditions the theoretical catalytic limit is 80-fold.

The hydrolysis of esters with acyl groups less electrophilic than the chloroacetyl group is catalyzed by hydroxamate anion II in a kinetically biphasic reaction. For example, in the reaction of II with *p*-nitrophenyl acetate (PNPA) in excess ((II) = 6.33×10^{-4} M, (PNPA) = 2.01×10^{-3} M, pH 8.26) one observes a rapid release, or burst, of *p*-nitrophenolate ion, followed by a slower release that is still 2.3 times faster than the spontaneous hydrolysis rate. In this reaction the catalytic efficiency of II is limited by the relative hydrolytic stability of the acylhydroxamic acid intermediate, N,O-diacetyl-N-methylhydroxylamine, formed in the initial reaction of II with PNPA.

One way to increase the lability of this intermediate is to introduce a second functionality into the catalyst that will assist deacylation intramolecularly. We have synthesized N-(2-dimethylaminoethyl)acetohydroxamic acid[16] (V) which incorporates a dimethylamino group as the second functionality. We find that the dimethylamino group has a profound effect on the catalytic efficiency of the hydroxamic acid; V catalyzes the hydrolysis of PNPA ((V) = 6.34×10^{-4} M, (PNPA)

(8) J. Houben, *Chem. Ber.*, **59**, 2878 (1926).
(9) O. Exner, *Collection Czech. Chem. Commun.*, **16**, 258 (1951).
(10) (I) = 1.94×10^{-3} M, (II) = 6.33×10^{-4} M, 0.1 M phosphate buffer. All reactions reported here were performed in 32.2% CH_3CN, ionic strength 0.2 M, and temperature 25.0 ± 0.2°.
(11) Reference 3, Vol. 1, pp 11–13.
(12) (I) = 4.9×10^{-5} M, (II) = $0.76–9.5 \times 10^{-3}$ M, 0.2 M borate buffer.
(13) Hydroxide ion concentrations were calculated from the equation pH = log (OH^-) + 14.58, which was found to be applicable at $\mu = 0.2$ M, 32.2% CH_3CN. See J. F. Kirsch, W. Clewell, and A. Simon, *J. Org. Chem.*, **33**, 127 (1968). Since the hydrolysis of III exhibited appreciable buffer catalysis, extrapolations to zero buffer concentration were made at each pH.
(14) Spectrophotometric determination at 260 nm of the concentration of anion II in D_2O and H_2O eliminated any uncertainty associated with a pK_a shift.
(15) M. L. Bender, E. J. Pollock, and M. C. Neveu, *J. Amer. Chem. Soc.*, **84**, 595 (1962). See also, T. St. Pierre and W. P. Jencks, *ibid.*, **90**, 3817 (1968).
(16) Synthesized by acetylation of 2-(N,N-dimethylamino)ethylhydroxylamine obtained from dimethylaminoacetaldoxime by a modification of the methods of H. Feuer and B. F. Vincent, Jr., *ibid.*, **84**, 3771 (1962).



V

$= 2.01 \times 10^{-3}$ *M*, pH 8.26) 25-fold over-all in a pseudo-first-order process. A detailed kinetic investigation will be presented elsewhere.

The data presented here establish that N-alkylhydroxamate ions are true catalysts of the hydrolysis of labile esters. In addition, they function effectively at very low concentration and in the neutral pH range. The catalytic rates that we observed are at least as large as those observed in PNPA hydrolysis catalyzed by imidazole,[17] the only other previously known catalyst of this kind. However, in their ease of synthesis, N-alkylhydroxamate ions hold an important advantage over imidazole. Most carboxylic acid esters may be converted to N-alkylhydroxamic acids under very mild conditions. This affords a convenient means of introducing these functionalities into higher molecular weight systems, such as the cycloamyloses,[18] that exhibit substrate binding. By utilizing the proximity and orientation effects afforded by these systems, we expect to realize the full catalytic potential of the N-alkylhydroxamates. Furthermore, since ester derivatives of the carboxyl groups at the active sites of both lysozyme[19] and pepsin[20] have been prepared, there is the attractive possibility that the active sites of these enzymes may be altered to contain an N-alkylhydroxamic acid, an alteration which should lead to enzymes of new functional group specificity.

(17) T. C. Bruice and G. L. Schmir, *J. Amer. Chem. Soc.*, **79**, 1663 (1957).
(18) R. L. Van Etten, G. A. Clowes, J. F. Sebastian, and M. L. Bender, *ibid.*, **89**, 3253 (1967).
(19) T. Y. Lin and D. E. Koshland, Jr., *J. Biol. Chem.*, **244**, 505 (1969).
(20) T. G. Rajagopalan, W. H. Stein, and S. Moore, *ibid.*, **241**, 4295 (1966).

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Enhanced Rates due to Apolar Interactions between Polymer and Substrate

Sir:

In previous publications[1-3] it has been shown that polyethylenimine (PEI) and some of its acyl derivatives possess extraordinarily high binding affinities for small organic molecules. This polymer is a highly branched, relatively compact, water-soluble macromolecule.[4] Its aliphatic acyl derivatives provide apolar binding sites in proximity to amine residues of the polymer. One might expect, therefore, to find progressively enhanced rates of aminolysis of substrates with increasingly large apolar substituents. Quantitative measurements of rates of aminolysis indeed reveal enhancements of several orders of magnitude.

Rates of cleavage of three acyl nitrophenyl esters were followed by the appearance of *p*-nitrophenolate ion as reflected by increased absorbances at 400 nm, measured with a Cary Model 14 spectrophotometer. The reaction was followed at pH 9.0, in 0.02 *M* tris(hydroxymethyl)aminomethane buffer, at 25°. Rate constants were determined from measurements under pseudo-first-order conditions, with the residue molarity of primary amine present in approximately tenfold excess. First-order rate graphs were linear for at least 80% of the reaction. With nitrophenyl acetate and nitrophenyl caproate, the initial ester concentration was 6.66×10^{-5} *M*. With nitrophenyl laurate at this concentration, aminolysis by polymer was too fast to follow and, therefore, both substrate and amine were diluted tenfold for rate measurements.

Polyethylenimines of different molecular weight ranges (PEI-6, PEI-18, PEI-600)[4] were obtained from Dow Chemical Co. The lauroyl derivative of PEI-6, containing 10% of the nitrogen residues conjugated to this acyl group, was prepared as described elsewhere.[3]

Table I lists first-order rate constants, corrected for hydrolysis of ester in buffer alone. Propylamine served as a reference amine; in its presence k (in min^{-1}) for aminolysis decreased progressively from 0.98×10^{-2} to 0.51×10^{-2} to 0.05×10^{-2} as the length of the acyl group increased from 2 to 12 carbons (see Table I). The sharp drop for nitrophenyl laurate may be the result of micelle formation[5] even at concentrations of 6×10^{-6} *M*.

Table I. First-Order Rate Constants for Amine Acylation by *p*-Nitrophenyl Esters[a]

Amine	$k \times 10^2$ min[b] *p*-Nitrophenyl acetate	*p*-Nitrophenyl caproate	*p*-Nitrophenyl laurate
Propyl	0.98	0.51	0.053
PEI-6[c]	3.60	1.47	0.11
PEI-18[c]	4.38	1.57	0.11
PEI-600[c]	4.60	1.80	0.17
L(10%)-PEI-6[d]	15.2	68.1	698

[a] Measurements made at pH 9.0 in 0.02 *M* tris(hydroxymethyl)-aminomethane buffer, 25°. Stock solutions of substrate were made in acetonitrile; hence the final buffer also contained 6.7% acetonitrile. [b] $k = k_a - k_0$, where k_a is the measured rate constant in the presence of amine and k_0 is that for the hydrolysis in Tris buffer alone; k_0 is 0.94×10^{-2} min^{-1} for the acetyl ester, 0.61×10^{-2} min^{-1} for the caproyl ester, and 0.023×10^{-2} min^{-1} for the lauroyl ester. [c] The numeral following "PEI" multiplied by 100 is the molecular weight of the polymer sample. [d] This sample of PEI-6 has 10% of its nitrogens acylated with lauroyl groups.

With nonacylated polyethylenimines (Table I) the rate constant is increased by a factor of about 4 over that of propylamine. This small enhancement may be due merely to the fact that a greater fraction of primary amine groups in the polymer are in the basic, NH_2 state. With these polyethylenimines, as with propylamine, k drops with increasing length of the hydrocarbon chain of the acyl nitrophenyl ester.

Markedly different trends are seen in the rate constants for aminolysis by lauroylpolyethylenimine (con-

(1) I. M. Klotz and A. R. Sloniewsky, *Biochem. Biophys. Res. Commun.*, **31**, 421 (1968).
(2) I. M. Klotz and V. H. Stryker, *J. Am. Chem. Soc.*, **90**, 2717 (1968).
(3) I. M. Klotz, G. P. Royer, and A. R. Sloniewsky, *Biochemistry*, in press.
(4) L. E. Davis in "Water-Soluble Resins," R. L. Davidson and M. Sittig, Ed., Reinhold Publishing Corp., New York, N. Y., 1968, pp 216–226.
(5) F. M. Menger and C. E. Portnoy, *J. Am. Chem. Soc.*, **90**, 1875 (1968).