nmr ($CDCl_3$) 11.15 (1 H, s), 9.12 (1 H, s), 3.52 (2 H, q), 2.74 (2 H, t), 2.0–0.6 ppm (20 H, m).

Anal. Calcd for $C_{12}H_{26}NOBF_4$: C, 50.20; H, 9.13; N, 4.88. Found: C, 50.47; H, 9.33; N, 5.01.

Registry No.—2a, 36955-98-3; 2b, 36994-06-6; 2c, 36989-94-3; 2d, 36989-95-4.

Reactivity of Hydroxamic Acids. Correlation with the Two-Parameter Taft Equation

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The problem of the separation of polar, steric, and resonance effects has recently been reviewed,[1] and further testing of the range of applicability of the empirical equations as well as the assumptions underlying them deserve further testing. The two-parameter eq 1 suggested by Taft[1,2] for use with aliphatic compounds correlates the data reported below for the acidic hydrolysis of a series of aliphatic hydroxamic acids. ρ^* and δ are constants to be determined for each reaction and set of reaction conditions and represent the susceptibility of the reaction system to polar and steric effects, respectively. σ^* and E_s are polar and steric substituent constants, respectively, characteristic of each substituent and are tabulated in the literature.[1,2]

$$\log k = \rho^*\sigma^* + \delta E_s + \log k_0 \quad (1)$$

The kinetics of amide hydrolysis have been studied extensively; nevertheless, uncertainties remain, especially for the acid-catalyzed reactions.[3] Three reports, to our knowledge, of kinetic studies of hydrolysis of the related hydroxamic acids exist; two report results for benzohydroxamic acid and a few of its derivatives at moderate[4] to very high acidities[5] and the third,[6] results for acetohydroxamic acid at very low acidity (pH >0.7). Table I reports results for the acidic dependence of the hydrolysis rate of propionohydroxamic acid at moderate acidities.

TABLE I

RATE CONSTANTS FOR PROPIONOHYDROXAMIC ACID HYDROLYSIS IN AQUEOUS *p*-TOLUENESULFONIC ACID AT 50.2° AND IONIC STRENGTH AT 0.494 *M*

$[H^+]$,[a] *M*	$10^5 k_{obsd}$[b]	$10^4 k_{obsd}/[H^+]$
0.494	22.0	4.45
0.247	9.88	4.00
0.124	5.27	4.25
		Av 4.23

[a] *p*-Toluenesulfonic acid. [b] Average pseudo-first-order rate constant, sec^{-1}.

The results of Table I are represented by eq 2, *i.e.*,

$$k_{obsd} = k_2[H^+] \quad (2)$$

the reaction is first order in catalytic acid and also in the hydroxamic acid. Equation 2 is consistent with the accepted bimolecular mechanism (eq 3 and 4) for acidic hydrolysis of benzohydroxamic acid[4,5] and amides[3] at moderate acidity. This mechanism requires k_2 to be a product of an equilibrium constant and a second-order rate constant.[4]

$$RCONHOH + H^+ \rightleftharpoons R\overset{+}{C}(OH)NHOH \quad (3)$$

$$R\overset{+}{C}(OH)NHOH + H_2O \longrightarrow \text{products} \quad (4)$$

Equation 1 should be applicable to the hydrolysis of acyl compounds following the bimolecular mechanism.[1,2] Table II lists the experimental results and log k calculated from eq 5 with the parameters determined by the method of least squares.[7] The reference substituent is methyl.

TABLE II

HYDROLYSIS RATES OF HYDROXAMIC ACIDS IN 0.249 *N* AQUEOUS *p*-TOLUENESULFONIC ACID AT 50.5°

Hydroxamic acid	Registry no.	$10^5 k_1$[a]	$10^5 k_2$[b]	$-\log k_2$	$-\log k_2$ (calcd)[c]
Aceto-	1113-25-3	11.0	44.2	3.355	3.438
Propiono-	2580-63-4	11.2	45.0	3.347	3.434
Isobutyro-	22779-89-1	3.92	15.7	3.804	3.608
Pivalo-	29740-67-8	2.17	8.71	4.060	4.126
Phenylaceto-	5330-97-2	4.27	17.1	3.767	3.726

[a] Pseudo-first-order rate constant, sec^{-1}. [b] Second-order rate constant, l. mol^{-1} sec^{-1}, $k_1/0.249$. [c] Calculated from eq 5.

$$\log k = -0.409\sigma^* + 0.526E_s - 3.438 \quad (5)$$

Equation 5 reproduces the log k values within 1 to 5% over a σ^* range of 0.515 (from phenylaceto, 0.215, to *tert*-butyl, −0.30) and an E_s range of 1.54 (from methyl, 0.00, to *tert*-butyl, −1.54). The coefficient of multiple regression[7] is 0.920. Neither σ^* nor E_s individually provide satisfactory correlation of the log k values. A log k *vs.* σ^* plot is quite scattered while a log k *vs.* E_s plot is a curve.

These results show that polar and steric effects are of comparable magnitude in the acid-catalyzed hydrolysis of hydroxamic acids. This result is in contrast to the acidic hydrolysis of amides and esters which shows very little or no dependence on polar effects.[1,2,8] The Taft steric substituent constants, E_s, implicitly allow for hyperconjugative effects.[9] A somewhat improved correlation for acidic hydrolysis

(1) J. Shorter, *Quart. Rev., Chem. Soc.*, **24**, 433 (1970).
(2) R. W. Taft, Jr., "Steric Effects in Organic Chemistry," M. S. Newman, Ed., Wiley, New York, N. Y., 1956, Chapter 13.
(3) C. O'Connor, *Quart. Rev., Chem. Soc.*, **24**, 553 (1970).
(4) D. C. Berndt and R. L. Fuller, *J. Org. Chem.*, **31**, 3312 (1966).
(5) A. J. Buglass, K. Hudson, and J. G. Tillett, *J. Chem. Soc. B*, 123 (1971).
(6) J. W. Munson and K. A. Connors, *J. Amer. Chem. Soc.*, **94**, 1979 (1972).
(7) D. A. Leabo, "Basic Statistics," 3rd ed, Richard D. Irvin, Inc., Homewood, Ill., 1968, Chapter 14.
(8) P. D. Bolton and G. L. Jackson, *Aust. J. Chem.*, **24**, 471 (1971).
(9) C. K. Hancock, E. A. Meyers, and B. J. Yager, *J. Amer. Chem. Soc.*, **83**, 4211 (1961).

of the aliphatic amides noted above was obtained when modified E_s values were used along with a parameter explicity allowing for hyperconjugative effects[8] rather than using the single parameter, E_s.

The rate constants in Table II are overall rate constants, *i.e.*, a composite for steps 3 and 4. Buglass, *et al.*,[5] have calculated rate constants for step 4 for the acidic hydrolysis of a series of para-substituted benzohydroxamic acids and report a positive Hammett ρ value for correlation of those rate constants, a result consistent with the bimolecular mechanism. An examination of the data in their[5] Table 6 indicates at best (with the *p*-hydroxy compound excluded) only a fair correlation between the observed overall rate constants and Hammett σ constants with a negative value for ρ. This result is consistent with our negative value for ρ^* for the overall rate constants for the aliphatic compounds.

Since $\rho^* < 0$ in eq 5, electron-donating groups accelerate the rate compared to that of the reference compound, acetohydroxamic acid. This is consistent with the greater electronegativity of hydroxyl compared to hydrogen in changing from amides to hydroxamic acids, provided that the polar effect on the protonation of hydroxamic acids is greater than the polar effect for the nucleophilic attack by water on the protonated intermediate in the bimolecular mechanism. The positive value for δ means that steric effects are rate decelerating compared to acetohydroxamic acid as would be anticipated.

Experimental Section

Aceto-, isobutyro-, and pivalohydroxamic acids have been described previously.[10] Propionohydroxamic acid was prepared by adaptation of the method used for preparation of isobutyrohydroxamic acid, purified by means of the copper salt, and crystallized from ethyl acetate, mp 93.2–95.0° (lit.[11] mp 92.5–93°). Phenylacetohydroxamic acid, mp 142.7–144.0° dec (lit.[12] mp 143–144° dec), was prepared by adaptation of the method used for benzohydroxamic acid.[4]

The 0.494 *M* *p*-toluenesulfonic acid solution (Table I) was prepared by addition of the acid to distilled water and titrated with standardized base. The 0.247 and 0.124 *M* solutions were prepared from the above solution by appropriate dilutions and with potassium chloride added to maintain the ionic strength at 0.494 *M*. The 0.249 *M* *p*-toluenesulfonic acid (Table II) was prepared by addition of the acid to double distilled water and titrated as above.

Kinetic measurements were made by use of the spectrophotometric method reported previously[4] using either a photoelectric colorimeter[4] (Table I) or a Beckman DU spectrophotometer (Table II) set at 520 nm. Pseudo-first-order rate constants were obtained from the slope of the appropriate graph.[4] The rate constants reported in column two in Table I are the average of five, two, and six runs, respectively, from highest to lowest catalytic acid concentration. The rate constants in Table II are averages of duplicate or triplicate measurements. Average deviation from the mean is less than 1.7%. Temperature control was ±0.05°. Initial concentration of hydroxamic acids in the kinetic runs was 0.012 *M*.

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(10) D. C. Berndt and H. Shechter, *J. Org. Chem.*, **29**, 916 (1964).
(11) L. W. Jones and L. Neuffer, *J. Amer. Chem. Soc.*, **39**, 659 (1917).
(12) K. Buraczewski, E. Czerwinska, Z. Eckstein, E. Grochowski, R. Kowalik, and J. Plenkiewicz, *Bull. Acad. Pol. Sci., Ser. Sci. Chim.*, **12**, 773 (1964).

Microbiological Reduction and Resolution of Prostaglandins. Synthesis of Natural $PGF_{2\alpha}$ and *ent*-$PGF_{2\beta}$ Methyl Esters

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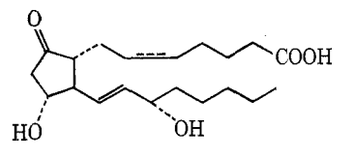
The total synthesis of racemic prostaglandins E_1 (**1**, 5,6-saturated) and E_2 (**1**, 5,6-cis double bond) and their



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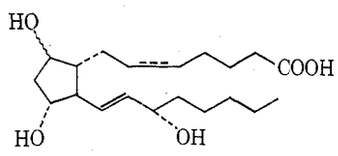

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methyl esters *via* bicyclo[3.1.0]hexane intermediates has previously been reported from these laboratories.[1] Chemical reduction of the 9-keto group of these compounds using sodium borohydride led to racemic $PGF_{1\alpha}$ (**2**, 9α,5,6-saturated), $PGF_{1\beta}$ (**2**, 9β,5,6-saturated), and $PGF_{2\alpha}$ (**2**, 9α,5,6-cis double bond), $PGF_{2\beta}$ (**2**, 9β,-5,6-cis double bond), respectively. Natural $PGF_{1\alpha}$ and $PGF_{2\alpha}$ have the 9*S* configuration while nat-$PGF_{1\beta}$ and $PGF_{2\beta}$ are 9*R*. Fermenting yeasts are known to reduce ketones to optically active secondary alcohols of the *S* configuration, the extent of stereoselectivity varying somewhat with the steric environment of the keto group.[2] Enzymatic reductions of some steroid ketones show high stereoselectivity.[3] It was thus of interest to us to determine the effect of enzymes of fermenting yeasts and other microorganisms on prostaglandins E_1 and E_2. Stereoselective microbiological reduction of a racemic prostaglandin 15-ketone **3** to **4** has recently been reported.[4]

Actively fermenting baker's yeast was found to reduce *nat*-PGE_1 and *nat*-PGE_2 slowly to $PGF_{1\alpha}$ and $PGF_{2\alpha}$, respectively. No appreciable amounts of the 9β epimers could be seen by thin layer chromatography of extracts, thus demonstrating the stereoselective

(1) (a) W. P. Schneider, U. Axen, F. H. Lincoln, J. E. Pike, and J. L. Thompson, *J. Amer. Chem. Soc.*, **91**, 5372 (1969); (b) U. Axen, F. H. Lincoln, and J. L. Thompson, *Chem. Commun.*, 303 (1969); (c) W. P. Schneider, *ibid.*, 304 (1969).
(2) (a) C. Newberg and F. F. Nord, *Chem. Ber.*, **52**, 2237 (1919). See also reviews by K. Kieslick, *Synthesis*, 147 (1969), and L. Verbit, *Progr. Phys. Org. Chem.*, **7**, 51 (1970). (b) R. MacLeod, H. Prosser, L. Fikentscher, J. Lanyi, and H. S. Mosher, *Biochemistry*, **3**, 838 (1964); see, however, Lemieux and Giguere, *Can. J. Chem.*, **29**, 678 (1951). (c) V. Prelog, *Ciba Found. Study Group* [*Pap.*], **2**, 84 (1959). (d) W. Acklin, V. Prelog, F. Schenker, B. Serdarević, and P. Walter, *Helv. Chim. Acta*, **48**, 1725 (1965).
(3) (a) E. Vischer and A. Wettstein, *Advan. Enzymol.*, **20**, 251 (1959); (b) W. S. Johnson, W. A. Vredenburgh, and J. E. Pike, *J. Amer. Chem. Soc.*, **82**, 3409 (1960).
(4) M. Miyano, C. R. Dorn, F. B. Colton, and W. J. Marsheck, *Chem. Commun.*, 425 (1971).