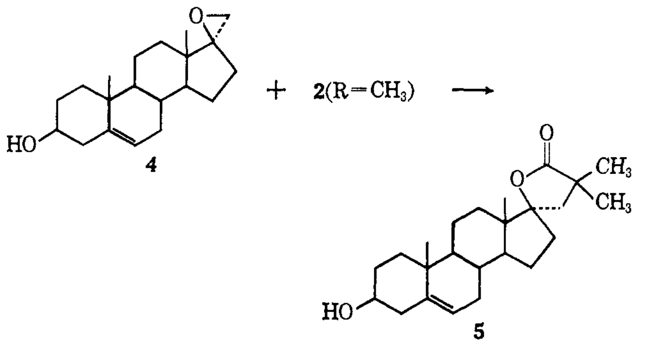
Table II. Synthesis of Tetramethyldicarboxylic Acids from Metalated Isobutyric Acid

$LiC(CH_3)_2CO_2Li + X(CH_2)_nX \longrightarrow HO_2C(CH_3)_2(CH_2)_nC(CH_3)_2CO_2H$

Alkylating agent	Tetramethyldicarboxylic acid, %
Ethylene dichloride	0
1,3-Dibromopropane	65
1,4-Dibromobutane	75 (97)[a]

[a] Crude yield.

The utility of metalated carboxylic acids (**2**) for synthetic purposes can be partially illustrated with the following examples. Addition of 2-methylbutyric acid, **1** ($R = C_2H_5$), to lithium diisopropylamide as above produced **2** ($R = C_2H_5$) in homogeneous solution. Subsequent addition of *n*-butyl bromide gave 2-ethyl-2-methylhexanoic acid (76%) on acidification and distillation.[13] Alkylation of **2** ($R = CH_3$) with 2,3-dichloropropene yielded 4-chloro-2,2-dimethyl-4-pentenoic acid (70%) which on hydrolysis in sulfuric acid[14] conveniently produced 2,2-dimethyllevulinic acid (98%). Finally, to illustrate the reaction of metalated carboxylic acids with epoxides, treatment of 17β,20-epoxy-17α-methyl-5-androsten-3β-ol (**4**)[15] with excess **2** ($R = CH_3$) at 40° produced spirolactone **5** (81%).



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[15] P. L. Creger, Dutch Patent 6,514,607 (1966); *Chem. Abstr.*, **65**, 10641*e* (1966); G. Drefahl, K. Ponsold, and H. Schick, *Chem. Ber.*, **97**, 3529 (1964); C. E. Cook, R. C. Corley, and M. E. Wall, Abstracts, 149th National Meeting of the American Chemical Society, Detroit, Mich., April 1965, p 45P; D. Bertin and L. Nedelec, *Bull. Soc. Chim. France*, 2140 (1964); G. Müller and A. Poittevin, French Patent 1,359,646 (1964).

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Acid-Catalyzed Ester Hydrolysis

Sir:

The mechanism of acid-catalyzed hydrolyses of ordinary esters is most frequently represented as occurring *via* water attack on preprotonated esters. Because the concentration of protonated ester is minute in aqueous solutions of dilute acids, general acid catalyzed attack of water possibly *via* a cyclic transition state has been proposed as an attractive alternative pathway.[1] An attempt is made in this article to assess whether the activation produced by protonation of a small fraction of ester molecules is sufficient to account for observed hydrolysis rates in weakly acid solutions. A comparison is made between the specific rate constant for water attack on protonated esters and that calculated from hydrolysis rates of esters chelated to transition metal ions.

Observed second-order rate constants for acid hydrolysis of ordinary esters such as ethyl acetate[2] at 25° are about 10^{-4} M^{-1} sec^{-1}. When these constants are multiplied by the acid ionization constants of about $10^{6.5}$ *M* for carboxylic acids and esters,[3] a first-order rate constant of about $10^{2.5}$ sec^{-1} is calculated for the rate of water attack upon protonated esters in aqueous solutions. Protonation of esters is known to occur at the carbonyl oxygen.[4] If the species with a protonated ether oxygen is advanced as the kinetically active one, its greater acid ionization constant decreases the concentration of kinetically significant protonated species which must be compensated by a correspondingly greater reactivity.[5] In this research, $10^{2.5}$ sec^{-1} is taken as the rate of water attack on the kinetically significant carbonyl oxygen protonated ester. The remainder of this paper attempts to determine whether this rate constant is reasonable.

An estimate may be made of the hydrolysis rate to be expected from placement of a positive charge on the carbonyl oxygen atom from two studies of transition metal ion catalyzed glycine ethyl ester hydrolysis. At 25° the first-order rate constant for water attack upon the dipositive cupric ion complex of glycine ethyl ester[6] is 4.3×10^{-5} sec^{-1}. The corresponding value for water attack upon N-protonated glycine ethyl ester[6] is 5×10^{-9} sec^{-1}. Since the rate for the cupric complex exceeds the last figure by almost 10^4, while the effect predicted for an increase of unit positive charge at the nitrogen atom is less than 10^2, hydrolysis in the cupric ion case proceeds *via* a chelated ligand with the transition metal ion positive charge located at the carbonyl oxygen. A similar argument for chelation has been presented for hydroxide ion attack at protonated and cupric ion complexes of glycine ethyl ester.[6] Though hydrolysis proceeds *via* a chelated cupric ion complex, it is not known to what extent the carbonyl oxygen is chelated to the cupric ion, the primary binding site of which is at the amino nitrogen.[6] Complete chelation might serve to increase the rate constant if it represents a value for a condition where the complexes are not chelated most of the time. It has been established that glycine ethyl ester is virtually completely chelated in the cobaltic complex $[Co(NH_2CH_2CH_2NH_2)_2(NH_2CH_2COOC_2H_5)]^{3+}$. At 25° the first-order rate constant for ester hydrolysis due to water attack

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[1] Ya. K. Syrkin and I. I. Moiseev, *Usp. Khim.*, **27**, 717 (1958); M. L. Bender, *Chem. Rev.*, **60**, 68 (1960).

[2] R. P. Bell, A. L. Dowding, and J. A. Noble, *J. Chem. Soc.*, 3106 (1955).

[3] E. M. Arnett, *Progr. Phys. Org. Chem.*, **1**, 223 (1963).

[4] G. Frankel, *J. Chem. Phys.*, **34**, 1466 (1961).

[5] G. Aksnes and J. E. Prue, *J. Chem. Soc.*, 103 (1959).

[6] H. L. Conley, Jr., and R. B. Martin, *J. Phys. Chem.*, **69**, 2914 (1965).

upon this tripositive complex[7] is 7.2×10^{-3} sec^{-1}, about 170 times faster than for the dipositive cupric complex. That this factor is about twice as large as might be predicted from the difference of one unit of positive charge in the two transition metal ion complexes may be due to only about half the cupric complexes being chelated at any one time or to a greater polarizing power for cobaltic ion at the carbonyl oxygen.

The rate constant from the second paragraph of $10^{2.5}$ sec^{-1} for water attack at carbonyl oxygen protonated ester of unit positive charge exceeds by $10^{6.9}$ and $10^{4.6}$ the respective rate constants for water attack of $10^{-4.4}$ sec^{-1} at the dipositive cupric chelate and $10^{-2.1}$ sec^{-1} at the tripositive cobaltic chelate of glycine ethyl ester. On the basis of the argument so far presented, the large rate advantages for the protonated ester over the transition metal ion chelates suggest that acid-catalyzed ester hydrolysis proceeds much too rapidly to be accounted for by water attack on the small concentrations of preprotonated ester existing in weakly acid solutions. The argument presented is an electrostatic one based on considerations of specific rate constants of species of known charge distribution. It is generally recognized, however, that the polarizing power of the proton even when hydrated is greater than that of metal ions in similar solvents. It is necessary, therefore, to attempt an estimate of the relative charge densities at the carbonyl carbon, where water attack takes place, due to the different polarizing powers of the hydrated proton and cupric or cobaltic ions located at the carbonyl oxygen atom.

The relative σ-bond polarizing powers due to the hydrated proton and cations at an atom attached to oxygen may be estimated from the acid ionization constants for loss of a proton from their respective hydration spheres according to eq 1, where H^+ is an abbreviation for the hydrated proton.

$$M(H_2O)_n{}^Z \rightleftarrows M(H_2O)_{n-1}(OH^-)^{Z-1} + H^+ \tag{1}$$

For M as H^+, Cu^{2+}, and Co^{3+}, the respective pK_a values[8] for eq 1 are -1.7, 7.3, and 1.7, indicating that the polarizing power of the proton is about $10^{9.0}$ and $10^{3.4}$ times greater than for the aquo metal cations. However, when cobaltic ion is combined with five nitrogen donors, its polarizing power appears much decreased since for eq 2 pK_a[8] is 6.2. A steady increase in pK_a for ionization from water

$$Co(NH_3)_5H_2O^{3+} \rightleftarrows Co(NH_3)_5OH^{2+} + H^+ \tag{2}$$

occurs as nitrogen is substituted for oxygen donors about the cobaltic ion.[8] The hydrated proton appears to be $10^{7.9}$ times more polarizing than cobaltic ion with five nitrogen donors. No corresponding information seems to be available for cupric ion where the pK_a for coordinated water ionization from a complex with one nitrogen donor is desired. Allowing one log unit per nitrogen donor, we may estimate the hydrated proton to be 10^{10} times more polarizing than cupric ion with one nitrogen donor.

Rate constants for water attack at carbonyl oxygen protonated esters may now be calculated by multiplying the rate constant for water attack at each metal ion chelate of glycine ethyl ester by the relative polarizing powers of hydrated proton and cation. We obtain for the cobaltic chelate, $10^{-2.1} \times 10^{7.9} = 10^{5.8}$ sec^{-1} and for the cupric chelate, $10^{-4.4} \times 10^{10} = 10^{5.6}$ sec^{-1}. These values are about $10^{3.2}$ times greater than the experimental value of $10^{2.5}$ sec^{-1} so that this last rate constant appears to be an attainable one. We conclude that acid-catalyzed hydrolysis of ordinary esters may well proceed by water attack on preprotonated ester.

Because of the symmetrical nature of ester hydrolysis and formation reactions[9] and the similar values of carboxylic acid and ester ionization constants[8] as suggested by their comparable dipole moments,[10] the conclusion advanced here is applicable to the formation as well as the hydrolysis reaction. Partitioning of the tetrahedral carbon addition intermediate to yield ester or acid is comparable in both acid[11] and metal ion[12] catalyzed reactions so that the conclusions are not affected by a change in the rate-limiting step.

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N-Sulfonylamines

Sir:

We wish to report the generation of a new class of electrophilic amine derivatives designated as N-sulfonylamines ($RN{=}SO_2$). Unlike the related N-sulfinylamines[1] ($RN{=}S{=}O$), the N-sulfonylamines studied so far appear to be stable only at low temperature in solution. Ethylsulfamoyl chloride[2] (II) reacts rapidly with 1 equiv of triethylamine in toluene solution at −78° to afford a nearly quantitative yield of precipitated triethylamine hydrochloride. Filtration at this temperature provides solutions of I, which undergoes mildly exothermic polymerization upon warming. Successful interception of the N-sulfonylethylamine was accomplished by the addition to this solution of a nucleophile such as aniline which results in a 21% yield of N-phenyl-N′-ethylsulfamide (III).[3,4]

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[2] Prepared by the interaction of ethylamine hydrochloride and sulfuryl chloride in diethyl ether solution: N. C. Hansen, *Acta Chem. Scand.*, **17**, 2141 (9163); G. Schulze and G. Weiss, Belgian Patent 667,311 (1966).

[3] Identified by mixture melting point (where appropriate) and infrared spectral comparison with an authentic sample.

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