handed or a right-handed screw sense in the 3_{10} structure.

The trough at 235 mμ observed for I in methanol suggests the 233-mμ minimum found for α-helical polypeptides,[9] while the 227-mμ trough in HFA suggests the minimum found for certain proteins thought to have the β-sheet structure.[10] The 205-mμ trough found in all our systems is probably the same as that found for the random-coil[9] structure of polypeptides.

The mean residue rotations observed for small peptides at the extrema of the optical rotatory dispersion curves have been found to be much smaller than in the cases for high molecular weight polyamino acids. This is to be expected, since the amide groups involved in intramolecular hydrogen bonding in these peptides are so engaged on only one of their sides,[2] leaving the other free to interact with solvent. Our data on dipeptides and tripeptides are similar in nature but do not indicate the presence of such secondary structure as has been found for tetra- and higher peptides.[2]

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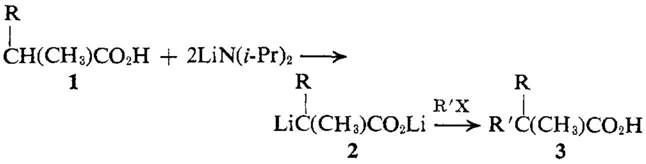
Metalated Carboxylic Acids. I. Alkylation

Sir:

Aliphatic carboxylic acids and their salts have not been reported to metalate by a simple, generalized process on treatment with Grignard reagents,[1] organolithium reagents,[2,3] or alkali metal amides.[4] Except for salts of acetic acid[4a] and methacrylic acid,[4b] homologous metalated carboxylic acid salts apparently decompose under conditions used for their formation.[4a] Arylacetic acids, as well as their salts and simple carboxyl derivatives, are exceptional in that they produce "Ivanov" reagents on treatment with Grignard reagents or "Ivanov-like" reagents on treatment with other organometallic agents.[5] Phenylacetic acid has been metalated also with sodium (potassium) amide in ammonia.[6] This communication reports the metalation of aliphatic carboxylic acids to be a general phenomenon which is illustrated by the metalation of isobutyric acid[7] (**1**, R = CH_3) on treatment with lithium diisopropylamide.



$$\underset{\mathbf{1}}{\overset{\text{R}}{\text{CH}}(\text{CH}_3)\text{CO}_2\text{H}} + 2\text{LiN}(i\text{-Pr})_2 \longrightarrow \underset{\mathbf{2}}{\text{Li}\overset{\text{R}}{\text{C}}(\text{CH}_3)\text{CO}_2\text{Li}} \xrightarrow{\text{R'X}} \underset{\mathbf{3}}{\text{R'}\overset{\text{R}}{\text{C}}(\text{CH}_3)\text{CO}_2\text{H}}$$

The addition of isobutyric acid, **1** (R = CH_3), to lithium diisopropylamide, prepared from *n*-butyllithium and diisopropylamine, in tetrahydrofuran–heptane (hexane) at 0° produced **2** (R = CH_3) in homogeneous solution. Metalated isobutyric acid, **2** (R = CH_3), is apparently quite stable in the indicated solvent system at least up to 40°. The success of the metalation can be attributed in large measure to the use of lithium as metal, which, among other factors, confers favorable solubility on the metalated species.[8] Homogeneous solutions of **2** (R = CH_3) of at least 1 *M* in tetrahydrofuran–heptane (hexane) (1:5, v/v) have been prepared. The existence of **2** (R = CH_3) could be demonstrated by alkylation with *n*-butyl bromide (iodide) to produce 2,2-dimethylhexanoic acid in preparatively useful yields (Table I).

The alkylation of **2** (R = CH_3) has synthetic utility for the preparation of highly hindered trialkylacetic acids. Several examples are illustrated in Table I. Useful yields were obtained for those alkyl halides that were not especially susceptible to elimination or related side reactions. The alkylation of dilithium derivative **2** (R = CH_3) appears to be superior, even for such a sterically hindered example, to the alkylation of sodium sodioacetate[9] and more direct than most syntheses of trialkylacetic acids.[10] The yields of product are comparable to those obtained for the alkylation of lithioisobutyronitrile.[11] When **2** (R = CH_3) was similarly treated with aliphatic dihalides, the tetramethyldicarboxylic acids listed in Table II were obtained.[12]

Table I. Synthesis of Alkyldimethylacetic Acids from Metalated Isobutyric Acid

$$\text{LiC(CH}_3)_2\text{CO}_2\text{Li} + \text{RX} \longrightarrow \text{RC(CH}_3)_2\text{CO}_2\text{H}$$

Alkylating agent	Alkyldimethylacetic acid,[a] %
n-Butyl bromide	80
n-Butyl iodide	89
Allyl chloride	61
Benzyl chloride	46
β-Bromophenetole	41
2-Bromoethyl ethyl ether	66
Cyclohexyl bromide	6

[a] Satisfactory combustion analyses and consistent spectral data have been obtained for all products, as well as satisfactory comparison of physical properties with reported values. Yields are based on purified product.

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[1] M. S. Kharasch and O. Reinmuth, "Grignard Reactions of Nonmetallic Substances," Prentice-Hall, Inc., New York, N. Y., 1954, p 948 ff.

[2] The reaction of carboxylic acids with 2 equiv of an organolithium has preparative value for the synthesis of ketones, particularly methyl ketones.[3]

[3] E. A. Braude, *Progr. Org. Chem.*, **3**, 188 (1955).

[4] (a) D. O. DePree and R. D. Closson, *J. Am. Chem. Soc.*, **80**, 2311 (1958); (b) D. O. DePree, *ibid.*, **82**, 721 (1960); (c) R. D. Closson, U. S. Patent 2,850,528 (1958); D. O. DePree and W. R. Ellis, U. S. Patent 2,852,559 (1958); R. D. Closson and D. O. DePree, U. S. Patent 2,918,494 (1959).

[5] The terms "Ivanov" and "Ivanov-like" reagents apparently originated with F. F. Blicke and H. Raffelson, *J. Am. Chem. Soc.*, **74**, 1730 (1952). For a recent review see P. E. Wright, Ph.D. Dissertation, University of Michigan, 1959; *Dissertation Abstr.*, **21**, 3642 (1960).

[6] C. R. Hauser and W. J. Chambers, *J. Am. Chem. Soc.*, **78**, 4942 (1956); W. J. Chambers, W. R. Brasen, and C. R. Hauser, *ibid.*, **79**, 879 (1957).

[7] The metalation of other aliphatic, olefinic, araliphatic, and toluic acids will be subjects of future reports.

[8] Contrast with the poor solubility of sodium sodioacetate.[4a,9]

[9] H. Hopff and H. Diethelm, *Ann.*, **691**, 61 (1966).

[10] C. Hennart, *Ind. Chim. Belge*, **30**, 820 (1965), reviews the various syntheses.

[11] K. Ziegler and H. Ohlinger, *Ann.*, **495**, 84 (1932).

[12] A. M Durr, Jr., H. H. Eby, and M. S. Newman, U. S. Patent 3,210,404 (1965); *Chem. Abstr.*, **64**, 1968*d* (1966) (for comparison with the preparation of α,α,ω,ω-tetraalkyldicarboxylic acids by alkylation of esters).

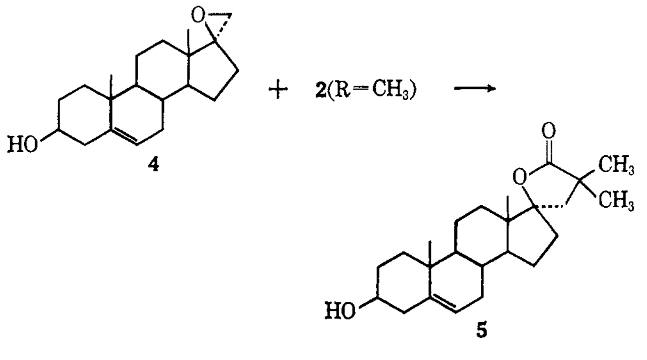
Table II. Synthesis of Tetramethyldicarboxylic Acids from Metalated Isobutyric Acid

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

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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[14] J. A. Marshall and D. J. Schaeffer, *ibid.*, **30**, 3642 (1965).

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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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