trans isomer showed an apparent molecular weight of only 269–311 at the higher molality of 0.0691–0.1159.

Registry No.—Benzenethiol, 108-98-5; indene, 95-13-6; trans,[20] mp 101°, 32819-87-7; trans,[20] mp 158°, 32819-88-8; cis,[20] mp 158°, 32819-85-5; cis,[20] mp 146°, 32785-03-8; diphenyl thioacetal of 1-indanone, 32819-86-6.

[20] See Figure 3.

α Anions of Carboxylic Acids. II. The Formation and Alkylation of α-Metalated Aliphatic Acids

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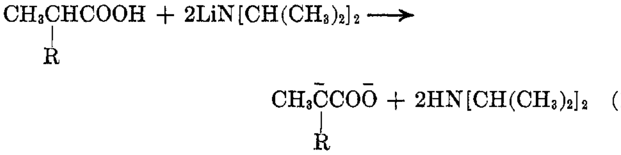
Received January 13, 1971

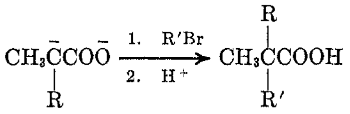
The degree to which α anions of straight chain and α-branched chain carboxylic acids are formed by reaction with lithium diisopropylamide in solutions of tetrahydrofuran (THF) and tetrahydrofuran containing hexamethylphosphoramide (HMPA) was established by deuteration and carbonation. The determinations indicate the extent of the metalations of straight and α-branched chain acids to be unaffected by HMPA. Straight chain acids are converted to α anions to the extent of 95% in either solvent system. HMPA assists the carbanion reactions by solubilizing insoluble dianions of straight chain acids and by accelerating their rate of alkylation in producing nearly quantitative yields of the α-branched acids. α-Branched chain acids are α metalated in both solvent media to the extent of 30–45% at −5 to 25° and to about 93% at 50°. The dianions of α-branched acids are soluble in THF without HMPA but the presence of HMPA is deleterious for these alkylations by inducing the elimination reaction between alkyl halide and the bases (unreacted amide and dianion). A steric effect in branched dianions increases olefin formation with increasing size of the alkyl substituents at the expense of alkylation. High conversions of α-branched acids to dianions are obtained in THF at 50°. The dianions alkylate to trialkylacetic acids in yields exceeding 90%. α lithiation of sodium and potassium alkanoates is less satisfactory, but alkylation of the dianions proceeds to high yields of α-branched acids. Carbonation and deuteration of α-lithiocarboxylates are recommended as a preparative synthesis of α-alkylmalonic acids and α-deuterioalkanoic acids, respectively. Monoolefinic acids containing isolated double bonds (oleic and undecylenic acids) α alkylate normally, but the more reactive double bonds in linoleic acid are altered by the strong base to produce a complex mixture of alkylated acids.

The direct introduction of a substituent into the α-carbon position in fatty acids has been limited to a few reactions, namely ionic halogenation,[2] sulfonation,[2] and free-radical substitution reactions.[3,4] An extensive series of classical, indirect reactions generally use the displacement of a facile leaving group at the 2 position, but these reactions require the initial introduction of the displaceable substituent at the designated site. Carbanions are highly reactive species that should provide the countervailing method for accomplishing α substitutions of fatty acids directly and propitiously. The unique opportunities α carbanions offer to derivatizations of fatty acids has not been exploited owing to the lack of adequate methods for generating this species.

Several groups of investigators have formerly undertaken the preparation of dianions of small chain carboxylic acids with limited success. In 1938, Morton, Fallwell, and Palmer[5] first demonstrated the intermediate formation of the α anion of sodium phenylacetate and sodium hexanoate using phenylsodium as the base for the abstraction of α-methylene protons. The presence of α anions as the reactive intermediates was demonstrated by carbonation that yielded phenylmalonic acid (60%) and butylmalonic acid (17%), respectively. Subsequently, other investigators have α metalated sodium phenylacetate with sodium (potassium) amide in liquid ammonia[6] and sodium acetate with sodamide at 200°.[7] The latter reaction was unsuitable in its application to propionic, *n*-butyric, and isobutyric acids.[7] Some of the preparative difficulties in these metalations were finally surmounted by Creger[8] who prepared α anions of isobutyric and 2-methylbutyric acids by means of lithium diisopropylamide in tetrahydrofuran (THF)–hexane (heptane) solution (eq 1). A single-step, high-yield synthesis



$$\underset{\displaystyle R}{CH_3CHCOOH} + 2LiN[CH(CH_3)_2]_2 \longrightarrow \underset{\displaystyle R}{CH_3\bar{C}CO\bar{O}} + 2HN[CH(CH_3)_2]_2 \quad (1)$$



$$CH_3\underset{\displaystyle R}{\bar{C}}CO\bar{O} \xrightarrow[2.\ H^+]{1.\ R'Br} CH_3\overset{\displaystyle R}{\underset{\displaystyle R'}{C}}COOH \quad (2)$$

R = Me, Et

of trialkylacetic acids by α alkylation of the dianions (eq 2) provided Creger with an elegant demonstration of the utility of his method.

In our preliminary publication[9] we reported the limitations of Creger's method in its application to straight chain and α-branched chain carboxylic acids from which low yields (30–60%) of dialkyl and trialkyl acetic acids, respectively, were obtained. The metalated straight-chain acids were insoluble in THF, but readily dissolved by the addition of the highly dipolar

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[1] Eastern Marketing and Nutrition Research Division, Agricultural Research Service, U. S. Department of Agriculture.

[2] H. J. Harwood, *Chem. Rev.*, **62**, 99 (1962).

[3] G. Sosnovsky, "Free Radical Reactions in Preparative Organic Chemistry," Macmillan, New York, N. Y., 1964, pp 137–139.

[4] C. Walling, "Free Radicals in Solution," Wiley, New York, N. Y., 1957, p 363.

[5] A. A. Morton, F. Fallwell, Jr., and L. Palmer, *J. Amer. Chem. Soc.*, **60**, 1426 (1938).

[6] C. R. Hauser and W. J. Chambers, *ibid.*, **78**, 4942 (1956).

[7] D. O. DePree and R. D. Closson, *ibid.*, **80**, 2311 (1958).

[8] P. L. Creger, *ibid.*, **89**, 2500 (1967).

[9] P. E. Pfeffer and L. S. Silbert, *J. Org. Chem.*, **35**, 262 (1970).

solvent, hexamethylphosphoramide (HMPA). This modification resulted in the preparation of dialkylacetic acids in excess of 90% yields. In contrast to dianions of straight chain acids, the dianions of α-branched carboxylic acids were soluble in THF, but in the presence of HMPA they alkylated to trialkyl acetic acids in yields that rapidly diminished with increasing size of the α branch chain. For example, yields as low as 9% alkylated product were observed in the case of 2-butylnonanoic acid. Shortly following this publication, Creger[10] reported an extension of his method to straight-chain acids whereby the dianions were prepared in the form of mixed lithium-sodium salts that alkylated to dialkylacetic acids in good yields.

The extreme difference in behavior of HMPA in alkylations of straight and α-branched acids indicated the need to clarify the role of the dipolar solvent and to find conditions for the quantitative formation of α anions of long-chain α-branched acids. Two sets of reactions for the straight and α-branched acids clearly required inquiry. One set of reactions is concerned with determining the extent of the metalations in the presence and absence of HMPA in THF solutions by the use of deuterium oxide (eq 3) and carbon dioxide (eq 4) as quenching agents. The second is a study of

$$RR'\overset{-}{C}CO\overset{-}{O} \xrightarrow{D_2O} RR'CDCOO^- \xrightarrow{H_3O^+} RR'CDCOOH \qquad (3)$$

$$RR'\overset{-}{C}CO\overset{-}{O} \xrightarrow[2.\ H_3O^+]{1.\ CO_2} RR'C(COOH)_2 \qquad (4)$$

$$R = \text{Alkyl};\ R' = \text{H, Alkyl}$$

the subsequent alkylations of the metalated species in the two-solvent systems. The present paper reports these results and includes in the study an extension of these reactions to a few examples of olefinic acids.

Results

Straight-Chain Acids.—The conversions of straight-chain acids to α anions were determined by deuterium oxide and carbon dioxide quenchings. The results of these analyses are recorded in Table I for measurements obtained on three examples of straight-chain acids. The results produced by the two techniques on the two long-chain carboxylic acids are in good agreement and provide an average value of 94% α anion formation in the solvent systems THF and THF-HMPA. The α metalations are completed within 30 min.

The results for α alkylations of straight-chain acids in THF in the presence and absence of HMPA are assembled in Table II. Conversions of the carboxylic acids to α-alkylated products are nearly quantitative in solutions of HMPA (1 mol per mol of carboxylic acid). Compared to the low conversions observed in THF alone, the conversions of hexanoic acid, chosen as representative of homologous straight-chain series, are optimum at mole equivalents of HMPA and carboxylic acid (Figure 1). The alkylations were completed in 90 min, as determined by periodic sampling of the reaction containing equimolar concentrations of HMPA and acid. Higher mole ratios afford no advantage aside from solubilizing less soluble carboxylate salts and dianions as shown by the examples of acetic and stearic acids (Table II).

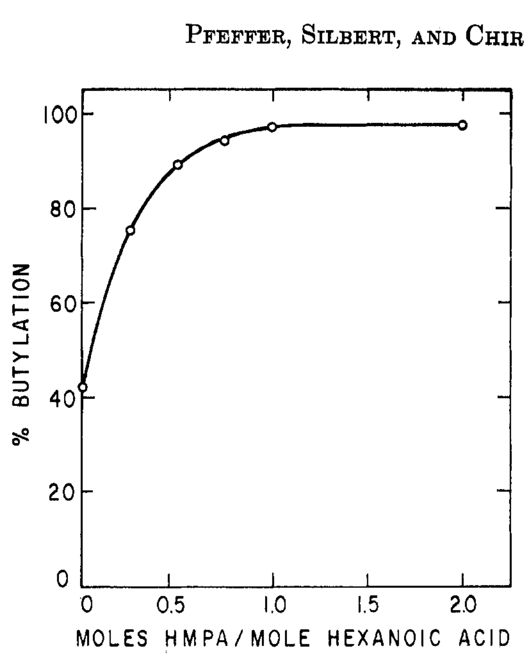

Figure 1.—α Butylation of hexanoic acid as a function of HMPA concentration. Dianion of hexanoic acid (0.247 *M*) and butyl bromide (0.370 *M*) in THF at 25°; time of reaction, 90 min.

Table I

Determination of α-Anion Content. Reaction of Metalated Straight-Chain Carboxylic Acids with D_2O and CO_2[a]

Dianion	α-D Acid, %[b-d] THF	α-D Acid, %[b-d] THF-HMPA	Dioic Acid, %[d,e] THF	Dioic Acid, %[d,e] THF-HMPA
(Acetate)				
$LiCH_2CO_2Li$			41	65[f]
(Hexanoate)				
$CH_3(CH_2)_3CHLiCO_2Li$	93	94	95[g]	
(Nonanoate)				
$CH_3(CH_2)_6CHLiCO_2Li$	92	92	95[h,i]	95[h,i]

[a] Anion solutions were quenched after stirring for 30 min at 25°. [b] Determined by mass spectral and nmr analyses of the corresponding methyl esters. [c] Accuracy ±2%. [d] Dianion preparations with 1 mol of HMPA, except for acetate. [e] Determination by glpc analysis of the corresponding methyl esters except for acetate. [f] Dianion preparation with 3 mol of HMPA; analysis by nmr. [g] *n*-Butylmalonic acid, mp 102–103° (lit. mp 103–104): P. E. Verkade and J. Coops, Jr., *Recl. Trav. Chim. Pays-Bas*, **49**, 568 (1930). [h] *n*-Heptylmalonic acid, mp 96–97° (lit. mp 83–95°): I. C. Promé and C. Asselineau, *Bull. Soc. Chim. Fr.*, **1964**, (1964). [i] The same value was obtained after heating for 5 hr at 50° followed by carbonation.

α-Branched Acids.—The results for the α metalations of α-branched acids, with and without HMPA, as determined by deuteration and carbonation quenchings are recorded in Table III. The values derived by the two techniques give good agreement for the individual acids in both solvent systems.

The data for α alkylations of a homologous series of α-branched hexanoic acids are assembled in Table IV and graphed in Figure 2 for comparison with the corresponding data obtained for α alkylations in HMPA solutions.

Olefinic Acids.—The monounsaturated acids, 10-undecenoic and *cis*-9-octadecenoic acids, were converted to their α anions and the acids then were regenerated by aqueous quenching. The recovered acids

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[10] P. L. Creger, *J. Amer. Chem. Soc.*, **92**, 1397 (1970).

TABLE II

PREPARATIONS OF α-ALKYL CARBOXYLIC ACIDS

Reactants			Yield, %[b]		Bp, °C (mm), or mp, °C
Acid	Alkyl bromide	Product acid[a]	THF	THF-HMPA	
CH_3CO_2H	$CH_3(CH_2)_3Br$	*n*-Hexanoic		34,[c] 58,[d] 82[e]	
$CH_3CH_2CO_2H$	$CH_3(CH_2)_3Br$	2-Methylhexanoic	53[f]	78	64[g]
$CH_3(CH_2)_4CO_2H$	CH_3CH_2Br	2-Ethylhexanoic		98[h]	70 (0.1)[i]
$CH_3(CH_2)_4CO_2H$	$CH_3(CH_2)_2Br$	2-Propylhexanoic		98[h]	92 (0.3)[j]
$CH_3(CH_2)_4CO_2H$	$CH_3(CH_2)_3Br$	2-Butylhexanoic	42[h]	90, 97[h]	89 (0.1)[k]
$CH_3(CH_2)_5CO_2H$	$CH_3(CH_2)_3Br$	2-Butylheptanoic	43	93	70–73 (30)[l]
$CH_3(CH_2)_7CO_2H$	CH_3CH_2Br	2-Ethylnonanoic			108–110 (0.2)[m]
$CH_3(CH_2)_7CO_2H$	$CH_3(CH_2)_2Br$	2-Propylnonanoic			124 (0.2)[n]
$CH_3(CH_2)_7CO_2H$	$CH_3(CH_2)_3Br$	2-Butylnonanoic	34	91	128–130 (0.2)[o]
$CH_3(CH_2)_7CO_2H$	$CH_3(CH_2)_7Br$	2-Heptyldecanoic		92	167–168 (0.5)[p]
$CH_3(CH_2)_{12}CO_2H$	$CH_3(CH_2)_3Br$	2-Butyltetradecanoic	29	87	172–173 (0.5)[q]
$CH_3(CH_2)_{16}CO_2H$	$CH_3(CH_2)_3Br$	2-Butyloctadecanoic	44	87[r]	45–46
$CH_2{=}CH(CH_2)_8CO_2H$	$CH_3(CH_2)_3Br$	2-Butyl-10-undecenoic		90	145–147 (0.5)
cis $CH_3(CH_2)_7CH{=}CH(CH_2)_7CO_2H$	$CH_3(CH_2)_3Br$	2-Butyl-*cis*-9-octadecenoic	25	90	199–200 (0.05)

[a] All compounds gave acceptable C and H analyses (±0.4). The data were made available to the referees and to the Editor. [b] Alkylations of dianions conducted at 25° for 90 min. Yields are based on distilled, recrystallized or chromatographed product except where indicated. [c] Using 1 mol of HMPA per mol of acid; obtained 17% 2-butylhexanoic acid as by-product. [d] Using 3 mol of HMPA per mol of acid; obtained 7% 2-butylhexanoic acid as by-product. [e] Using 3 mol of HMPA per mol of acid; dianion prepared at 50° (2 hr) prior to alkylation; obtained 8% 2-butylhexanoic acid as by-product. [f] This yield was reported in ref 10 for the alkylation of the mixed Li–Na metalated acid. [g] Lit. bp 105° (5 mm): P. A. Levene and R. E. Marker, *J. Biol. Chem.*, **98,** 5 (1932). [h] Conversions determined by glpc. [i] Lit. bp 88–89° (1 mm): K. Shishido, K. Sei, and H. Nozaki, *J. Org. Chem.*, **27,** 2681 (1962). [j] Lit. bp 97° (1 mm): J. Wotiz, *J. Amer. Chem. Soc.*, **73,** 693 (1951). [k] Lit. bp 137–138° (12 mm): R. Friedling, S. N. Aminov, and A. Terent'ev, *Dokl. Akad. Nauk SSSR,* **156** (5), 1133 (1964). [l] Lit. bp 170–173° (28 mm): M. Sy, N. Buu-Hoi, and N. Dat-Xuong, *C. R. Acad. Sci.*, **239,** 1224 (1954). [m] Lit. bp 117–118° (5–6 mm): E. Bowden and H. Adkins, *J. Amer. Chem. Soc.*, **56,** 689 (1934). [n] Lit. bp 160–162° (10 mm): J. Braun, H. Kräper, and H. Weinhaus, *Chem. Ber.*, **62B,** 2880 (1929). [o] Lit. bp 148–149° (3 mm): B. F. Armendt and R. Adams, *J. Amer. Chem. Soc.*, **52,** 1289 (1930). [p] Lit. bp 184–187° (2–3 mm): C. M. Creer and R. Adams, *ibid.*, **52,** 2541 (1930). [q] Lit. bp 180–184° (4 mm): W. M. Stanley, M. S. Jay, and R. Adams, *ibid.*, **51,** 1261 (1929). [r] Insolubility of the dianion was overcome by using 2 mol of HMPA per mol of acid.

TABLE III

DETERMINATION OF α-ANION CONTENT.[a] REACTION OF METALATED α-BRANCHED CHAIN NONANOIC ACIDS WITH D_2O AND CO_2

	α-D Acid, %[b,c]		Dioic acid		
Dianion	THF	THF-HMPA	Product	Conversion, %[d]	Mp, °C
2-Methylhexanoic[e]			Methylbutyl malonic	78	97–98[f]
2-Ethylnonanoic	42		Ethylheptyl malonic	43, 72[g]	105–106
2-Propylnonanoic	41	40	Propylheptyl malonic	43, 67,[g] 15[h]	110.0–111.5[i]
2-Butylnonanoic	34, 92[k]	36	Butylheptyl malonic	38, 86,[j] 94[k]	117.5–118[l]
2-Octylnonanoic (2-Heptyldecanoic)		28	Octylheptyl malonic	31, 93[k]	*m*

[a] 30 min allotted for metalations before termination. [b] Analysis by mass spectrometry. [c] Accuracy ±2%. [d] Determined on the methyl esters by glpc; same results obtained for carbonation of the α anion in the presence and absence of HMPA. [e] Used in place of 2-methylnonanoic acid. [f] Lit. mp 98–99°: A. Norris and T. W. J. Tucker, *J. Amer. Chem. Soc.*, **55,** 4700 (1933). [g] Carbonation carried out on dianion following removal of volatile reaction products. [h] Dianion prepared with 6 mol of lithium diisopropylamide per mol of acid. [i] Lit. mp 110–111°: J. Braun, H. Kräper, and H. Wienhaus, *Chem. Ber.*, **62B,** 2880 (1929). [j] Six hours allotted for metalation before carbonation. [k] Metalation conducted at 50° for 2 hr; same result obtained in presence or absence of HMPA. [l] Lit. mp 117°: P. A. Levene and F. A. Taylor, *J. Biol. Chem.*, **54,** 351 (1922). [m] Oily product purified by chromatography on a silica gel column gave satisfactory elemental analysis.

showed no change in position of the double bond on the basis of the following analyses. The acids were oxidatively cleaved and the resulting mono- and dibasic acids obtained were quantitatively analyzed by glpc. Trans absorption of the double bond at 965 cm^{-1} was absent in both examples, indicating neither migration nor isomerization of the double bond.

Following confirmation of the integrity of the double bond in the dianions of 10-undecenoic and *cis*-9-octadecenoic acids, butylation gave their respective α-butyl unsaturated acids (Table II).

Linoleic acid (*cis*-9-*cis*-12-octadecadienoic acid) reacts with lithium diisopropylamide to give a highly colored anion solution. Butylation of this anion solution resulted in a complicated glpc pattern of alkylated and nonalkylated products.

Discussion

α Metalations.—Lithium salts of straight-chain carboxylic acids (monoanions) have low solubilities in THF; for example, lithium nonanoate has a solubility of 1.5 mg/100 ml in THF that increases to only 20 mg/100 ml in solutions containing 2 molar equiv of HMPA. Despite their low concentrations in these media, the salts α lithiate in both media to the extent of 95%. The resultant solutions were colloidal (milky) in THF and homogeneous (clear) in the presence of HMPA. Carboxylate salts at the extreme ends of the series, namely, lithium acetate and lithium octadecanoate, metalated poorly in THF solutions, but high conversions were obtained in HMPA solutions.

HMPA participates in the metalation process by solubilizing the dianions. Organolithium compounds

TABLE IV

PREPARATIONS OF TRIALKYL ACETIC ACIDS[a]

Reactant acid	Product[b,c]	Registry no.	Yield, %, 25° [d]	Yield, %, 50° [e]	Bp, °C (mm)
2-Methylhexanoic	2-Methyl-2-butylhexanoic	17306-50-2	85		97 (0.1)
2-Ethylhexanoic	2-Ethyl-2-butylhexanoic	32970-62-0	78		136–137 (1)
2-Propylhexanoic	2-Propyl-2-butylhexanoic	33021-12-4	72	93	142 (0.5)
2-Butylheptanoic	2,2-Dibutylheptanoic	32970-63-1	68	93	140–142 (0.5)
2-Butylnonanoic	2,2-Dibutylnonanoic	32970-64-2	66	92	160–161 (0.2)

[a] α-Butylation of the α-branched acids using butyl bromide. [b] Separation of product from unreacted acid is effected by shaking the mixture with 10% $NaHCO_3$ solution (see Experimental Section). [c] All compounds gave acceptable C and H analyses (±0.4). The data were made available to the referees and to the Editor. [d] Preparation of dianion in THF without HMPA at 25° for 30 min before alkylation. [e] Preparation of dianion in THF without HMPA at 50° for 2 hr before alkylation.

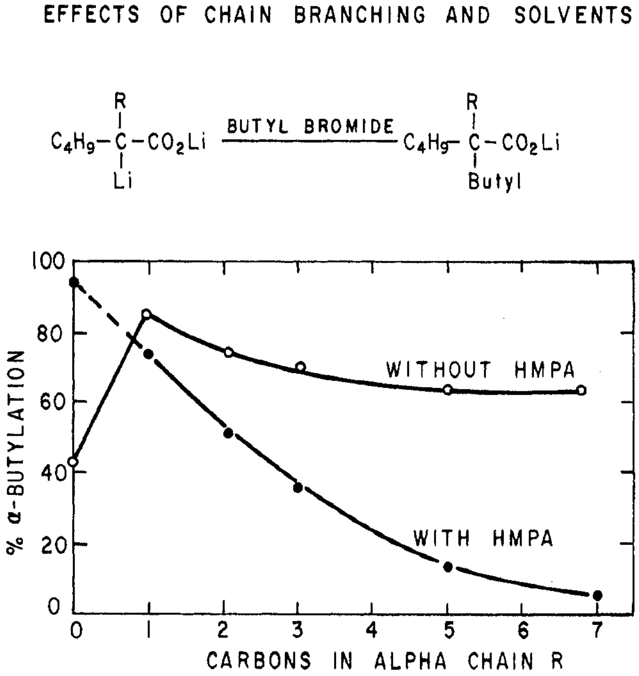
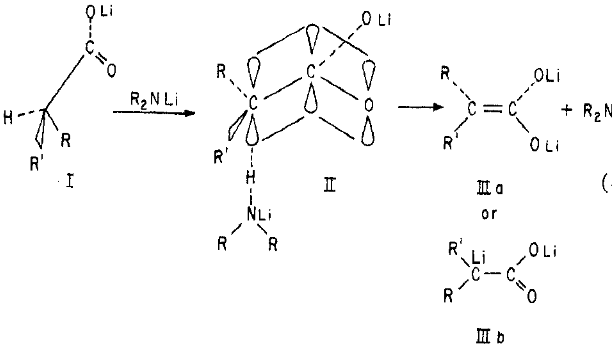


Figure 2.—Effect of HMPA on the per cent butylation of α-branched hexanoic acids. Reaction at 26° using 1 mol of HMPA per mol of acid.

are known to associate to higher molecular weight aggregates, their degrees of polymerization (n = 2–6) varying with solvent and structure.[11] The polymeric structures are altered by polar solvents by interactions that lengthen or cleave the electrostatic bond of the ion pair.[12] The interaction between certain organolithium compounds has been described as an association between one molecule of HMPA and the counterion in the solvent-separated ion pair.[13] From the limited data acquired, the behavior of α-lithiated lithium salts of carboxylic acids may be explained in these terms. They exhibit high degrees of association in THF (n = 65–250) based on molecular weight averages for dianions prepared from α and β olefinic acids).[14] These extensively high associations would account for their colloidal state in THF. It may be inferred from their solubilization in HMPA solutions that the aggregations are disrupted to simpler species by a molecular association with the dipolar solvent. Although the plot in Figure 1 was derived to determine the optimum HMPA–dianion relationship for alkylating dianions (at a prescribed set of conditions), the attainment of maximum yield where HMPA and dianion are present in equimolar amounts suggests a 1:1 correspondence in their association.

The lithium salts of α-branched chain acids, in contrast to straight-chain acids, are completely soluble in THF. The rate of dianion formation of the α-branched acids in comparison with the straight-chain members under similar reaction conditions (25°, quenched after 30 min) is slower and depends upon the size of their alkyl branchings, *e.g.*, yields diminished from α-methyl (78%) to α-octyl (31%) (Table III and Figure 2). Longer times were required to complete the metalations at room temperature as observed with α-butylnonanoic acid, which produced 86% dianion in 6 hr. Proton abstraction from the α position in the branched-chain acids is apparently hindered by classical steric effects, although these may possibly include stereoelectronic factors related to the type noted for α deprotonation of cyclic ketones.[15] The α-alkyl substituents attached to the acetate moiety in salt I (eq 5) hinder formation of the transition state II in which the p orbitals are in contiguous overlap. The activation energy of this barrier is surmounted by a small elevation in temperature to 50°. Under these conditions α metalations are approximately quantitative (94%) in 2 hr.



(5)

The formation of carbanions from their "carbon acid" in metalation reactions may be simply treated as an equilibrium process.[16] Accordingly, α metalation of carboxylate salts may be formulated as an equilibrium in accordance with eq 6. Our efforts to improve

$$RR'CHCOO^- + R_2N^- \rightleftharpoons RR'C^-COO^- + R_2NH \quad (6)$$

metalations of α-branched acids at ambient temperature by treatment of the reaction as an equilibrium phenomenon gave only limited success. In accord-

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(11) J. M. Mallan and R. L. Bebb, *Chem. Rev.*, **69**, 693 (1969).

(12) H. E. Zaugg and A. D. Schaefer, *J. Amer. Chem. Soc.*, **87**, 1857 (1965).

(13) L. L. Chan and J. Smid, *ibid.*, **90**, 4654 (1968).

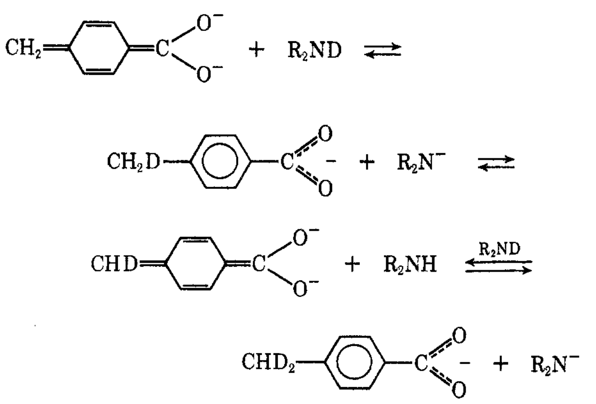
(14) P. E. Pfeffer and L. S. Silbert, *J. Org. Chem.*, **36**, 3290 (1971).

(15) E. J. Corey and R. A. Sneen, *J. Amer. Chem. Soc.*, **78**, 6269 (1956).

(16) D. J. Cram, "Fundamentals of Carbanion Chemistry," Academic Press, New York, N. Y., 1965.

ance with the mass law, removal of the volatile diisopropylamine is expected to shift the reaction to completion. The removal of the amine and solvent at 25° *in vacuo* did indeed increase the α anion content from about 43 to 68%, although prolonged evacuation gave no further improvement in dianion content. Increasing the relative concentration of reactants on either side of the equilibrium was not successful. On the left side of the equation, increasing the concentration of lithium diisopropylamide from 2 to 6 mol per mol of acid decreased the dianion content to 15%, a result that is contrary to expectation; on the right side of the equation addition of the large excess of diisopropylamine (6 mol per mol of acid) to a solution of dianion (94% content based on carbonation) had no effect on the dianion content. The extent of formation of α-branched dianion exceeds 90% but the reaction is evidently not prescribed by simple equilibrium considerations.

Additional but incomplete evidence for an equilibrium process was suggested from our lithiation studies carried out on the aromatic acids, *o*- and *p*-toluic acids.[17] Proton abstraction from the methyl substituent leads to dianion formation by extensive conjugation. Deuteration of the dianions by *N*-deuteriodiisopropylamine results in multiple exchange with the methyl protons as indicated by eq 7 for two stages of exchange.


(7)

α Alkylations.—In view of the nearly quantitative conversions of straight-chain acids to dianions in either solvent system, α alkylations would be expected to be essentially quantitative in both systems. Quantitative conversion was observed in HMPA solution in which alkylation was completed in 90 min at 25° with 1.5 mol of butyl bromide per mol of carboxylic acid. In THF alone under the same conditions, conversions were only 30–50%. Attempts to quantitate alkylations in THF by imposing more forceful conditions, *e.g.*, conducting alkylations with 3 mol of butyl bromide per mol of acid at 50° for 5 hr, did not improve yields beyond 87%. These comparative experiments illustrate that HMPA, in addition to solubilizing dianions, also accelerates the alkylation rates. A preliminary kinetic investigation of the alkylations was attempted to determine the rates in THF and THF–HMPA solutions but the complexity of the kinetics precluded their continuation for our purpose. The examination, nevertheless, confirmed a rate enhancement in HMPA relative to THF: it was observed that the dianion of nonanoic acid (0.163 *M*) in THF at 10° is half butylated by butyl bromide (0.393 *M*) in 140 min compared to only 20 min in THF containing HMPA (0.163 *M*). The largest alkylation rate occurred when HMPA and dianion are equimolar (Figure 1).

Detailed studies on organolithium reagents underscore the complexity of their reactions.[11,19] In the reported cases, the reactions are described by fractional orders which are in accord with the aggregation state of the organolithium. The aggregation state is disrupted by complexation with polar solvents in formation of a solvent-separated ion pair of higher reactivity than the original aggregate. A strong dipolar solvent like HMPA (μ = 4.30 D[20]) should accordingly be more efficient in associations with metalated carboxylates than THF (μ = 1.7 D[21]) by forming a complex of higher reactivity, presumably a solvent-separated ion pair.

Straight-chain acids are cleanly monoalkylated in HMPA solutions, since the gas chromatograms show no significant evidence of dialkylated products. For example, propionic acid gave only 0.4% dialkylation in comparison with 14% dialkylation obtained from the mixed lithium–sodium salts of the dianions.[10] Even acetic acid may be primarily monoalkylated to the straight-chain homolog, if extensive conversion of acetate to dianion is obtained before alkyl halide is added (eq 8a). In THF α metalation of lithium acetate is slow and incomplete so that alkylation to the straight-chain homolog (primary product) encounters competition by metalation (eq 8b) and alkylation of the homolog to α-branched acid (secondary product). The combined effects of HMPA and temperature on controlling acetate conversion to dianion is made evident by the following observations. Metalation and butylation of acetic acid at 25° in THF containing 1 molar equiv of HMPA gave a mixture of 34% *n*-hexa-

$$\overset{-}{C}H_2COO^- + RBr \longrightarrow RCH_2COO^- + Br^- \qquad (8a)$$

$$[(CH_3)_2CH]_2\overset{-}{N} + RCH_2COO^- \longrightarrow [(CH_3)_2CH]_2NH + R\overset{-}{C}HCOO^- \qquad (8b)$$

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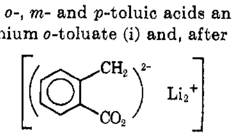
[17] Unpublished studies: Prior to completing this work, Creger[18] had reported the α-lithiation of *o*-, *m*- and *p*-toluic acids and dimethylbenzoic acid. He prepared lithiated lithium *o*-toluate (i) and, after removal of volatile components, obtained nmr evidence for the retention of diisopropylamine in the ratio of one molecule of amine per molecule of *o*-toluic acid. Treatment of the dianion resulted in no incorporation of deuterium in the isolated *o*-toluic acid. This was explained by his proposal of a molecular complex formed between the dianionic species and diisopropylamine wherein the amino proton is exclusively transferred in a noncompetitive process. In our limited study, we α-lithiated *o*- and *p*-toluic acids and by carbonation determined that 25 and 75% dianions, respectively, had formed. After quenching the dianions with deuterium oxide, analysis of the isolated acids showed 6 and 32% deuterium (d_1 only) incorporation in *o*- and *p*-toluic acids, respectively. These experiments did indicate the occurrence of a competitive proton-transference process, although it is less extensive than in an aliphatic dianion. The evidence of exchange was acquired on the *p*-toluate dianion and was obtained by the sequence of operations involving removal of all volatile components after dianion formation, injection of *N*-deuteriodiisopropylamine, reevacuation for removal of volatile components, and finally quenching with H_2O. Deuterium incorporation (mass spectral analysis) was observed in 52% of the molecules in a distribution consisting of 31.7% d_1, 15.9% d_2, and 4.8% d_3.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noic and 17% α-butylhexanoic acids, whereas in 3 molar equiv of HMPA, the primary product increased to 58% and the secondary product diminished to 7%. Reaction at 50° in 3 molar equiv of HMPA gave a mixture of 82% *n*-hexanoic and 8% α-butylhexanoic acids that together represent 98% alkylation.

α-Metalated α-branched acids are slowly alkylated in THF at 25° in formation of trialkyl acetic acids in moderate yields [65–75% for the series with the exception of the α-methyl branch (85%)]. Because the yield of alkylated product (Table IV) is about twice the initial carbanion concentration at room temperature (Table III), it is apparent that α anion is progressively generated during the course of alkylation. Since the formation of tertiary carbanions is accelerated at 50° and approaches completion at this temperature, alkylations to trialkyl acetic acid derivatives are correspondingly rapid and complete.

In HMPA solutions, the yields of α-butylated products derived from a series of α-alkyl hexanoic acids sharply decline as the alkyl branch is increased from methyl (75%) to heptyl (9%) (Figure 2). The decline in yield is accompanied by the formation of olefin which stems from attack on alkyl bromide by unreacted diisopropylamide and tertiary carbanion and which occurs to a greater extent in HMPA. The evidence for the participation of both bases in the elimination reaction is indicated by the following results. (i) In solutions without carboxylic acid, elimination from alkyl halide by amide base in THF–HMPA was about twice the elimination noted in THF without cosolvent. In the butylation of 2-butylheptanoic acid in THF–HMPA, (ii) the dianion preparation of 34% content gave only 15% alkylation but approximately 80% elimination, whereas (iii) the dianion preparation of 94% content gave 50% alkylation and 50% elimination. (iv) The dianion preparation of 94% content in THF–HMPA, stripped free of diisopropylamine to eliminate the possibility of amide reformation, also on butylation gave 50:50 alkylation–elimination. The results of i and ii demonstrate elimination through the agency of amide base and those of iii and iv by α-branched dianion. The mechanism of the elimination reaction is unclear but it is unquestionably assisted by HMPA, which seems to amplify the steric effect of branching in the dianion.

Effect of Mixed Cations. -The low solubilities of sodium and potassium carboxylates illustrated by potassium nonanoate (1.5 mg/100 ml THF and 17 mg/100 ml THF containing 2 molar equiv of HMPA) are comparable to the low solubilities of lithium carboxylates. The poorly solubilized sodium and potassium salts α-lithiate in THF in 2 hr to the extent of 25 and 1% dianion, respectively (Table V), compared to 95% in 30 min for lithium salts. After metalation of the potassium salt, the dianion content was determined by carbonation and alkylation on the separate solution and solid phases of the heterogeneous mixtures and observed to be present only in the solution phase. HMPA (2 molar equiv) increased metalation from 1 to 14% (Table V). Efforts to increase dianion formation by heating to 40° resulted in considerable loss of dianion by reaction with solvent. Apparently, dianions associated with higher atomic weight counterions are more ionic and more reactive with solvents than dianions associated exclusively with lithium counterions.

TABLE V

REACTIONS OF α-METALATED SALTS OF NONANOIC ACID IN THF.[a] EFFECT OF COUNTERION ON YIELDS

	Yield, %		
Counterions	D_2O	CO_2	RBr
$[Li_2]^{2+}$	95	98	~50, 95 (HMPA)[b]
$[LiNa]^{2+}$	23[c]	10,[c] 27[d]	86[d]
$[LiK]^{2+}$	0[c,e]	1,[c,f] 14 (HMPA)[c,g]	100,[c] 15 (HMPA)[c,g]

[a] Reactions in THF solution except where indicated. [b] 1 molar equiv of HMPA. [c] Sodium and potassium nonanoates were prepared by neutralization in methanol and the isolated salts were dried over P_2O_5 prior to use. [d] Sodium salt prepared *in situ* by NaH neutralization of nonanoic acid. [e] Extent of formation too small for reliable determination. [f] Determined by glpc analysis. [g] 2 molar equiv of HMPA.

Because of the limited metalation of potassium salts, lithium diisopropylamide is largely unreacted and potentially available to dehydrohalogenate alkyl halides. Nevertheless, α alkylations of potassium salts are quantitative in THF when solutions contain excess amide and alkyl halide. The surprising quantitative nature of this reaction indicates the continuous generation of dianion during alkylation and the dianion's relatively greater reactivity toward halide. In the presence of HMPA, dehydrohalogenation by amide predominates, since dianion formation is insufficiently increased.

Analytical and Preparative Utility of Quenching Agents.[22]—Alkylations provide useful information on dianions but cannot be used for quantitative measurements of dianion content. The metalated carboxylate salts are not quenched by alkyl halides but metalation continues simultaneously with alkylation of the dianions. On the other hand, the results of carbonation and deuteration of α-lithioalkanoates (Tables I and III) indicate the utility of these methods for dianion analyses. Reliance on carbonation and deuteration as measures of dianion content was based on the nearly quantitative metalations obtained from straight-chain carboxylates in THF–HMPA at −5° and from α-branched chain carboxylates in THF at 50°.

Carbonation and deuteration have some limitations in dianion analyses, although carbonation is generally more sensitive. A striking difference between these methods of analysis is revealed by α-lithiated *p*-toluate, which carbonated to the extent of 75% compared to 32% deuteration.[17] In some instances, deuteration may provide a more reliable index of dianion content; for example, other workers have shown that carbonation values of sodium α-sodioacetate were about half those of deuteration.[23,24] In that case, complications inherent in the technique were evident since the carbonations of a heterogeneous solid phase system were forced at high temperatures. By comparison, carbonations of the analogous α-lithiated acetate were mild when carried out in liquid media below room temperature, the results (Table I) being in reasonable accord with alkylations (Table III).

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Quantitative carbonations and deuterations of dianions should be advantageous in synthesis for preparations of alkyl malonic acids and α-deuterioalkanoic acids, respectively. The method is particularly valuable for preparations of α-deuterio acids compared to alternative methods that require high temperatures and long reaction times and are less specific for monodeuteration.[25-27]

Olefinic Acids.—Isolated double bonds in olefinic acids such as 10-undecenoic and *cis*-9-octadecenoic acids are not altered positionally or geometrically in formation of their dianions by lithium diisopropylamide. These olefinic acids are alkylated to good yields of α-branched unsaturated acids (see Table II).

A highly colored solution is produced when linoleic acid is metalated. Alkylation of the dianion results in a complicated mixture of products. The reactive double bonds of this acid are altered by strong basic media, since it is well established that skipped double bonds in this acid conjugate and isomerize geometrically by proton abstraction from the reactive 11-carbon position.[28] The products from this reaction were not further characterized but are expected to be mixtures of α-branched and chain-branched diolefinic acids containing isomerized double bonds.

Experimental Section

Materials.—Tetrahydrofuran was obtained dry and oxygen free by distillation from a solution of ketyl (benzophenone and sodium). Hexamethylphosphoramide was distilled from sodium hydride at reduced pressure and stored over molecular sieves under a nitrogen atmosphere. *n*-Butyllithium (1.6 *M* in hexane solution) was obtained from Foote Mineral Co. Diisopropylamine was distilled and stored over 5A molecular sieves prior to use.

Equipment.—Analyses by glpc were conducted on an F & M Model 500 gas chromatograph equipped with a thermal conductivity detector and disc integrator and using the following columns: 6 ft × $^1/_4$ in. 25% DEGA, 2% H_3PO_4; 6 ft × $^3/_{16}$ in. 10% Dow Corning 710 silicone oil, 2% H_3PO_4.

***α*-Anion Preparation.**—The following procedure described for the preparation of *n*-nonanoic acid in THF–HMPA solution is typical of the general method used for both straight-chain and α-branched-chain acids. The method was appropriately modified, where warranted, for variations in temperature and use or concentration of HMPA.

Anhydrous THF (65 ml) and diisopropylamine (9.8 g, 0.098 mol) were added to a dry flask purged with nitrogen and maintained under a nitrogen atmosphere. After cooling the mixture to −20°, *n*-butyllithium in *n*-hexane solution (60 ml of 1.6 *M*, 0.098 mol) was added in a controlled manner to prevent the temperature from exceeding 0°. *n*-Nonanoic acid (6.95 g, 0.044 mol) was added dropwise while maintaining the temperature of the reaction below 0°. A milky white solution formed that turned homogeneous after the addition of HMPA (9 ml, 0.05 mol). The reaction was completed by stirring at room temperature for 30 min.

***α*-Anion Analysis.**—THF and THF–HMPA solutions (50 ml each) containing the dianion of a carboxylic acid (0.0125 mol) were prepared from carboxylic acid (0.0125 mol) and lithium diisopropylamide (0.0265 mol) by the above procedure.

A. D_2O Quenching.—An aliquot (10 ml) was sampled, quenched in D_2O (9 ml, 0.45 mol), and stirred for 5 min. After acidification with 10% HCl and three extractions of the aqueous phase with petroleum ether (bp 30-60°) (10-ml portions), the petroleum ether solutions were combined and extracted with 10% HCl to facilitate removal of HMPA and with five portions of water to reestablish the protium content of the carboxylic acid grouping. The organic layer was dried, the solvent was evaporated, and the residue was distilled. Methyl esters of the acids were prepared by means of diazomethane and passed through a preparative gas chromatograph (3 ft × $^3/_8$ in. column, 10% DEGS), and the trapped samples were examined for their deuterium content by mass spectrometry. Methyl esters of the original nondeuterated acids were used as standards for examination of their P + 1 peak contribution.

B. CO_2 Quenching.—The remainder of the dianion solution was treated with CO_2 (bone dry) for 1 hr at −10° in preparation of the malonic acid derivatives. Because of the low solubility of several dioic acids in petroleum ether, diethyl ether was used as the solvent in the work-up and for isolation of the acids. The malonic acid derivatives and unreacted acid were esterified with diazomethane and the methyl ester mixture was examined by glpc.

Preparation of *α*-Alkyl Carboxylic Acids from Straight-Chain Acids. A. With HMPA.—The following preparation of 2-butylnonanoic acid in THF solution containing HMPA illustrates the general procedure.

n-Butyl bromide (6.05 g, 0.044 mol) was added rapidly at 0° to the dianion of nonanoic acid prepared in HMPA solution (see α-Anion Preparation). The exothermicity of the reaction elevated the temperature to 18°. The reaction was completed by stirring the mixture for 1.5 hr at room temperature. The product was isolated by neutralization with ice-cold 10% HCl (150 ml) and two extractions with petroleum ether (175-ml portions). (Note: sufficient HCl should be present to neutralize HMPA as well as the alkali.) The combined organic layers were washed three times with 10% HCl (100-ml portions), water, and saturated sodium chloride solutions. The organic layer was dried over anhydrous sodium sulfate and the solvent was evaporated after filtration to obtain the crude product (9.1 g, 97% yield) consisting of 2-butylnonanoic acid (99%) and nonanoic, acid (1%) by glpc analysis. Pure 2-butylnonanoic acid (8.5 g, 90% yield) was obtained by distillation, bp 128–130° (0.2 mm).

B. Without HMPA.—The procedure is identical with the above method except for the omission of HMPA in the reaction. The anion solution remained cloudy and heterogeneous. The addition of *n*-butyl bromide was not accompanied by a significant, exotherm due to the slow rate of reaction. After work-up, distillation of the resulting product gave pure 2-butylnonanoic acid (3.2 g, 34%).

Lithiation and Alkylation of Potassium Nonanoate.—The following reaction described for potassium nonanoate may be applied to other potassium and sodium salts of monocarboxylic acids.

Potassium nonanoate (8.6 g, 0.044 mol) on addition to a solution of lithium diisopropylamide (0.066 mol) in THF (65 ml) at 25° formed the dianion in association with mixed lithium–potassium counterions. Butylation with butyl bromide (13.7 g, 0.1 mol), was monitored by glpc analysis and was quantitatively completed in 2 hr.

Preparation of Trialkyl Acetic Acids From *α*-Alkyl Carboxylic Acids. A. General Method.—Solutions of metalated α-branched carboxylic acids were prepared as described under α-Anion Preparations. Formation of these dianions was completed by heating at 50° for 2 hr. The alkylations and general work-up were carried out as described above. Final separation of the trialkyl acetic acid from unreacted dialkyl acetic acid was effected by preferential aqueous sodium bicarbonate extraction of the latter acid from a petroleum ether solution of the mixture.

B. "Equilibrium" Method *via* Removal of Diisopropylamine.—A solution of 2-propylnonanoic acid (1 g, 0.005 mol) was metalated with lithium diisopropylamide (1.06 g, 0.01 mol) in THF (20 ml) by the described procedure. After stirring the solution at room temperature for 30 min, the solvent and liberated diisopropylamine were removed at room temperature *in vacuo* (0.1 mm) in a film evaporator and the volatile components were recovered in an acetone–Dry Ice trap. The crystalline salts were redissolved in anhydrous THF and carbonated at −10° for 1 hr. The products were isolated by elementary work-up procedures and esterified by diazomethane. Analysis by glpc indicated that the ester mixture consisted of 2-propyl-2-heptyl dimethyl malonate (67.8%) and 2-propyl methyl pelargonate (32.2%).

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Acidification with dilute HCl of the trapped volatile solution, evaporation of solvent and water by azeotropic distillation, and drying for 5 hr at 120° yielded diisopropylamine hydrochloride (1.12 g) equivalent to 65% metalation.

A control experiment was carried out on diisopropylamine (1 g, 0.01 m) as a check on the method for the quantitative isolation of the amine salt and to ensure the absence of water of hydration after drying. Acidification, isolation of the salt, and drying gave a dry salt weighing 1.31 g (theory 1.35 g).

C. Isolation of Olefin.—A dianion solution prepared from 2-butylheptanoic acid (3.0 g, 0.016 mol) was alkylated at 25° with 1-bromooctane (3.08 g, 0.016 mol) in THF–HMPA in the manner formerly described. After reaction (1.5 hr), the solution was acidified and extracted with petroleum ether and the extracts were reextracted sequentially with dilute HCl, water, and 5% sodium hydroxide solution. The solvent was removed by distillation and the residue was carefully distilled (bp 120–121°) to give a colorless liquid fraction (1.45 g, 80% yield) which was confirmed to be 1-octene by glpc retention time, ir, and nmr. The same procedure carried out at 25° in the absence of HMPA gave 0.54 g of 1-octene (30% yield).

α Metalation of Oleic Acid. Analysis for Double Bond Migration (von Rudloff Method).[29]—Oleic acid was α metalated in the prescribed manner and regenerated from the salt by acidification. Samples (0.035 g each) of the treated oleic acid and of untreated oleic acid as a control were separately weighed into Erlenmeyer flasks (50 ml capacity). To each flask were added the oxidant solution [7 ml of an aqueous solution comprised of sodium periodate (21 g) and potassium permanganate (25 ml of 0.1 *N*) diluted to 1 l.], potassium carbonate (0.009 g in 1.4 ml of water), and *tert*-butyl alcohol (8.5 ml). The solutions were stirred (72 hr) until clear. A pellet of potassium hydroxide was added to each solution, the alcohol was removed on a steam bath under a stream of nitrogen, and the solutions were acidified with several drops of concentrated HCl. The materials were extracted three times with chloroform (25 ml portions) and dried, and the combined solutions were evaporated to the organic acid residues under a nitrogen stream. These were each esterified to the methyl esters and analyzed *via* glpc. The samples gave identical chromatograms consisting of only two products, dimethyl azelate and methyl pelargonate, in agreement with the retention times for the authentic compounds.

Registry No.—2-Butyloctadecanoic acid, 33021-13-5; 2-butyl-10-undecenoic acid, 32970-65-3; 2-butyl-*cis*-9-octadecenoic acid, 33016-09-0; ethylheptylmalonic acid, 32970-66-4; actylheptylmalonic acid, 32970-67-5.

Acknowledgment.—The authors express their appreciation to S. F. Osman and C. J. Dooley for the mass spectral analyses.

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Metal Ion Promoted Dehydrohalogenation of Secondary Alkyl Halides

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Received July 12, 1971

Orientation in dehydrohalogenation of 2-alkyl iodides and bromides by silver nitrate, perchlorate, acetate, and nitrite and mercuric nitrate in aprotic and protic solvents under conditions of kinetic control has been determined. Strong preference for formation of internal olefins and *trans*- to *cis*-2-alkene ratios of 1.1–2.8 were observed. In aprotic solvents, metal halide catalysis was negligible, and orientation was somewhat affected by variation of the metal ion, the metal counterion, the leaving group, the solvent, and the 2-alkyl group. Reactions in protic solvents were complicated by metal halide catalysis. The mechanism of metal ion promoted dehydrohalogenation of 2-alkyl halides is discussed.

Electrophilic assistance by mercuric and silver ions in replacement reactions of alkyl halides has been the subject of numerous investigations in recent years.[3–16] Kinetic and stereochemical studies have revealed that silver salt catalyzed substitutions of 2-alkyl halides do not proceed by a simple carbonium ion mechanism.[5,6,12–14] Such conclusions raise questions concerning the mechanism of the competing elimination reactions, about which little is known. An investigation of metal ion promoted dehydrohalogenation from 2-alkyl halides therefore seemed warranted.

Of the available methods for studying β eliminations from 2-substituted alkanes, determination of the effect of experimental variables upon positional and geometrical orientation[17,18] of the olefinic products appeared most suitable for an initial examination.

In only two instances has orientation in metal ion assisted elimination from 2-alkyl halides been considered. Unfortunately, in the reported olefin-forming reaction of 2-bromobutane with silver nitrate in water and *tert*-butyl alcohol,[20] possible complication due to catalysis by silver bromide[16,21] was apparently ignored. In the second study, reaction of 2-octyl bromide with silver nitrate in acetonitrile produced approximately 2% 1-octene and 14% 2-octenes.[12] The isomeric 2-octenes were not separated.

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