

Esterification by Alkylation of Carboxylate Salts. Influence of Steric Factors and Other Parameters on Reaction Rates¹

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Alkylation of carboxylate salts with alkyl halides in dipolar aprotic solvents is an efficient method of esterification. The reaction kinetics were studied to determine the effects of variation of such parameters as gegenions (alkali metals), solvents, alkyl halide, and carboxylate structures. The reactions of numerous unhindered and hindered carboxylates with alkyl halides show small variation in rate relative to the large divergent rates observed in conventional acid-catalyzed esterification of the corresponding carboxylic acids. However, over a restricted range, the rate data for a group of carboxylate structures provided a correlation with increasing steric bulk leading to a converse application of Newman's rule of six. Rate constants for salts of aromatic acids were correlated well by Hammett parameters.

The classical acid-catalyzed methods of esterification of carboxylic acids with alcohols are recognized as having limited applications.^{3,4} They are generally ineffective for the esterification of sterically hindered acids and of compounds containing acid-sensitive functional groups. Esterification of most carboxylic acids with diazoalkanes⁴ or with the newer reagents, 1-alkyl-3-*p*-tolyltriazenes,⁵ are effective but restricted in practicality to analytical preparations of methyl, ethyl, and propyl esters. Other recently developed procedures of reacting carboxylic acids with triethyloxonium fluoroborate⁶ or of carboxylate ion with dimethyl sulfate,⁷ while applicable to sterically hindered acids, are similarly limited to the preparations of ethyl and methyl esters, respectively. Less direct methods that require severe thermal conditions or conversion to more reactive intermediates such as the acid chlorides, the 2-butyl chlorosulfite,⁸ or the tetramethylammonium salt⁴ lack quantitation, convenience, and generality.

Reaction of metal salts of carboxylic acids with organic halides is a simple, though neglected, method of preparing esters. Although several reports⁹⁻¹¹ have disclaimed the value of metal salt alkylations, recent studies¹²⁻¹⁵ have uncovered the method's general potentialities. Earlier uses of silver or alkali metal carboxylate salts in the presence or absence of amine^{16,17} or in aprotic solvent^{18,19} were confined to preparations of esters derived from the reactive benzyl or allylic halides. However, quaternary ammonium salts and highly polar aprotic solvents, either alone or in combination, have been shown to facilitate the direct alkylation of carboxylate salts for preparations of glycidyl esters,^{20,21} lactones,²² triglycerides,^{23,24} and straight-chain aliphatic esters.^{9,10,12,13,25-28a}

We have recently introduced and developed carboxylate salt alkylations in hexamethylphosphoramide^{28b} (HMPA)-ethanol cosolvent as a rapid, quantitative method of preparing esters.¹³ More importantly, we found the method to be uniquely superior for esterifications of highly hindered aliphatic and aromatic acids, the classes of acids that had been bypassed by former investigators of carboxylate salt alkylations. A subsequent report¹⁴ confirmed these findings and provided indications of more rapid alkylations in neat HMPA. A comparable rapid, mild, and quantitative esterification of severely hindered carboxylic acids has been unattainable under acid-catalyzed conditions.²⁹⁻³¹

To date, there has been no systematic and quantitative investigation of rates of carboxylate salt alkylations; all former reaction conditions were determined empirically. The present kinetic study was therefore initiated to acquire essential data for the factors affecting rates including the correlation of structural variations in the carboxylate salts.

Results and Discussion

The second-order alkylation rates of carboxylate salts are influenced by the nature of the cation, solvent, and organic halide. Clarification of the effects of these parameters with model carboxylates was essential for establishing efficient conditions for rate measurements of the series of carboxylate structures.

Carboxylate anions in association with large (soft) counterions are more reactive than with small (hard) counterions because of higher charge separation with the former.³² The extent of the cation effect in salt alkylations was examined under a prescribed set of experimental conditions for which the results are recorded in Table I. Although the

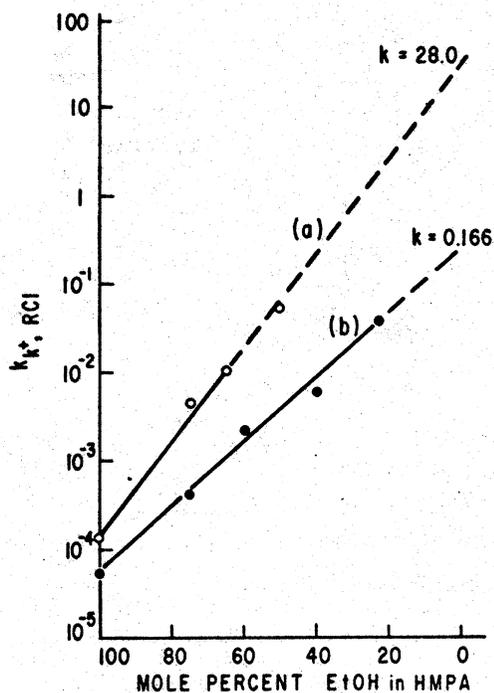


Figure 1. Determination of rate constants for the alkylation of potassium 2-methyl-2-propylpentanoate with (a) 1-iodopentane in mixtures of HMPA–EtOH; (b) 1-bromopentane in HMPA–EtOH. Rate constants k_{K^+} : (a) 28.0 l/mol s and (b) 1.66×10^{-1} l/mol s obtained for the pure aprotic solvents were determined by extrapolation to 0 mol % EtOH concentration.

anticipated order of increasing reactivity $Li < Na < K < Cs$ was observed in the series, the relative acceleration of Cs/Li was only a doubling in rate. Consequently, potassium was chosen as a convenient standard cation for the kinetic measurements obtained in this work.

Alkylation rates with primary alkyl iodides and bromides were inconveniently slow in alcoholic solutions and too rapid in dipolar aprotic solvents for accurate measurements. Attempts to reduce the rates to an acceptable measurement range in the latter solvents by high dilution were unsuccessful owing to inaccuracies in measurement of the potentiometric end points used to follow the changes in carboxylate anion concentration. An effective compromise for moderation of the rates in dipolar aprotic solvents was attained by alcoholic dilution in which the dipolar aprotic solvents ranged in concentration from 0–50 mol % for 1-iodopentane and 0–80 mol % for 1-bromopentane reactions. In each series, the specific rate constant k was plotted against the mole ratio of solvent composition and the absolute value of k in the neat solvent was obtained by extrapolation.³³ The semilogarithm plot of rate constants vs. mol % ethanol–HMPA in Figure 1 illustrates the efficacy of the extrapolation technique.

The structure of the diluent alcohol also influenced the rate. The rate constants increased by more than fourfold from methanol (relative rate 1) to ethanol (3.8) to 2-propanol (4.3) in 25:75 mol % HMPA–alcohol. The rate sequence is apparently a function of the relative differences in hydrogen bonding of the alcohols to carboxylate anion, the more acidic alcohol providing the more effective proton donation.

Rapid and nearly complete alkylation of carboxylate salt with reactive organic halides has been previously demonstrated in nonpolar^{16,17} and polar solvents.^{18,19} With less reactive alkyl halides, the use of dipolar aprotic solvents for alkylation has been marginally successful.^{12,24} Normant¹² obtained only moderate yields of esters in HMPA–tetrahydrofuran mixtures, although he anticipated higher conver-

Table I. Effect of Gengenion on Alkylation Rate of 2-Methyl-2-propylpentanoate with 1-Iodopentane at 60 °C^a

| Gengenion | $k \times 10^3$, l./mol s ^a | Rel rate |
|-----------------|---|----------|
| Cs ⁺ | 4.2 | 2 |
| K ⁺ | 3.3 | 1.5 |
| Na ⁺ | 2.3 | 1.1 |
| Li ⁺ | 2.1 | 1 |

^a Solvent: HMPA–EtOH (1:1 v/v).

Table II. Rates of Alkylation in Dipolar Aprotic Solvents. Reaction of 1-Chlorohexane and Potassium 3,3-Dimethyl-2-ethylbutanoate at 60 °C

| Solvent | $k \times 10^2$, l./mol s | k_{HMPA}/k_s ^a |
|--------------------|----------------------------|-----------------------------|
| HMPA | 8.2 | 1 |
| NMP ^b | 1.2 | 6.8 |
| Me ₂ SO | 1.2 | 6.8 |
| DMF | 0.83 | 9.8 |

^a k_s indicates other solvents in series. ^b *N*-methylpyrrolidone.

Table III. Halogen Leaving Group Effect on the Alkylation Rate of Potassium 2-Methyl-2-propylpentanoate in HMPA at 60 °C

| Primary alkyl halide | k , l./mol s ^a | Rel rate |
|----------------------|-----------------------------|----------|
| 1-Iodopentane | 28.0 | 587 |
| 1-Bromopentane | 0.166 | 35 |
| 1-Chlorohexane | 0.00470 ^b | 1 |

^a Rate constant obtained by the graphical extrapolation of the alcohol dilution rate data (Figure 1). ^b Measured directly in pure HMPA.

sions at higher concentrations. The method was subsequently applied by Mitchell²⁴ for preparations of triglycerides that were obtained in low to moderate yields by reaction of sodium carboxylate with mono- and diacyloxychloropropanes in neat HMPA, *N,N*-dimethylformamide (DMF), or dimethyl sulfoxide (Me₂SO). In the present solvent study, potassium 3,3-dimethyl-2-ethylbutanoate was selected as the model reactant and 1-chlorohexane as the unactivated alkyl halide. The results of alkylations at 60 °C in four dipolar aprotic solvents are listed in Table II. Under these conditions, no reaction took place in pure ethanol as expected, although other workers^{9,24} had reported forcing the reaction between unactivated alkyl chlorides and carboxylate anions at elevated temperatures up to 165 °C. In our present studies, we have found HMPA to be the most effective solvent for halogen displacement. The rates of displacement were tenfold greater than in DMF and sevenfold greater than in either Me₂SO or *N*-methylpyrrolidone (NMP). The order of increasing effectiveness of the solvents on anion reactivity paralleled the order of their corresponding potassium solvation potential described by Parker and Owensby.³⁴ Thus, the greater cation separation induced by more effective solvation of the potassium counterion generated a relatively more reactive carboxylate anion.

The order of reactivity of halogen in organic halides in S_N2 reactions is $I > Br > Cl$. The order is also observed for alkylation of potassium 2-methyl-2-propylpentanoate with primary halide (Table III) whereby iodide and bromide react 590 and 35 times, respectively, more rapidly than chloride. While the rate constant for the alkyl chloride alkylation could be determined in pure HMPA, the rate constants of the very rapid bromide and iodide alkylations ne-

Table IV. Comparison of Alkylation of Potassium Carboxylates in Me₂SO with Acid-Catalyzed Esterification of Free Carboxylic Acids in Methanol

| Registry no. | Carboxylic acid | pK _a | $k_{K^+,RCI} \times 10^3$, l/mol s ^a | $k_{K^+,RI}$, l/mol s ^b | $k_{H^+,MeOH}$, l/mol s ^c | "6" number | $k_{K^+,RI}^d / k_{H^+,MeOH}$ |
|--------------|--|-----------------|---|--|--|---------------|-------------------------------|
| 327-62-8 | CH ₃ CH ₂ CO ₂ H | 5.93 | 4.61 | 2.70 | 0.440 | 0 | 6.13 |
| 19455-23-3 | (CH ₃) ₃ CCO ₂ H | 6.45 | 4.90 | 2.8 | 0.019 | 0 | 147 |
| 19455-00-6 | CH ₃ (CH ₂) ₄ CO ₂ H | 5.90 | 5.50 | 3.2 | 0.260 | 3 | 12.3 |
| 58220-00-1 | (CH ₃ CH ₂ CH ₂) ₂ (CH ₃)CCO ₂ H | 6.59 | 7.00 | 4.10 ^e | | 6 | |
| 58220-01-2 | CH ₃ CH ₂ CH ₂ CH ₂ (CH ₃ CH ₂ CH ₂)- CHCO ₂ H | 6.37 | 6.95 | 4.07 | 0.0048 | 6 | 900 |
| 58220-02-3 | (CH ₃) ₃ CCH ₂ CO ₂ H | 6.26 | 8.40 | 4.93 | 0.012 | 9 | 400 |
| 58220-03-4 | (CH ₃) ₃ CCH(CH ₂ CH ₃)CO ₂ H | 6.50 | 11.7 | 6.86 | <4.0 × 10 ⁻⁵ | 12 | >1.7 × 10 ⁵ |
| 58220-04-5 | [(CH ₃) ₂ CH] ₂ CHCO ₂ H | 6.48 | 10.2 | 5.98 | <4.0 × 10 ⁻⁵ | 15 | >2.1 × 10 ⁵ |
| 58220-05-6 | [(CH ₃) ₂ CH]CH[(CH ₃) ₃ C]CO ₂ H | 6.76 | 14.5 | 8.51 | <4.0 × 10 ⁻⁵ | 15 | >2.1 × 10 ⁵ |
| 58220-06-7 | [(CH ₃) ₂ CH] ₃ CCO ₂ H | 7.36 | | | | 18 | |
| 58220-08-9 | 9(10)-Carbomethoxystearic acid | | 4.6 | 2.70 | | 3 | |
| 58267-05-3 | Methyl 9(10)-Carboxystearate | | 9.9 | 5.81 | | 6 | |
| 58220-07-8 | (E)-CH ₃ CH ₂ CH ₂ CH=CHCO ₂ H | | 2.50 | 1.46 | | 3 | |
| 58229-38-2 | (E)-CH ₃ CH ₂ CH=CHCH ₂ CO ₂ H | | 2.71 | 1.59 | | 2 | |
| 112-80-1 | (Z)-CH ₃ (CH ₂) ₇ CH=CH(CH ₂) ₇ C- O ₂ H | | 7.60 | 4.46 | | 3 | |

^a Rate constants for reaction with 1-chlorohexane were determined at 60 °C over 3 half-lives. ^b $k_{K^+,RI}$ (rate constant with 1-iodopentane) was calculated by multiplication of $k_{K^+,RCI}$ by the appropriate conversion factor 587. ^c Data from Loening et al. (ref 30). All rates have been corrected to 60 °C. ^d $k_{K^+,RI}/k_{H^+,MeOH}$ is the relative rate of alkylation with 1-iodopentane compared with acid-catalyzed methanol esterification. ^e Note that multiplication of this rate by the appropriate conversion factor obtained for k_{HMPA}/k_{Me_2SO} (Table III) yields 27.8, the value obtained in the extrapolation of the plot in Figure 1.

cessitated determination by the alcohol dilution-extrapolation method described above.

Reaction of a long-chain primary alkyl halide, 1-iododecane, and potassium 2-methyl-2-propylpentanoate in HMPA (60 °C) gave no indication of a competitive elimination process as shown by the absence of decene. The corresponding reaction with a long-chain secondary alkyl halide, 2-bromooctane, under the same conditions produced appreciable quantities of octene (36%) and starting free acid. The same amount of olefin was also produced at 25 °C. Although an earlier report¹⁴ has demonstrated the quantitative formation of ester in alkylations of carboxylate salts with secondary halides, it should be emphasized that these reactions were performed in solutions containing both base and alkyl halide in excess. In the latter work, competitive elimination has undoubtedly taken place, but since the carboxylic acid produced is rapidly deprotonated by excess base it is not lost and alkylation may be quantitative. Although the reaction may be deemed useful for the preparation of secondary alkyl esters, the rates with secondary halides were not determined because of the complications of the dehydrohalogenations.

Elucidation of rates with variation in cation, solvent, and halide permit the establishment of optimum alkylation conditions for preparative use as well as for kinetic measurements. The combination of alkyl iodides and cesium salts in HMPA offers the most rapid alkylations. The rate data, however, may permit more practical choices. For the kinetic measurements of a series of carboxylic acid structures, our choice of potassium counterion, primary alkyl chloride, and Me₂SO was considered propitious for accurate measurements in a convenient concentration range and time span. The rate constants reported for 1-iodopentane alkylations $k_{K^+,RI}$ are calculated values obtained by multiplying the appropriate chloride alkylation rate constant $k_{K^+,RCI}$ by the conversion factor derived from data in Figure 1. The results permit a parallel comparison of anion alkylation rates with acid-catalyzed esterification rates for a series of carboxylate structures. The pseudo-second-order rate constants for the acid-catalyzed process k_{H^+} are literature values corrected to 60 °C.²⁹ It is well known that the rate of acid-catalyzed esterification diminishes with increasing steric bulk of the carboxylic acid as indicated by

the data assembled in Table IV, column 4. Comparison of the anion alkylation rate constants (column 3) shows these constants to be larger than the acid-catalyzed rate constants (column 4) and further shows a slight overall increase in the former k 's with an increase in steric bulk. This suggested that steric effects increased the nucleophilicity of the carboxylate anion. The increased reactivity may be attributed to steric inhibition to solvation of the crowded anion.

In an effort to correlate the dependence of carboxylate structure with reactivity, we attempted a comparison of the nucleophilicity of the carboxylate anion as measured by the log $k_{K^+,RCI}$ with proton affinity as characterized by the pK of the corresponding free acids. pK measurements were performed in aqueous methanol (50:50 v/v), a solvent mixture chosen for convenient comparison of the pK data with data of other investigators³¹ (see column 1, Table IV). The pK of 3,3-dimethylbutanoic acid was periodically measured throughout the study to monitor the accuracy of the new constants. A semilog plot of the anion alkylation rate constants of α -alkyl substituted potassium carboxylates vs. apparent pK of the corresponding free carboxylic acids in aqueous methanol at 40 °C showed wide scattering. In two comparative examples, propionate vs. 2,2,2-trimethylacetate and 2-propylhexanoate vs. 2-methyl-2-propylpentanoate, we find the same $k_{K^+,RCI}$ but different pK values. The grid evidently does not provide any discernible correlation between aliphatic carboxylate structure and nucleophilicity.

A well-known method of correlating structure with nucleophilicity is Newman's rule of six or six-number.³⁰ Newman's rule provides an empirical correlation of the steric effects of substituents for reactions at an unsaturated function such as the addition of alcohol to the carbonyl of a carboxylic acid. The rule has also been amplified to include the attacking atom in the six-rule scheme.³⁵ In accordance with the rule, the atoms effectively providing steric hindrance to addition to a carbonyl function are separated from the attacking atom in the transition state by a chain of four atoms. By designating either the carbonyl oxygen or the attacking atom as the "1" position, the interfering atoms will be located at the "6" position (Figure 2a). In the coiled aliphatic chain with normal bond lengths and bond

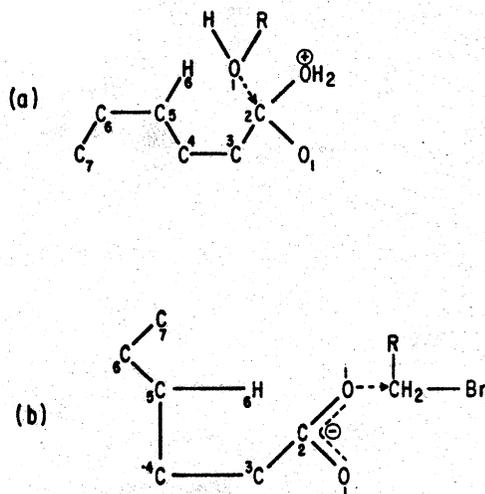


Figure 2. (a) Coiled conformation for transition state of acids in esterification. (b) Coiled conformation for transition state of anions in alkylation.

angles, the attacking atom is blocked more effectively by an atom at the 6 position than at the 5 or 7 positions.³⁰ In the case of a few (three or six) atoms in the 6 positions, rotation about the C₃-C₄ bond displaces the blocking atom from the path of the attacking nucleophile whereas the presence of nine or more atoms in the 6 positions increases the difficulty of twisting the chain into permissible conformations to avoid interactions with the 1 position. In Table IV, columns 4 and 5, it is evident that acid-catalyzed esterification rates are slow ($\sim 10^{-2}$) for a six-number of 9 and rapidly diminish to 10^{-5} - 10^{-6} l/mol s for a six-number of 12 and higher.

In contrast to the order of reactivity for acid-catalyzed esterifications, carboxylate alkylations show the converse effect of an overall increase in rate with increase in bulk (Table IV, columns 3, 4, and 5). Since the six-number is a qualitative expression of steric effects in acid-catalyzed esterification, it seemed reasonable to expect the six-number to also be applicable to a correlation of steric bulk in anion alkylation rate constants except that increasing bulk would be directly related to increasing reactivity. In the coiled conformation of the carboxylate chain in the transition state, the oxygen atoms are designated the 1 positions and the atoms located at the 6 positions exercise steric effects on the cation-anion association. Interference with the cation-anion interaction or exclusion of solvation of the anion increases the anion activity (Figure 2b). Unlike the alcohol oxygen in acid-catalyzed esterification, the reacting carbon atom of the alkylating reagent lies outside the direct sphere of influence of the 6 position atoms and is, therefore, excluded from the numbering scheme. The conformation of the carboxylate anion chain is a five-member ring arrangement compared to the six-atom ring system in acid-catalyzed alcoholysis.

In a plot of $\log k_{K^+, RCl}$ vs. six-number (Figure 3) an excellent linear correlation was obtained for which the correlation coefficient is 0.992. Although the overall effect of steric bulk on rate seems subtle because of the relatively narrow rate constant range, the implications for the consequences of structural crowding are evident. Steric inhibition to solvation induced by increased crowding about the carboxylate center may raise the energy of the ground state relative to the transition state. The larger the observed rate constant, the greater would be the relative degree of "nakedness"^{36,37} associated with the reacting anion. For structurally dissimilar carboxylates having a six-number of zero such as 2,2,2-trimethylacetate (a trialkyl acetate) and

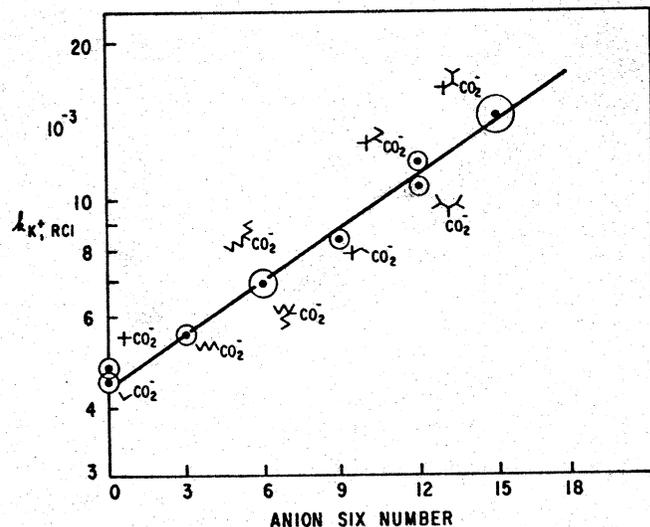
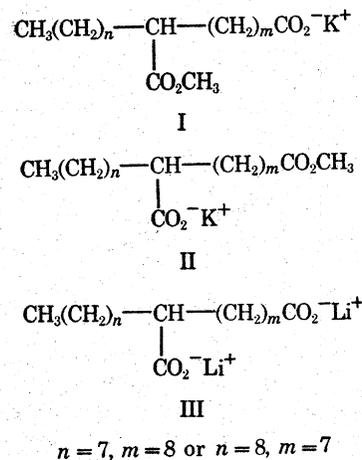


Figure 3. Plot of $\log k_{K^+, RCl}$, l/mol s, for alkyl-substituted potassium carboxylates reacting with 1-chlorohexane in Me₂SO at 60 °C vs. six-number; correlation coefficient 0.992.

propionate (a monoalkyl acetate) or carboxylates with a six-number of 6 such as 2-methyl-2-propylpentanoate (a trialkyl acetate) and 2-propylhexanoate (a dialkyl acetate), the anion six-number correlation necessitates that each pair of anions have the same rate constant. It is evident in Figure 3 that these predictions are in agreement with our findings. On the basis of inductive effects, the more highly α -substituted salts would be expected to react faster than the less substituted members. Inductive effects of aliphatic substitutions at the α carbon, unlike steric crowding at the 6 position, do not appear to exert a measurable change in reactivity. The plot further suggests that both 6-position carbon and hydrogen atoms produce a comparable rate acceleration since all plotted compounds have been classified without regard to the size of the 6-position atom. In contrast, Newman's³⁰ findings showed a larger relative decrease in rate with increase in size of the blocking atom. Based on the excellent correlation given by the $\log k_{K^+, RCl}$ vs. six-number, extrapolation of the plot in Figure 3 permits the prediction of rate constants for the alkylation of many hindered carboxylates.

As an illustration of competitive alkylation for positionally isomeric dibasic acid salts, we studied the reaction of potassium 9(10)-carboxystearate (I) and methyl 9(10)-potassium carboxystearate (II). The results in Table



IV indicate that the internal carboxylate in isomer II is alkylated more than twice as rapidly as the terminal carboxylate of isomer I. The difference in reactivity is further em-

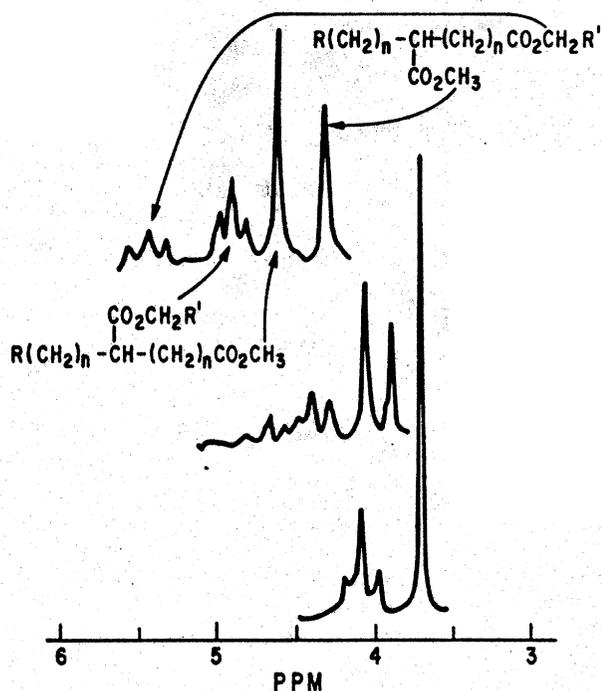


Figure 4. Proton NMR spectrum of a mixture of methyl 9(10)-carboxystearate and pentyl 9(10)-carboxystearate: sample in 350 μ l of CCl_4 ; Me_4Si as internal standard. Lower spectrum, 40 mg of mixed esters. Middle spectrum, 40 mg of mixed esters plus 5 μ l of 0.288 M CCl_4 solution of $\text{Eu}(\text{fod})_3$. Upper spectrum, 40 mg of mixed esters plus 10 μ l of 0.288 M CCl_4 solution of $\text{Eu}(\text{fod})_3$.

phasized by the competitive alkylation of the dilithium salt of 9(10)-carboxystearic acid (III).³⁸ Reaction of III in HMPA with 1 equiv of *n*-pentyl iodide yielded a mixture of unalkylated (16%), monoalkylated (41%), and dialkylated (43%) products.³⁹ After acidification of the reaction mixture, the remaining free carboxylic acid sites were esterified with diazomethane. However, GLC resolution of the mixed esters was unsuccessful. Analysis of the mixture of the two isomeric mixed methyl pentyl esters which was first isolated by preparative GLC as a mixture in a single fraction was performed by proton NMR using $\text{Eu}(\text{fod})_3$ pseudocontact shift reagent. The peak intensities illustrated in Figure 4 revealed that the methyl substitution at the terminal carboxyl group was double the methyl substitution at the central carboxyl group. The product distribution by NMR analysis corroborates the relative alkylation reactivities established by the kinetic data for I and II. Although in this example the alkylation technique does not lend itself to unusually high positional alkylation specificity, the alkylation is distinctly advantageous for the esterification of dioic acids. Specifically, utilizing either half-ester salts such as I or II, it is possible to synthesize positionally pure mixed

diesters, thereby obviating the problem of random transesterification generally associated with acid-catalyzed procedures.⁴⁰

The effect of unsaturation in proximate positions to the carboxylate function was examined for the members listed in Table IV. The rates of alkylation of isomeric unsaturated carboxylates, potassium (*E*)-3-hexenoate and potassium (*E*)-2-hexenoate, were each one-half the rate of potassium hexanoate. However, a double bond located at an isolated position with respect to the reactive site as in potassium (*Z*)-9-octadecenoate does not appear to diminish the reactivity to alkylation. Unexpectedly, the rate constant for potassium (*Z*)-9-octadecenoate was approximately 50% larger than the constant for the shorter chain saturated hexanoate. A larger relative reaction rate was also noted for the alkylation of the internal carboxylate of the long-chain methyl 9(10)-carboxystearate relative to similarly hindered (six-number, 6) short-chain carboxylate salts (see Table IV, entries 4, 5, and 11). It is conceivable that the longer chain salts exclude solvent from the reactive site, thereby increasing their reactivity relative to the short-chain homologues. Unfortunately, reliable rate constants for the potassium salt of long-chain saturated fatty acids such as stearic acid could not be obtained owing to their extreme insolubility in Me_2SO . Notwithstanding this hindrance to its kinetic measurement, potassium stearate may nevertheless be rapidly and quantitatively alkylated routinely by this method of esterification.

The alkylation of salts of substituted aromatic carboxylates were similarly studied to assess the effects of electron donation and withdrawal on the rapidity of reaction. The entries in Table V, column 1, demonstrate that alkylation rates were diminished by electron withdrawal and accelerated by electron donation. The same trend has been observed for acid-catalyzed esterification of substituted benzoic acid derivatives (Table V, column 3).²⁹ The kinetics of alkylation were directly dependent on the reactivity of the nucleophilic carboxylate anion. Hammett plots comparing the sensitivity of anion alkylation and acid-catalyzed esterification to substituents are shown in Figure 5. The least-squares probable error for the reaction constant ρ obtained for both acid-catalyzed esterification²⁹ and alkylation was 0.05. This value compares favorably with Hammett's probable error of 0.067 for a series of 39 reactions.⁴¹ Comparison of slopes for carboxylate alkylation ($\rho = -0.79$) and acid-catalyzed esterification ($\rho = -0.58$) shows the former to be 30% more sensitive to substituent effects.

Like the aliphatic series, the aromatic carboxylate salts also show increased reactivity with increase in steric crowding (Table V). β -Isodurylic acid (2,4,6-trimethylbenzoic acid) cannot be esterified under normal acid-catalyzed conditions, even though the three methyl groups are activating. The compound's resistance to esterification by alcohol

Table V. Comparison of Aromatic Carboxylic Acid Esterifications. Alkylation of Potassium Carboxylates in Me_2SO vs. HCl -Catalyzed Methanolysis of Carboxylic Acids

| Registry no. | Potassium carboxylate salt | $k_{\text{K}^+, \text{RCl}} \times 10^4$ ^a | $k_{\text{K}^+, \text{RI}}$ ^b | $k_{\text{H}^+, \text{MeOH}} \times 10^3$ ^c | $k_{\text{K}^+, \text{RI}} / k_{\text{H}^+, \text{MeOH}}$ |
|--------------|----------------------------|---|--|--|---|
| 15922-01-7 | <i>p</i> -Nitrobenzoate | 3.12 | 0.183 | 1.15 | 122 |
| 15163-59-4 | <i>o</i> -Nitrobenzoate | 2.42 | 0.142 | 0.172 | 825 |
| 51550-68-6 | <i>p</i> -Bromobenzoate | 7.72 | 0.453 | 1.57 | 288 |
| 582-25-2 | Benzoate | 10.3 | 0.604 | 2.93 | 206 |
| 16518-25-5 | <i>p</i> -Methylbenzoate | 14.0 | 0.821 | 2.25 ^d | 364 |
| 52509-81-6 | <i>p</i> -Methoxybenzoate | 20.0 | 1.17 | | |
| 53756-55-1 | 2,4,6-Trimethylbenzoate | 20.0 | 1.17 | Too slow | |

^a $\text{RCl} = \text{C}_6\text{H}_{13}\text{Cl}$, $k_{\text{K}^+, \text{RCl}}$ in l./mol s. ^b $\text{RI} = \text{C}_5\text{H}_{11}\text{I}$, $k_{\text{K}^+, \text{RI}}$ in l./mol s calculated from 1-chlorohexane data by multiplication by 587. ^c Data taken from Hartman and Borders (ref 29) for $k_{\text{H}^+, \text{MeOH}}$ at 60 $^\circ\text{C}$. ^d This point falls off the line; however, the least-squares probable error for ρ of 0.05 does not reflect this because more than ten points were used in the original study.

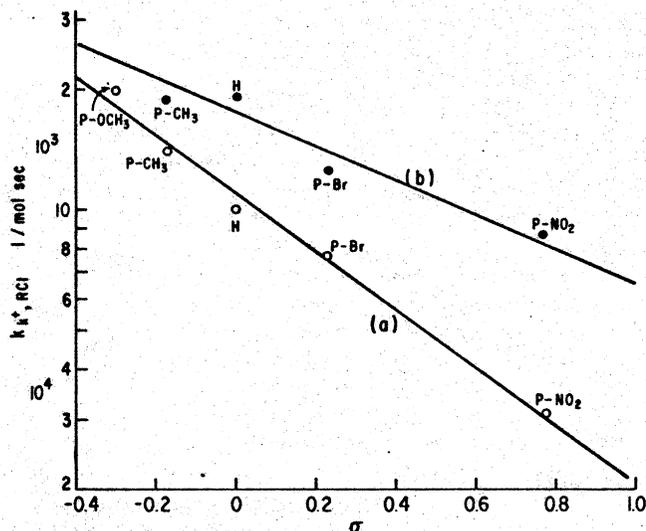
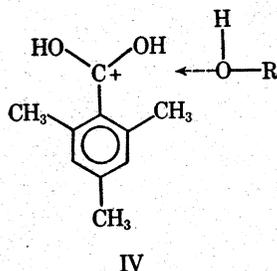


Figure 5. Hammett semilogarithm plot of rate constants of reaction vs. σ constants. (a) Rates of alkylation of aromatic carboxylates with 1-chlorohexane in Me_2SO (60°C) $\rho = -0.73$. (b) Rates of acid-catalyzed esterification ($0.02\text{--}0.1\text{ M HCl}$) in methanol (60°C) $\rho = -0.58$, data obtained from Hartman and Borders (ref 29).

is due primarily to the steric restrictions imposed about the protonated tetrahedral intermediate IV. Alkylation of the



corresponding carboxylate salts circumvents the problem of steric hindrance at the tetrahedral carbonium ion site in IV by attack at either of the nonhindered oxygen anions in the sp^2 -hybridized carboxylate structure. β -Isodurylate is one of the fastest reacting carboxylates in the aromatic series, the reactivity being attributed to desolvation of the anion in its ground state. For this type of highly hindered aromatic acid, anion alkylation with alkyl iodide is a highly efficient mode of preparing esters as indicated by the ratio of rate constants of anion alkylation to acid alcoholysis (Table V, column 5). The *o*-nitro substituted benzoate in which the nitro group hinders the carboxylic function shows the largest relative rate ratio among the members of the series. The field effect as well as the inductive effect of the nitro substituent is evidently attenuated at the oxygen atoms one carbon removed from the ring in the anion relative to the strong deactivating ortho effect felt at the ring bonded carbonyl site in the corresponding acid.

Experimental Section

Materials. All solvents were carefully purified by fractional distillation. Hexamethylphosphoramide was distilled from calcium hydride at reduced pressure and the center cut refractionated, bp 56°C (0.3 mm). *N,N*-Dimethylformamide, bp $148\text{--}150^\circ\text{C}$, was stirred over potassium hydroxide, decanted, and distilled from sodium bicarbonate. Me_2SO was distilled at 70°C (10 mm). *N*-Methylpyrrolidone was initially dried by azeotropic distillation with benzene followed by fractional distillation at 80°C (10 mm).

Detection of free base in each solvent was obtained by potentiometric titration with 0.01 M HClO_4 in 2-propanol-ethylene glycol (1:1 by volume). Solvents requiring 0.5 ml of titrant per 20 ml were repurified. A blank determination was made prior to each kinetic experiment.

Instrumentation. Potentiometric titrations were carried out with a standard glass electrode and a Fischer Model 320 expanded scale research pH meter.⁴²

GLC analysis was performed on a Model 5750 Hewlett-Packard F & M programmable gas chromatograph equipped with an Intronics Model CRS-11HSB digital readout system.

NMR analysis was performed on a JEOL C-60H spectrometer.

Kinetic Measurements. Carboxylate salt (approximate concentrations 0.0150 M) and alkyl halide (approximate concentration 0.0450 M) were accurately weighed and dissolved in the appropriate solvents and thermostated at 60°C . To each of four 50-ml volumetric flasks in the thermostated bath were pipetted the carboxylate salt solution (10 ml) and the alkyl halide solution (10 ml), the resulting mixture containing alkyl halide to carboxylate salt in the approximate molar ratio of 3:1. At periodic intervals the contents of each flask were quenched in a 250-ml Erlenmeyer flask containing 15 ml of 2-propanol-ethylene glycol 50:50 v/v solution at -70°C . Quantitative transfer of the reaction solution was completed with an additional washing of 15 ml of the solvent mixture and the contents titrated potentiometrically with a standard solution of approximately 0.010 M HClO_4 in 50:50 v/v 2-propanol-ethylene glycol using a glass electrode. The inflection point of each titration curve corresponding to the remaining unreacted salt was determined by evaluation of the second derivative of the potentiometric curve using two points above and two points below the sharp change in millivolt potential (apparent pH). Rate constants were calculated from the standard second-order expression

$$k = \frac{a \ln(A/A_0)(B_0/B)}{t(bA_0 - aB_0)}$$

where A_0 = initial concentration of carboxylate salt, A = concentration of carboxylate salt remaining at time t , B_0 = initial concentration of alkyl halide, B = concentration of alkyl halide remaining at time t , and a and b are integral coefficients in the balanced chemical equation.

All rate constants were examined for competency by least-squares analysis, correlation coefficients, and standard deviation calculations. In general all k 's gave a correlation coefficient for second-order kinetic of 0.995 or better.

Preparation of Di- and Trialkyl Acetic Acids. Di- and trialkyl acetic acids were prepared according to the α -anion alkylation procedure previously described.⁴³ However, unlike ordinary monoalkyl acetic acids, 3-methylbutanoic acid dianion was insoluble and, therefore, required heating for 2 h at 50°C in THF-HMPA prior to alkylation. Owing to the increased solubility imparted by the branching of the *tert*-butyl acetate dianion, no HMPA was required as cosolvent.

Using the α -anion procedure⁴³ for the metalation of 3-methylbutanoic acid we obtained 90% alkylation with 1-iodoethane to give 2-ethyl-3-methylbutanoic acid. 2-Isopropyl-3-methylbutanoic acid was prepared similarly through the α -alkylation of 3-methylbutanoic acid with 2-bromopropane in approximately 50% yield.

Preparation of Carboxylate Salts. All carboxylate salts were prepared by titration of the corresponding carboxylic acids in ethanol with standard solutions of CsOH , KOH , NaOH , and LiOH , using phenolphthalein as end point indicator. The solvent was removed by rotary film evaporation and the salts dried in vacuo (0.01 mm) at 50°C for 24 h. When additional purification was required, the salts were crystallized from appropriate solvents and triturated with hydrocarbon. Potassium nonanoate was recrystallized from THF, potassium 2-methyl-2-propylpentanoate was recrystallized from isopropyl alcohol, and potassium 2-propylhexanoate was triturated with hexane, as were the remaining salts when additional purity was desired. The salts were kept dry by storage in a desiccator over P_2O_5 .

pK Measurements of Carboxylic Acids. The ionization constants were measured according to the method of Newman and Fukunaga.³¹ The determinations were made by potentiometric titration using a glass electrode and standard pH meter in 50 vol % methanol-water at 40°C . The ionization constants were calculated by the standard pH equation at $\frac{1}{4}$, $\frac{1}{2}$, and $\frac{3}{4}$ neutralization points. The system was standardized before and after each titration with 0.05 M phthalate buffer for pH 4.03, 0.05 M phosphate buffer for pH 6.84, and 0.01 M borax buffer for pH 9.07.

Reaction of Dilithium 9(10)-Carboxystearate with 1-Iodopentane. Dilithium 9(10)-carboxystearate (0.50 g , 1.52 mm) was dissolved in 15 ml of HMPA (containing 3 ml of ethyl alcohol to increase the salt's solubility). To this solution at 85°C (0.347 g , 1.75 mm) of 1-iodopentane was added with mechanical stirring. The reaction was allowed to proceed for 15 min , quenched with water

(200 ml), acidified with 10% hydrochloric acid, and extracted three times with petroleum ether. The petroleum ether layer was washed four times with 30-ml portions of dilute HCl and water followed by sodium thiosulfate solution to remove any liberated iodine. The organic layer was dried and solvent removed by rotary evaporation to yield 0.66 g of crude product. The crude product was treated with an ethereal solution of diazomethane and the mixture of esters examined by GLC using a 5 ft \times 0.125 in. 5% SE-30 column programmed from 180 to 260 °C at 4 °C/min. The chromatogram showed the presence of four products: (1) methyl 9(10)-carboxymethoxystearate (16%), retention time 3 min; (2) a mixture of methyl 9(10)-carboxypentoxystearate and (3) pentyl 9(10)-carboxymethoxystearate (total 41%), retention times 6 and 6.2 min, respectively (peaks were not resolvable); and (4) pentyl 9(10)-carboxypentoxystearate (43%), retention time 12 min. The above mixture was injected onto a 2-ft 10% silicone gum rubber GLC column at 180 °C and the unresolved mixture of peaks 2 and 3 were preparatively trapped. Analysis of the products of this mixture (2 + 3) was performed by NMR using $\text{Eu}(\text{fod})_3$ shift reagent.

NMR Analysis of 9(10)-Carboxystearic Acid Esters Using $\text{Eu}(\text{fod})_3$ in CCl_4 . GLC-trapped samples containing a mixture of isomers, methyl 9(10)-carboxypentoxystearate and pentyl 9(10)-carboxymethoxystearate, were analyzed as follows. Approximately 40 mg of sample mixture was dissolved in 350 μl of CCl_4 containing 2% Me_4Si . The spectrum of this mixture displayed a sharp methoxy singlet at δ 3.7. Upon addition of 10 μl of $\text{Eu}(\text{fod})_3$ solution (0.288 M) the methoxy singlet split into two distinct singlets at δ 4.3 and 4.6. The lower field singlet was attributed to methyl 9(10)-carboxypentoxystearate and the upper field singlet to pentyl 9(10)-carboxymethoxystearate after comparison with the spectra of known mixtures of these two pure components. The integrated ratio of the δ 4.3 to the δ 4.6 resonances was 2:1, respectively.

Preparation of Potassium 9(10)-Carboxymethoxystearate by Selective Hydrolysis of Methyl 9(10)-Carboxymethoxystearate.⁴⁴ Methyl 9(10)-carboxymethoxystearate (5 g, 0.0154 mol) was dissolved in 25 ml of methanol containing H_2O (0.277 g, 0.0154 mol) and KOH (0.954 g, 0.0145 mol). The solution was stirred and refluxed for 2 h and solvent removed on a rotary film evaporator. The solid residue was extracted with ether to remove any unreacted dimethyl ester. A small sample of the remaining half methyl ester potassium salt was checked for isomeric purity by treating it with excess *n*-pentyl iodide in HMPA at 80 °C for 1 h. The resulting mixed ester was examined by GLC using a 5 ft \times 0.125 in. 5% SE-30 column programmed from 180 to 260 °C at 4 °C/min. The chromatogram showed one peak which corresponded to the mixed esters methyl 9(10)-carboxypentoxystearate and pentyl 9(10)-carboxymethoxystearate and a trace of pentyl 9(10)-carboxypentoxystearate. NMR analysis using the $\text{Eu}(\text{fod})_3$ technique described above confirmed that the reaction product was 96% pentyl 9(10)-carboxymethoxystearate and 4% methyl 9(10)-carboxypentoxystearate.

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Registry No.—1-Iodopentane, 628-17-1; 1-bromopentane, 110-53-2; 1-chlorohexane, 544-10-5.

References and Notes

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