Table I

Relative Esterification Rates in Methanol of α-Methyl- and β-Methyl-Substituted Aliphatic Acids

No.	α-Methyl acid, $(R_1)(R_2)CHC(R_3)(CH_3)COOH$	β-Methyl acid, $(R_1)(R_2)(CH_3)CCH(R_3)COOH$	$k\beta/k\alpha$	Temp, °C	Ref
1	$(CH_3)_2CHCOOH$	$CH_3CH_2CH_2COOH$	1.5	40	1
2	$CH_3CH_2CH(CH_3)COOH$	$CH_3CH(CH_3)CH_2COOH$	1.2 (1.1)	40	1 (3)
3	$(CH_3)_3CCOOH$	$CH_3CH_2CH(CH_3)COOH$	2.7	40	1
4	$CH_3CH_2CH_2CH(CH_3)COOH$	$CH_3CH_2CH(CH_3)CH_2COOH$	1.2	65	5
5	$CH_3CH_2C(CH_3)_2COOH$	$CH_3CH(CH_3)CH(CH_3)COOH$	2.3	65	5
6	$CH_3CH_2C(CH_3)_2COOH$	$CH_3CH_2CH(C_2H_5)COOH$	2.3	65	5
7	$(CH_3)_2CHCH(CH_3)COOH$	$(CH_3)_3CCH_2COOH$	1.5 (1.6)	15–20 (65)	1 (5)
8	$CH_3CH_2CH_2CH_2C(CH_3)_2COOH$	$CH_3CH_2CH_2CH_2CH(C_2H_5)COOH$	1.6	50	This report
9	$(CH_3)_2CHCH_2C(CH_3)_2COOH$	$(CH_3)_2CHCH_2CH(C_2H_5)COOH$	2.2	50	This report
10	$(CH_3)_3CC(CH_3)_2COOH$	$(CH_3)_3CCH(C_2H_5)COOH$	<1[6]	40	1

Table II

Determination of Relative Esterification Rates in Methanol at 50° of α-Methyl- and β-Methyl-Substituted Aliphatic Acids

Fraction remaining after partial esterification		
α-Methyl acid (A) 2,2,4-Trimethylpentanoic acid[a]	β-Methyl acid (B) 2-Ethyl-4-methylpentanoic acid[b]	Log B/log A
0.6622	0.4150	2.13
0.6413	0.4014	2.05
0.5428	0.2589	2.21
0.5503	0.2621	2.24
0.4704	0.1775	2.29
0.4553	0.1731	2.23
2,2-Dimethylhexanoic acid[c]	2-Ethylhexanoic acid[d]	Log B/log A
0.8118	0.7208	1.57
0.6714	0.5319	1.58
0.5054	0.3298	1.63
0.3272	0.1750	1.56
0.1791	0.0731	1.52

[a] Registry number, 866-72-8. [b] Registry number, 108-81-6. [c] Registry number, 813-72-9. [d] Registry number, 149-57-5.

sonable to put forth the following generalization: a β-methyl-substituted saturated aliphatic acid esterifies with methanol at a greater rate (~1.8 times as fast at 40°) than the corresponding α-methyl acid.

Although the above statement deals only with certain isomeric pairs of acids, it certainly presents a multitude of "exceptions" to the generally accepted conclusion that a methyl substitution at the β carbon is more effective in reducing the esterification rate than a methyl substitution at the α carbon. How the conclusion developed in this present report can be employed to predict more satisfactorily the effect of structure on esterification rates will be the topic of a forthcoming paper.

Experimental Section

Materials. Purity of the acids was indicated by the neutralization equivalent (144.2 calcd) and the per cent area by glc under the conditions described in the next section.

2-Ethylhexanoic acid, neut equiv 144.6, glc per cent area 99.8, was obtained from Baker Chemical Co.

2-Ethyl-4-methylpentanoic acid, neut equiv 144.8, glc per cent area 99.1, was obtained from Pfaltz and Bauer.

2,2-Dimethylhexanoic acid, neut equiv 145.1, glc per cent area 95.7, was prepared by alkaline permanganate oxidation of 2,2-dimethyl-1-hexanol obtained from K & K Laboratories.

2,2,4-Trimethylpentanoic acid, neut equiv 146.5, glc per cent area 98.6, was prepared by alkaline permanganate oxidation of 2,2,4-trimethyl-1-pentanol obtained from Pfaltz and Bauer.

Methyl myristate, glc per cent area 99.8, was obtained from Lachat Chemicals Inc.

Gas–Liquid Chromatography. Chromatography was carried out with a Beckman GC 4 chromatograph equipped with a flame ionization detector which was interfaced with a Perkin-Elmer PEP-1 data processer. The column was 6 ft by ⅛ in. stainless steel packed with 20% diethylene glycol adipate polyester and 3% phosphoric acid on 60/80 mesh Gas-Chrom P. Column temperature was 150°, inlet temperature was 200°, and helium flow was 25 cc/min.

Determination of the Relative Esterification Rates. The reaction mixture was composed of 20 ml of methyl alcohol, 2 drops of each of the two acids whose esterification rates are to be determined, and 2 drops of methyl myristate, the internal standard. It is, of course, necessary that all three components are adequately resolved by the chromatographic method. Six drops of concentrated hydrochloric acid was added; the mixture was divided up into a number of small screw-cap tubes and heated in an aluminum block at 50 ± 0.5°. Samples were analyzed at various times over a 4-hr heating period. Readouts from the data processer were given as fraction remaining of each of the acids. The relative esterification rate was calculated from the equation

$$\frac{k_{\beta\text{-methyl acid}}}{k_{\alpha\text{-methyl acid}}} = \frac{\log \text{fraction remaining of } \beta\text{-methyl acid}}{\log \text{fraction remaining of } \alpha\text{-methyl acid}}$$

Readouts and the calculated relative esterification rates are given in Table II.

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Absence of Catalysis of Salicylate Ester Hydrolysis by Hexadecyltrimethylammonium Bromide Micelles

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Received April 19, 1974

Rate enhancements by cationic micelles have been observed in the base-catalyzed hydrolysis of several carboxylic esters having good leaving groups.[1] With simple alkyl esters rate retardations have been observed; they have been

Table I
Hydrolysis of Methyl and Hexyl Salicylate at 25° [a]

[Ester], M	[CTAB], M	pH	$k \times 10^5$, sec^{-1}
10^{-3} M methyl salicylate		9.2^b	1.59 ± 0.02
		9.2^b	1.69 ± 0.03
	0.00497	9.2^b	1.12 ± 0.05
	0.00500	9.2^b	0.605 ± 0.036
	0.0505	9.2^b	0.281 ± 0.009
		10.0^c	1.95 ± 0.09
		10.0^c	3.24 ± 0.09
		10.0^c	1.88 ± 0.09
		10.0^c	3.66 ± 0.15
	0.00500	10.0^c	1.67 ± 0.05
	0.00500	10.0^c	2.60 ± 0.34
		10.25^d	1.69 ± 0.09
		10.25^d	5.49 ± 0.08
		10.25^d	4.94 ± 0.48
	0.00501	10.25^d	2.16 ± 0.09
	0.00497	10.25^d	2.20 ± 0.12
	0.00501	10.25^d	2.40 ± 0.05
10^{-3} M hexyl salicylate	0.00503	9.2^b	0.132 ± 0.005
	0.00111	10.0^c	0.143 ± 0.006
	0.00348	10.0^c	0.206 ± 0.006
	0.00454	10.0^c	0.221 ± 0.004
	0.00500	10.0^c	0.192 ± 0.004
	0.00551	10.0^c	0.237 ± 0.002
	0.00654	10.0^c	0.188 ± 0.008
	0.01000	10.0^c	0.187 ± 0.007
	0.00501	10.25^d	0.226 ± 0.006

[a] All solutions contain 0.02 M NaCl. [b] 0.02 M borax buffer. [c] 0.02 M carbonate buffer, 50% base. [d] 0.03 M carbonate buffer, 75% base.

attributed to solubilization of the esters in the micellar core.[2] This explanation does not seem adequate; why are not the esters with good leaving groups also solubilized in the micellar core?

Phenols are known to be solubilized in the outer portions of both nonionic and ionic micelles;[3,4] since salicylate esters have a phenolic hydroxyl group, they are good candidates for this type of solubilization. As a result of our thermodynamic studies on the binding of organic solutes to micelles of hexadecyltrimethylammonium bromide (CTAB),[5] it occurred to us that hydrolysis of salicylate esters might be effectively catalyzed by CTAB. Methyl salicylate has a small negative enthalpy of transfer (ΔH_{trans}) from H_2O to 0.1 M CTAB solutions, but salicylic acid, one of its hydrolysis products, interacts very favorably with CTAB micelles ($\Delta H_{\text{trans}} = -9.25$ kcal/mol, $\Delta G_{\text{trans}} = -2.06$ kcal/mol). If this interaction were important in the rate-determining step for salicylate ester hydrolysis, a rate acceleration in the presence of CTAB could be expected.

Table I presents pseudo-first-order rate constants for the hydrolysis of methyl and hexyl salicylate in CTAB. Because of the low solubility of hexyl salicylate in water, rates for its hydrolysis in the absence of CTAB were not obtained. The collected data do not show good reproducibility, but they are of sufficient quality for our purposes. The poor reproducibility is thought to be a consequence of the colorimetric method's sensitivity to pH. Also salicylate esters may form complexes with boric acid.[6]

The presence of CTAB makes little if any difference in the rate of hydrolysis of the salicylate esters, indicating that the CTAB micelle's favorable interaction with salicylic acid is not felt in the rate-determining step.

We would like to suggest an explanation for the difference in sensitivity of esters with good compared to poor leaving groups to micellar catalysis. We will limit our discussion of good leaving groups to the p-nitrophenoxide ion, because p-nitrophenyl esters have been used so extensively[1] in work on micellar catalysis.

For alkaline hydrolysis of p-nitrophenyl esters formation (and reversion to reactants) of the tetrahedral intermediate is clearly rate determining. This is not true for simple alkyl esters. Since hydroxide ion is involved in this step, the effect of a positively charged micellar surface on its activity will be important; if the micellar surface facilitates OH^- attack (by some mechanism other than simple approximation of reactants) on esters, the p-nitrophenyl ester hydrolyses will be accelerated.

For simple alkyl esters, the availability of water or some other proton donor is important in the rate-determining step (expulsion of alcohol from the tetrahedral intermediate). This results in alkaline hydrolysis of these esters being less favorable at or near the micelle surface than in bulk solution. Lapinte, *et al.*,[7] has also observed rate retardations in CTAB solutions for reactions where water is involved as a proton donor; CTAB solutions are regarded as being similar to DMSO in this respect.

The explanation in the preceding paragraph assumes that expulsion of alkoxide ion from the tetrahedral intermediate in hydrolysis of simple alkyl esters does not occur. This is contrary to the work of Jencks[8] on tetrahedral addition compounds formed from the N,O-trimethylenephthalimidium cation and aliphatic alcohols. For salicylate esters water can also be involved in the formation of the tetrahedral intermediate, since these compounds are known to be subject to intramolecular general base catalysis.[9] If formation of the tetrahedral intermediate is in fact rate determining for the salicylate esters (as it is for p-nitrophenyl esters) the observed effect of CTAB on their hydrolysis can still be rationalized.

Experimental Section

Esters. Methyl salicylate (Fisher Scientific, U. S. P.) was used as received. n-Hexyl salicylate was prepared from salicylic acid and 1-hexanol using p-toluenesulfonic acid and p-toluenesulfonyl chloride as catalysts.[10] Following work-up, distillation at reduced pressure through a glass helices packed column removed most of the unreacted 1-hexanol. Two cuts, bp 90–93° (0.05 mm), contained about 88% ester (12% 1-hexanol) and were used in the kinetic studies.

Hexadecyltrimethylammonium Bromide (CTAB). The CTAB (City Chemical Corp.) was recrystallized from CCl_4, then dried *in vacuo* for at least 24 hr at 60°. Titration of the CTAB using $AgNO_3$ gave a molecular weight of 363 (actual 364.5); its cmc (bromide ion selective electrode) was 9.1×10^{-4} M.

Kinetic Studies. All buffer components were reagent grade; the water for the buffer solutions was boiled prior to use. The increase in salicylic acid concentration during the hydrolysis reactions (at 24.95 ± 0.06°) was followed by monitoring the absorbance of its $FeCl_3$ complex[11] at 532 nm using a Beckman DU spectrophotometer. The blank used contained $FeCl_3$ in acidic solution. The presence of CTAB did cause a decrease in extinction coefficient, but Beer's law still was obeyed. The A_∞ values were determined after 10 half-lives, and they are the average of at least two determinations. Some difficulty in obtaining consistent color development (formation of the complex) was encountered. This is thought to be due to the sensitivity of the salicylic acid–ferric ion reaction to the pH of the solution.

Acknowledgment. Support of this work by the National Science Foundation through a predoctoral fellowship to L. J. M. is gratefully acknowledged.

Registry No.—Methyl salicylate, 119-36-8; hexyl salicylate, 6259-76-3; CTAB, 57-09-0.

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Dimethyl β-Ketoadipate

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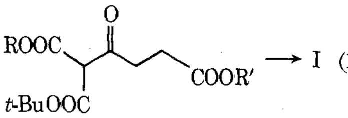
Received April 30, 1974

Several years ago there was reported a new and improved synthesis of several esters of the important biomolecule β-ketoadipic acid (I).[1] The starting materials employed were alkyl *tert*-butyl malonate and β-carboalkoxypropionyl chloride (eq 1). We report here an improvement

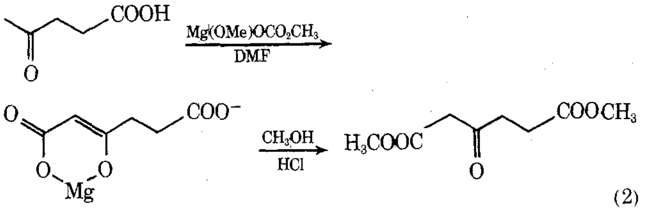
$\mathrm{ROOCCH_2COO\text{-}\mathit{t}\text{-}Bu + ClOCCH_2CH_2COOR' \longrightarrow}$



(1)

in the preparation that (a) avoids the problem of synthesis of the starting materials above and (b) employs cheap levulinic acid as starting material.

Carboxylation of levulinic acid by the procedure of Finkbeiner and Wagner[2] followed by Fischer esterification of the crude product affords a 92% isolated yield of dimethyl β-ketoadipate. There was no evidence for formation of the isomeric dimethyl acetylsuccinate or products from multiple carboxylation (eq 2). The near-quantitative yield of this preparation requires use of a large (tenfold) excess of the carboxylating agent methylmagnesium carbonate. The regioselective nature of this reaction is consistent with the findings of Crombie, *et al.*, in an analogous case.[3]



(2)

Dimethyl β-Ketoadipate. A solution of 10.6 g (91.4 mmol) of levulinic acid (Eastman Technical) in 360 ml (920 mmol) of 2.56 *M* methylmagnesium carbonate in dimethylformamide (DMF)[2] was heated at 135° for 24 hr. The DMF was removed by distillation under vacuum at 60°. Trituration of the residue with ether gave after filtration and air drying of 136 g of yellow solid. The solid was suspended in 820 ml of methanol in a 3-l., three-necked, round-bottom flask equipped with a mechanical stirrer, a condenser, and a gas inlet tube. After cooling to −10°, hydrogen chloride was passed over the mixture until saturation had occurred. After standing overnight and warming to 25°, the mixture was concentrated at 40° under reduced pressure. The syrupy residue was poured on ice and the aqueous solution was extracted four times with chloroform. The organic extracts were washed with saturated bicarbonate solution and water and dried over anhydrous sodium sulfate. Distillation through an 1-in. Vigreux column gave 15.8 g (92% yield) of dimethyl β-ketoadipate as a colorless liquid: bp 94–96° (0.35 mm) [lit.[1] bp 110–111° (0.25 mm)]; nmr ($CDCl_3$) δ 2.70 (4 H, A_2B_2 multiplet), 3.49 (2 H, singlet), 3.62 (3 H, singlet), and 3.67 (3 H, singlet).

Registry No.—Dimethyl β-ketoadipate, 5457-44-3; levulinic acid, 123-76-2.

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Phenacyl Kojate Compared with Crown Ethers

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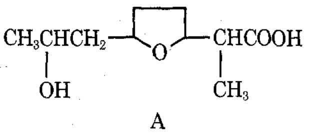
Received June 12, 1974

Crown ethers are of interest because of their ability to form complexes with sodium chloride and related salts. Following Pedersen's papers[1] there has been considerable development of this area. A comprehensive summary[2] has appeared recently. It lists 107 references, most of which are selected from the past decade. The area is diverse, and includes carbohydrates, for example. One obtains $C_{12}H_{22}O_{11} \cdot 2CH_3COOK$ when ether is added to a 0.02 *M* solution of sucrose[3] in ethanol that contains 0.4 *M* potassium acetate. Again, Sidgwick and Brewer[4] reported that the dihydrate of sodio-1-phenyl-1,3-butanedione was soluble in toluene whereas the anhydrous sodio derivative was insoluble. This observation was confirmed and extended by Bright, Milburn, and Truter.[4]

Nonactin is a neutral antibiotic, $C_{40}H_{64}O_{12}$, obtainable from *actinomyces*. It is a macrocyclic ester that yields four molecules of hydroxy acid A on saponification. Nonactin[5]



A

binds KCNS to form a complex wherein K^+ is surrounded by eight oxygens, four coming from the four ether oxygens and four from the four ester carbonyls. Also there are acidic