[Contribution from the Ammonia Department of E. I. du Pont de Nemours and Company]

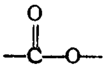
Influence of Structure on Saponification. Improved Analytical Technique for Esters

By W. M. D. Bryant and Donald Milton Smith

The saponification of esters as an analytical method has received most attention in connection with the chemistry of natural glycerides and waxes, and in this restricted field the optimum conditions of time, temperature and reagent concentrations are well known. However, standard treatises on organic analysis[1,2,3] have little to say regarding the systematic application of the saponification technique to carboxylic esters of varied structure, even in the field of aliphatic chemistry, and it may be concluded that these conditions have not been investigated for any wide variety of esters, although specific information in this field is greatly needed. The literature contains a large mass of data for the rate of alkaline hydrolysis of esters, but the usual experimental conditions differ so radically from those of analysis that the data are of little use in this connection. On the other hand, relative rate experiments carried out under conditions approximating those of analysis are of real value in predicting requirements for quantitative saponification.

Although it is unlikely that a single analytical procedure could be extended successfully to all types of carboxylic esters, the present research indicates that it is possible, with a well-defined knowledge of structural influences, to modify a basic analytical method so that almost any type of carboxylic ester can be quantitatively saponified. The experimental procedure employed differs from those in general use, and the apparatus requirements are greatly simplified by the absence of refluxing equipment. Saponification is carried out in a closed glass vessel using an excess of 2 N sodium hydroxide in 90% methanol instead of under reflux using 0.5 N alkali. For most esters the reaction mixture is heated for thirty minutes at 60°, conditions sufficiently mild to minimize interference of aldehydes and ketones. More stable esters are saponified at 100° for longer periods of time depending on their structure. The use of 2 N instead of the usual 0.5 N sodium hydroxide permits the reaction to be completed at a lower temperature. The presence of water in the caustic solution is beneficial to saponification in alcoholic media[4] but in excess of 10% was found to decrease excessively the solvent action of methanol upon the sample. Over thirty esters, chiefly aliphatic, were investigated and the conditions for their quantitative saponification recorded. Almost all classes of carboxylic esters can be analyzed by this method with a precision of ±0.3% or better.

To provide a means of predicting the time requirements for complete saponification of substances not included in the present program, a study was made of the relative rates of saponification of a group of esters of varied structure under conditions approximating those of analysis (see Table I). These experiments were conducted with sufficient precision for the purpose, but without the refinements employed in conventional rate studies. Because the 2 N sodium hydroxide of the regular procedure was too reactive to show clearly the differences in rate produced by structural changes, 0.5 N alkali was used instead.

It is known that the introduction of alkyl side chains in close proximity to the ester carboxyl tends to retard saponification. The present work shows that a retarding effect is observed whether alkyl substitution occurs in the acyl or alkoxyl portion of the molecule, but is more pronounced the closer to the  $-\overset{\displaystyle O}{\overset{\|}{C}}-O-$ group it occurs. α-Alkyl hindrance in the acid radical was found appreciable even in the simplest examples, the isobutyrates, and was intensified on passing to the five and six carbon acids, and also on increasing the number of α-alkyl groups (*e. g.*, ethyl trimethylacetate). Steric hindrance arising from α-alkyl substitution in the alkoxyl radical is less pronounced in the simple case of straight chain secondary alcohol derivatives, but is intensified by further alkyl substitution to form either tertiary or branched chain secondary alkoxyl groups. This effect is modified by alkyl interchange involving a replacement of the original group by

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(1) J. F. Thorpe and M. A. Whiteley, "A Student's Manual of Organic Chemical Analysis," Longmans, Green & Co., London, 1926.

(2) Hans Meyer, "Analyse und Konstitutionsermittlung organischer Verbindungen," Julius Springer, Berlin, 1931.

(3) H. C. Sherman, "Methods of Organic Analysis," The Macmillan Co., New York, 1917.

(4) J. F. M. Caudri, *Rec. trav. chim.*, **48**, 422 (1929).

methoxyl from the solvent. Verkade[5] has shown that the corresponding interchange in ethanol solutions can be extremely rapid. Simultaneous steric blocking from both the alkoxyl and acyl portions of the molecule gives rise to esters of extraordinary stability toward alkali. 2,4-Dimethylpentyl-3 trimethylacetate requires over two weeks' heating at 100° with 2 *N* sodium hydroxide in order to be saponified completely, while methyl abietate with just the tertiary carboxyl requires only eighteen hours for complete cleavage. Indications of the effect of other structural changes are apparent in Table I.

TABLE I

INFLUENCE OF STRUCTURE UPON THE RATE OF SAPONIFICATION AT 60°

Sodium hydroxide in 90% methanol; initial normality, 0.5 *N*

Ester	Side chains (Number and location)	% Saponified in *t* min.		
		t = 10	20	30
n-Butyl acetate[a]	None	99.5	100.0	100.0
n-Propyl propionate	None	97.5	99.5	100.0
Ethyl *n*-butyrate[a]	None	90.0	98.5	100.0
Ethyl *n*-valerate[a]	None	88.0	98.0	100.0
n-Butyl *n*-butyrate	None	89.5	98.0	100.0
n-Amyl *n*-caproate[a]	None	94.0	99.5	100.0
Ethyl malonate	None	95.5	97.5	99.5
Isobutyl propionate	β, alkoxyl	99.5	100.0	100.0
Isobutyl *n*-butyrate[a]	β, alkoxyl	91.0	98.0	100.0
Isopropyl propionate	α, alkoxyl	95.0	99.5	100.0
s-Butyl acetate[a]	α, alkoxyl	98.5	100.0	100.0
2,2-Dimethylbutyl-3 acetate	α, 2β alkoxyl	38.5	62.0	76.5
2,4-Dimethylpentyl-3 acetate	α,β alkoxyl	9.0	14.0	19.0
t-Butyl acetate[a]	2α, alkoxyl	31.5	76.0	88.0
Methyl isobutyrate	α, acyl	75.0	93.0	98.0
Ethyl isobutyrate	α, acyl	79.0	93.5	97.5
Methyl 2-methylbutanoate	α, acyl	40.5	64.0	77.0
Methyl 3-methylbutanoate	β, acyl	58.0	83.5	91.0
n-Propyl isobutyrate	α, acyl	67.0	91.0	97.0
Ethyl 2-methylbutanoate	α, acyl	20.0	33.0	44.5
Ethyl 3-methylbutanoate[a]	β, acyl	51.0	76.0	90.0
Ethyl tiglate	α, acyl	22.0	44.5	60.0
Methyl 2-methylpentanoate	α, acyl	26.0	42.0	54.0
Ethyl trimethylacetate	2α, acyl	6.0	18.0	27.5
Ethyl ethylmalonate[a]	α, acyl	62.0	68.0	77.5
Ethyl diethylmalonate	2α, acyl	7.0	9.0	11.0
Isobutyl isobutyrate	α, acyl; β, alkoxyl	55.0	90.5	97.5
2,4-Dimethylpentyl-3 trimethylacetate	2α, acyl; α,β, alkoxyl	0.1	0.4	0.7
Cyclohexyl acetate[a]	α, alkoxyl[b]	98.5	99.0	100.0
Phenyl acetate	α, alkoxyl[b]	94.0	98.5	100.0
n-Butyl phthalate	2α, acyl[b]	58.0	75.0	84.0

[a] Contained 2% or less of inert contaminant, but corrected to 100%. [b] Structure not strictly analogous to acyclic examples.

Only a few rate experiments were made using esters of the aromatic and hydroaromatic series. Phenyl and cyclohexyl acetates saponify rapidly, the time requirements resembling those of the straight chain aliphatic esters. *n*-Butyl phthalate is a little less reactive than ethyl isobutyrate, but more so than ethyl 2-methylbutanoate. A number of other esters of varied structure which gave quantitative results under mild experimental conditions were not further investigated. In this classification were included pentaerythritol tetracetate, benzyl benzoate, phenyl benzoate, cyclohexyl phthalate, and the typical γ- and δ-lactones, phthalide and coumarin. The introduction of unsaturated linkages or hydroxyls is seen to produce no appreciable hindrance, even when involving the α-position.

Experimental

Esters Investigated.—The majority of the esters used in the present research were Eastman chemicals, which with one exception were used without further purification. Practically all analyzed better than 98%, the difference being unsaponifiable matter. *Phthalide* (m. p. 73.6°, corr.) was obtained from British Drug Houses, Ltd., and *coumarin* (m. p. 69.5°, corr.) was a gift from Dr. W. H. Carothers. Professor F. C. Whitmore kindly placed at our disposal some *2,2-dimethylbutyl-3 acetate* (b. p. 140° at 732 mm.). The remaining esters were either prepared synthetically[6] or purified by careful fractionation. The *phthalate* and *trimethylacetate* of *2,4-dimethylpentanol-3* have probably not been previously described, hence an outline of their synthesis will be given. Similarly, since the physical constants of *t-butyl acetate* reported in the literature do not agree well with those obtained in this research and since the success of the synthetic method with tertiary alcohols is somewhat surprising, this preparation also will be considered.

2,4-Dimethylpentyl-3 Phthalate.—Six moles 2,4-dimethylpentanol-3, 4.5 moles of pyridine, and 1000 g. of toluene were placed in a reaction flask equipped with stirrer, dropping funnel and reflux condenser. Two moles phthalyl chloride in 200 g. toluene was added to the above mixture during one hour. The perceptible heat evolution was then supplemented by an electric heater and the mixture maintained at gentle reflux for two hours. The mixture was cooled, then washed successively with water, 3%

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(5) P. E. Verkade and A. H. A. de Willigen, *Rec. trav. chim.*, **54**, 353 (1935).

(6) In this connection the assistance of Mr. R. F. Cockerill is gratefully acknowledged.

hydrochloric acid, 3% aqueous sodium hydroxide and again with water. Toluene and the residual alcohol were distilled off under 100 mm. and the ester at 170–180° (head temperature) at 1 to 2 mm. The product was almost water-white, very viscous, and had a faint honey-like odor. Physical constants: b. p. 231° (20 mm.); n^{25}_D 1.4903 ± 0.0002; d^{25}_4 1.0040 ± 0.0002; yield, 85% based on phthalyl chloride.

2,4-Dimethylpentyl-3 Trimethylacetate.—Half a mole of the alcohol and 1 mole of pyridine in 500 g. of xylene were treated with 0.5 mole of trimethylacetyl chloride (b. p. 104–105°) in 50 g. of xylene as above. After washing and removal of xylene by distillation, the residue was fractionated at 95 mm., the ester boiling at 127.5–128°. The odor was faint and cedar-like. Physical constants: n^{25}_D 1.4150 ± 0.0002; d^{25}_4 0.847 ± 0.001; yield, better than 80% theoretical based on alcohol. In these syntheses molal ratios and solvents were varied to simplify purification by distillation.

***t*-Butyl Acetate.**—Although direct action of acetyl chloride upon *t*-butanol yields chiefly *t*-butyl chloride as product,[7] $(CH_3)_3COH + CH_3COCl \longrightarrow (CH_3)_3CCl + CH_3COOH$, the addition of pyridine was found to direct the reaction along its normal course, $(CH_3)_3COH + CH_3COCl + C_5H_5N \longrightarrow (CH_3)_3COOCCH_3 + C_5H_5N, HCl$. This was established by means of the authors' hydroxyl method,[8] supplementary determinations of Cl ion having shown that no chlorine fixation accompanied the reaction.

A 62% yield of ester based on *t*-butanol was obtained as follows: 2.5 moles of pyridine in 435 g. of xylene were treated with 1.3 moles of acetyl chloride dissolved in 435 g. more of xylene (requires thirty minutes), stirring the while and cooling in ice water. To the cold suspension of acetylpyridinium chloride was added 0.7 mole of *t*-butanol and the mixture heated two hours with stirring in a water-bath at 65 ± 3°. After standing overnight the mixture was poured into 1 liter cold water, shaken, separated and the lower layer discarded. Residual pyridine and acid were removed by 2 washings with 300 cc. of 50% aqueous acetic acid, followed by water, then the calculated amount of 0.5 *N* sodium hydroxide (determined by titration of small aliquot), and finally more water. The first distillation (from xylene) yielded 70 g. crude ester, b. p. 78–107°; the second, 50 g. 98% ester, b. p. 96–98°; the final fractionation yielded ester boiling at 97.9° (corr.), and analyzing 99%. No evidence of *t*-butyl chloride or unreacted alcohol was observed in the distillations. Physical constants: n^{25}_D 1.3840 ± 0.0002; d^{25}_4 0.8620 ± 0.0002.

Comparison of refractive index and density figures for isomeric butyl derivatives given in "International Critical Tables"[9] indicates these quantities are, in general, numerically lower for *t*-butyl than for the corresponding less branched isomers. The constants of our *t*-butyl acetate conform to this generalization, while those of the acetate prepared by Henry[10] do not.

Acetate	Reference	n^{20}_D	d^{20}_4
n-Butyl	"I. C. T."	1.3951	0.882
Isobutyl	"I. C. T."	1.3997	.871
s-Butyl	"I. C. T."	1.389	.870
t-Butyl	This research	1.3875	.868
t-Butyl	Henry	1.39469	.8958

No other literature values for the tertiary ester could be found.

Analytical Procedure

Twenty cc. of 2 *N* sodium hydroxide in 90% methanol are delivered into a 250-cc. g. s. volumetric flask (graduation unnecessary) using a precision buret. Sufficient sample is weighed or measured into the flask so that not more than half and preferably only one-third of the available alkali will be used. The sample is then placed in a water-bath[8] (p. 62) at 60 ± 1°, and after momentarily raising the stopper to allow for expansion of the included air, is firmly stoppered and maintained at that temperature for thirty minutes. The flask is then removed, cooled in ice, and titrated with standard 0.5 *N* aqueous hydrochloric acid to a phenolphthalein or thymol blue end-point. At least one and preferably two blank experiments are conducted with each group of samples. The difference between the acid titers of the blank and the sample is a measure of the number of equivalents of ester present.

Certain types of esters require more severe treatment for complete saponification, in which case the reaction is carried out in a citrate of magnesia bottle or in a sealed Pyrex bomb tube, and the vessels are heated at 100° for two hours, eighteen hours (overnight), or longer as required. Temperatures higher than 100° are not desirable since caustic oxidation or dehydrogenation may result.

A homogeneous reaction mixture is essential.[11] Most esters, in the amount required for analysis, are soluble in 90% methanol. Where this fails, dry methanol or *n*-propanol can be added in amounts up to 20 cc. Acetone may be used in the thirty-minute treatment at 60°, but is badly attacked in two hours at 100°.

Some precautions are necessary in measuring alkali for the individual experiments. The best precision was obtained by using a moderately rapid buret of the bottom-filling type (with three-way stopcock) graduated in 0.1 cc. and filled either by gravity or gentle suction. The top should be plugged with a pierced stopper. If the 20 cc. of solution always is withdrawn from the same graduated portion of the buret to escape minor calibration errors, a reproducibility of ±0.1% is readily attainable. Results with Lowy pipets were less satisfactory.

Relative Rate Experiments

The effect of time upon the saponification of a large group of esters was investigated using a procedure in most respects identical with that described above. Two-cc. samples (1 cc. in a few cases) of each ester were heated at 60° with 80 cc. of 0.5 *N* sodium hydroxide (instead of 20 cc. of 2 *N*) in 90% methanol for periods of ten, twenty and thirty minutes, respectively. The samples were withdrawn from the bath, rapidly cooled and titrated with standard acid. Time of heating was measured to ±0.5

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[7] L. Henry, *Compt. rend.*, **142**, 129 (1906); A. Butlerov, *Ann.*, **144**, 7 (1867).

[8] Smith and Bryant, THIS JOURNAL, **57**, 61 (1935).

[9] "International Critical Tables," Vol. I, McGraw-Hill Book Co., Inc., N. Y., 1926.

[10] L. Henry, *Rec. trav. chim.*, **26**, 438 (1907).

[11] This applies only to the initial mixture. Separation of sodium salts at a later stage is frequent and apparently without effect upon the result.

minute and the temperature to ±1°. The samples were calculated to a weight basis by means of their densities. Control experiments indicated that the errors introduced by failure to use equivalent quantities of the various esters were small. The results given in Table I should be correct to about ±0.5%, except the ten minute experiments, in which the error is probably greater.

Analytical Results

The following esters were saponified completely by the above procedure after thirty minutes at 60°: *t*-butyl, cyclohexyl and phenyl acetates; pentaerythritol tetraacetate; isopropyl and isobutyl propionates; methyl, *n*-propyl and isobutyl isobutyrates; diethylene glycol diisobutyrate; methyl 2-methylbutanoate, ethyl 3-methylbutanoate, methyl and *n*-propyl 2-methylpropenoates; ethyl malonate, tartrate and citrate; phenyl and benzyl benzoates; *n*-butyl and cyclohexyl phthalates, and the lactones phthalide and coumarin. The ester content, calculated from the average of at least two determinations each, was in no case outside the limits 98.9–100.5%, and only with coumarin did the precision fall below ±0.3%, in this case due to poor end-points with both phenolphthalein and thymol blue. Brom thymol blue indicator was employed in the experiments with phenyl acetate and benzoate, to minimize the acidic reaction of phenol. Esters requiring the more severe two-hour treatment at 100° were: 2,2-dimethylbutyl-3 and 2,4-dimethylpentyl-3 acetates; ethyl 2-methylbutanoate, ethyl trimethylacetate, methyl 2-methylpentanoate and ethyl tiglate. These analyzed 100.0–100.8%, with a precision of ±0.2%. 2,2-Dimethylbutyl-3 acetate appears in this category although results only 0.4% lower were obtained after thirty minutes at 60°. Ethyl ethylmalonate and ethyl diethylmalonate, methyl abietate, and 2,4-dimethylpentyl-3 phthalate gave quantitative conversions only after seventeen to eighteen hours at 100°. These approached theoretical within 99.0–101.1% with a maximum error of ±0.8%. 2,4-Dimethylpentyl-3 trimethylacetate was unique in that it required four hundred hours of heating at 100° for complete saponification. The process was only 84% complete after two hundred hours. Results of 101.6 ± 0.4% of the theoretical were obtained for the longer interval. These experiments were conducted in Pyrex bomb tubes, using 2 *N* sodium hydroxide in absolute methanol to ensure homogeneity. Results in 90% methanol solution were similar but erratic.

Interfering Substances

In thirty minutes at 60°, pure ketones did not affect appreciably the above procedure as shown by experiments with acetone, butanone-2, pentanone-3, heptanone-4, 2,4-dimethylpentanone-3 and mesityl oxide. Longer heating at 100° produces interference in some cases. Most aldehydes interfere with the method if present in excess of a few per cent.

Summary

1. A procedure has been developed for the quantitative saponification of esters of widely varying structure. Choice of experimental conditions is guided by relative rate experiments designed to show the effect of steric hindrance. The method has been applied to 34 esters, chiefly aliphatic.
2. The phthalate and trimethylacetate of 2,4-dimethylpentanol-3 have been synthesized.
3. *t*-Butyl acetate has been prepared from acetyl chloride and *t*-butanol in the presence of pyridine.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF WASHINGTON SQUARE COLLEGE, NEW YORK UNIVERSITY]

Photoelectric Colorimetry. VIII. "The Starch–Iodine System"[1]

BY RALPH H. MÜLLER AND MARY HELEN MCKENNA

The starch–iodine system has been the object of many investigations and the contemporary status of the subject is well summarized in Gmelin.[2] The use of the reaction between starch and iodine for analytical purposes has been limited on account of the complexity of the system, *i. e.*, the dependence upon concentration of starch, iodine, iodide, total volume and the temperature. Despite this Turner[3] has used it for some time for the colorimetric determination of iodine and recently Woodard[4] has developed a procedure with appropriate corrections for apparent deviations from Beer's law.

We have made photoelectric titrations which throw some light on the true behavior of this system and yield an interpretation of the reaction which eliminates most of the need for empirical correction.

Apparatus

All titrations were made with a photoelectric photometer employing a barrier-layer cell. The circuit has been described.[5] The only modifica-

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(1) Read before the Microchemical Section, Kansas City, Mo., Meeting of the American Chemical Society, April, 1936.

(2) Gmelins "Handbuch der anorganischen Chemie," Vol. VIII, 1933, p. 200.

(3) R. G. Turner, THIS JOURNAL, **52**, 2768 (1930).

(4) H. Q. Woodard, *Ind. Eng. Chem.*, *Anal. Ed.*, **6**, 331 (1934).

(5) R. H. Müller, *ibid.*, **7**, 223 (1935).