[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF SARAH LAWRENCE COLLEGE]

The Reversible Dissociation of *t*-Butyl Esters. Structural Effects and Reactions Mechanism

BY ROLF ALTSCHUL

The conversions of three carboxylic acids to the corresponding *t*-butyl esters by means of *i*-butene have been described in a previous paper.[1] Quantitative measurements defined this esterification as a reversible reaction, with its drive to the equilibrium state supported by catalytic amounts of sulfuric acid under anhydrous conditions in dioxane.

$$RCOOC(CH_3)_3 \underset{k_1}{\overset{k_2}{\leftrightarrows}} RCOOH + CH_2{=}C(CH_3)_2 \quad (1)$$

The dissociation equilibrium constants K_d represent the relationship between the three components.

$$K_d = (\text{acid})(\text{isobutene})/(\text{ester}) \quad (2)$$

$$K_d = k_1/k_2 \quad (3)$$

The quantitative measurements in this present publication have been carried out on a larger series of esters to supplement the original exploratory data. This study has the dual objective commonly served by kinetics: its results permit a more accurate interpretation of the reaction mechanism, and they afford additional insight into the general problem of structure and reactivity in a manner to reveal a rigid law for some cases while facilitating at least semiquantitative predictions for all. In the outline below the experimental results will be tabulated first; their significance to the relationship between structure and reactivity will be discussed next, along with some conclusions about the elementary reaction steps.

Results

In Table I the K_d constants for seven esters are summarized. They were determined, as previously, by acidimetric and bromometric titrations of samples at equilibrium.[1] The pK_a values in the table refer to the known parent acid ionization constants.[2] These quantities as well as the k_2 data in the third column are included here for the subsequent discussion. The specific esterification rates (k_2) were computed by means of equation 3 from the experimental results for K_d and for k_1, the latter being summarized in Table II below. The K_d values above were substantiated later by readings on the equilibrated kinetic runs.

TABLE I

CONSTANTS FOR THE ESTERIFICATION OF CARBOXYLIC ACIDS WITH *i*-BUTENE IN DIOXANE CONTAINING 0.835 M./L. OF H_2SO_4, AT 25°

Ester	K_d m./l.	k_2 l./(hr. × m.)	pK_a
t-Butyl benzoate, I	0.68[a]	0.49[b]	4.203
t-Butyl *p*-nitrobenzoate, II	.28[a]	.24	3.425
t-Butyl acetate, III	.70[a]	.99	4.757
t-Butyl anisate, IV	.72	.82	4.47
t-Butyl *p*-chlorobenzoate, V	.35	.57	3.979
t-Butyl *m*-nitrobenzoate, VI	.44	.19	3.494
t-Butyl 3,5 dinitrobenzoate, VII	.11	.22	2.80

[a] These constants have been reported previously, *cf.* ref. 1. [b] This constant has been checked experimentally as reported below.

TABLE II

DISSOCIATION RATES OF *t*-BUTYL ESTERS IN DIOXANE CONTAINING 0.835 M./L. OF SULFURIC ACID AT 25°

Ester	Run	Method	k_1[a] (hr.)$^{-1}$	pk_1
I	..	Acidim., Manometr.	0.33[b]	0.48
II	8	Manometr.	.067	1.18
III	6H[c]	Acidim.	.69	0.16
IV	5	Manometr.	.59	0.23
V	10	Manometr.	.20	0.70
VI	6	Manometr.	.082	1.09
VII	11	Acidim.	.024	1.62

[a] These recorded k_1 constants are *corrected* values, the catalyst concentration varying within 1.5% of the indicated average value (0.835 m./l.). The corrections were easily applicable since k_1 has been previously determined as a function of sulfuric acid molarity (*cf.* ref. 1). The consequent shifts from the experimental values are small and insignificant even in the most extreme case. [b] This constant has been reported before, see ref. 3. [c] This run was carried out by Miss Joanne Herbert.

Manometric studies, based on the vapor pressure of *i*-butene, greatly facilitated the determinations of the k_1 rate constants in Table II. This method utilized a thermostated Van Slyke instrument; it has been described in detail before.[3] It could not be applied to the volatile ester III.

The preceding papers have described the mathematical analysis of the data to yield the rate constants.[1,3] All graphs were linear over the entire reaction course, thus precluding autocatalysis. The initial ester concentrations were selected according to considerations of maximum accuracy compatible with solubility requirements. The *primary* readings of typical runs are included in the experimental part.

An additional check on our formulations was afforded through the *experimental* constant k_2 for Compound I, for which the values of K_d and k_1 are most accurately known.[1,3] The calculated quantity (Table I) and the manometric measurement matched perfectly, better than the experimental accuracy would promise. Since this is our first experimentation with an esterification rate, the

---

[1] Altschul, THIS JOURNAL, **68**, 2605 (1946).

[2] Dippy, *Chem. Rev.*, **25**, 151 (1939).

[3] Altschul and Herbert, THIS JOURNAL, **70**, 351 (1948).

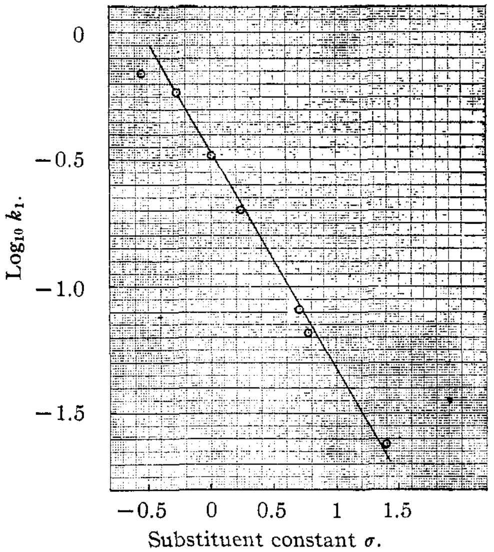


Fig. 1.—Evaluation of Hammett reaction constant for the dissociation rates of *t*-butyl esters in dioxane, containing 0.835 m./l. of sulfuric acid, at 25°: from left to right, compounds III, IV, I, V, VI, II, VII.

relevant data are fully reported in this publication (Table V). Over at least 80% of its course the addition reaction observes the linear relationship postulated by the mathematical function for a reversible bimolecular process.[4] The resulting rate constant is $k_2 = 0.49$ liter (moles × hours)$^{-1}$.

Interpretation.—The previously exposed nearly constant (k_1K_a) product[5] appears to prevail for all aromatic esters, over a forty-seven-fold

$$pk_1 + pK_a = 4.61 \pm 0.07 \qquad (4)$$

range of K_a constants within the indicated limits. This is perhaps relevant to the reaction mechanism,[1,6] for which the initiating step was written as a reversible conversion of the ester to its conjugate acid, necessary for the subsequent slow and rate-controlling dissociation.[7] The inverse function represented by Equation (4) above can be interpreted as progressively further displacements of the precursor equilibria to the left for the stronger carboxylic acids.

A more quantitative formulation is possible for the functional relationship between *Structure and Reactivity*. An apparent simple correlation, widely recognized between series of equilibrium or rate constants pertaining to reactions of para- or meta-substituted benzoic acid derivatives, has found its expression in the "Reaction Constants ρ" and "Substituent Constants σ."[8] Such rigid parallelism of reactivity is credited to identical entropy differences between reactants and products, thus reducing changes of chemical activity to elementary physical concepts, welcome and amenable in their simplicity.[9]

In line with the Hammett definition

$$\sigma = \log K_a - \log K_a^0 \qquad (5)$$

our substituent constants were computed either from the known K_a values (Table I), or were taken directly from the literature,[5] to be plotted against the logarithm of the k_1 constants. Our case exemplifies the fundamental relationship particularly well, as is evident from Fig. 1. The resulting reaction constant, derived graphically from the slope, $\rho = -0.841$. It is clearly relevant only to the aromatic esters, while the aliphatic compound III does not fall within the limitations of the rigid law.[10] The *negative* value of the reaction constant indicates least reactivity for the derivative of the strongest acid, in distinct contrast to other reaction of esters.[8]

Although all three series of constants (k_1, k_2, and K_d) rise with falling K_a values, this dependence is sensitive only for the k_1 data (Table I). For the others a ninety-fold depression of acidity effects only a 6.4-fold increase of K_d and a 4.5-fold increase of k_2 (compare III and VII). These differences are so small that a precise interpretation according to the Hammett formulation is incompatible with the relatively large experimental error.[1]

From a synthetic point of view, the K_d and k_2 constants are of course most essential, defining, as they do, the speed and extent of esterification with *i*-butene. Qualitatively speaking, the trend promises slightly *faster* yet *less complete* conversions for the *weaker* carboxylic acids.

Activation Energies.—In combination with preceding measurements at 35° the data provide for an estimate of the energies of activation for the dissociation of three esters in the presence of 0.835 m./l. of sulfuric acid.[1] Ester I, $\Delta E = 17$ kcal./mole[3]; Ester II, $\Delta E = 16$ kcal./mole; Ester III, $\Delta E = 20$ kcal./mole.

Experimental

Materials.—The previous batches of dioxane, 100% sulfuric acid and benzoic acid were used.[3] The esters were generally synthesized either by direct esterification of the carboxylic acids with *i*-butene,[1] or by the pyridine-acid chloride method.[6,11] Much of the relevant information is listed in Table III.

The solid esters were purified by crystallization, while distillations through all-glass distilling assemblies was applied to the liquids. Samples of esters prepared through the acid chloride were tested with alcoholic silver nitrate; the results were uniformly negative, with the exception of compound V which gave a very slow positive reaction,

---

[4] Conant and Bartlett, *ibid.*, **54**, 2881 (1932).

[5] Reference 1, footnote 16.

[6] Cohen and Schneider, THIS JOURNAL, **63**, 3382 (1941).

[7] Reference 1, Equation 3.

[8] Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., New York, N. Y., 1940, Chapter VII.

[9] (a) Ref. 5, Chapters III, IV, VII; (b) Remick, "Electronic Interpretation of Organic Chemistry," John Wiley & Sons, Inc., New York, N. Y., 1943, Chapter VII; (c) Wheland, "The Theory of Resonance," John Wiley & Sons, Inc., New York, N. Y., 1944, Chapters VII, VIII.

[10] For Compound III, the substituent constant obviously has no physical meaning. It was obtained through Equation (5) only in order to be presented in the graph along with the related benzoate esters.

[11] Norris and Rigby, THIS JOURNAL, **54**, 2088 (1932).

TABLE III

PREPARATION AND PHYSICAL CONSTANTS OF *t*-BUTYL ESTERS

Ester	Method	Physical constants	Reference
I	Pyr. + RCOCl	B. p. (2–3 mm.) 75–79°;	6, 11
	Acid + C_4H_8	n^{23}D 1.4893; d_{24} 0.993	1
II[a]	Acid + C_4H_8	M. p. 115–116°	1, 12
III[a]	Acid + C_4H_8	B. p. (755 mm.) 95.5–96.5°	1
	$Ac_2O + C_4H_9OH$	n^{27}D 1.3827; d_{28} 0.855	11
IV	Pyr. + RCOCl	B. p. (2.5–3 mm.) 162–162.5°; n^{25}D 1.5370; d_{25} 1.0424	...
V[b]	Pyr. + RCOCl	B. p. (3 mm.) 158.5°; n^{25}D 1.5041; d_{25} 1.1011	...
VI	Pyr. + RCOCl	M. p. 31°; d_{25} 1.1513; n^{25}D 1.511[c]	...
VII[d]	Pyr. + RCOCl	M. p. 141–142°	13
	Acid + C_4H_8	M. p. 141–142°	

[a] This preparation was carried out by Miss Lucille J. Holljes. [b] This preparation was carried out by Mrs. Cynthia H. Yoder. [c] Density and refractive index were determined for the supercooled liquid. [d] This preparation was carried out by Mr. Jon J. Sugrue.

presumably due to solvolysis of the nuclear-substituted halogen.

For more complete details as to synthetic procedures the previous publications should be consulted.[1]

Combustion analyses of the previously unrecorded esters IV, V and VI, were carried out by Dr. Carl Tiedcke: Calcd. for IV: C, 69.22; H, 7.75. Found: C, 69.71; H, 8.01. Calcd. for V: C, 62.11; H, 6.16. Found: C, 61.90; H, 6.10. Calcd. for VI: C, 59.21; H, 5.87. Found: C, 59.63; H, 5.96.

Quantitative Measurements. K_d Constants.—The previous technique was applied in all details. Samples of known initial molarities were stored in sealed ampoules in a thermostatic bath at 25 ± 0.1° until equilibrium was attained within a few days. They were then analyzed for the concentration of acid and of *i*-butene by means of acidimetric and by means of bromometric titrations, respectively.[1,3] The results are summarized in Table I in the text.

k_1 Constants.—Both the manometric and the volumetric methods have been outlined in detail before[1,3] and were followed throughout with only one minor change for the acidimetry involving compound VII, as follows: Aliquot samples were added to a slight excess of *warm* standard aqueous alkali. This prevented temporary precipitation of the organic acid, which, without this modification, tended to separate along with the ester and was slow to redissolve. After immediate rapid cooling, back-titration with standard hydrochloric acid followed as usual. Blank tests revealed absence of saponification under these conditions. The experimental results of two representative runs are tabulated below in the customary manner.

The terminology in the column heads of Table IV has been chosen in accord with the preceding publications[1,3]: p_i signifies the partial pressure of *i*-butene, while Q stands for the variable term in the integrated rate equation.

TABLE IV

DISSOCIATION OF *t*-BUTYL ESTERS IN DIOXANE SOLUTIONS, CONTAINING SULFURIC ACID, AT 25 ± 0.1° (MANOMETRIC MEASUREMENTS)

Hours	p_i, cm.	Q	Hours	p_i, cm.	Q
Run 5; $(IV)_0$ = 0.481 m./l.			Run 10; $(V)_0$ = 0.277 m./l.		
$(H_2SO_4)_0$ = 0.818 m./l.			$(H_2SO_4)_0$ = 0.847 m./l.		
0.28	0.45	2.53	0.58	0.08	3.72
.40	1.46	2.78	0.77	0.49	4.03
.57	3.15	3.32	1.58	1.89	5.49
.72	4.75	3.96	2.07	2.55	6.48
.94	6.52	4.98	2.42	2.95	7.29
1.06	7.54	5.76	3.00	3.67	9.21
1.30	8.84	7.13	3.45	4.06	10.62
1.55	10.19	9.30	3.87	4.39	12.26
1.75	11.11	11.58	4.53	4.94	16.23
1.92	11.69	13.62	5.10	5.27	20.02
2.47	13.22	24.42	5.78	5.67	27.30
2.90	14.02	40.90	7.12	6.27	62
3.67	14.92	148	7.60	6.37	78
4.12	15.07	....	8.03	6.49	112
4.59	15.27	....	9.35	6.77	....
4.90	15.27	....	9.62	6.77	....

k_2 Constant.—For the manometric determination of the esterification rate, 5 cc. of 1.695 molar sulfuric acid and 1 cc. of dioxane was introduced into the van Slyke chamber and degassed, followed by admission of 4 cc. of a dioxane solution containing 1.572 m./l. of benzoic acid and roughly 1.72 m./l. of *i*-butene. Readings were taken as usual, and, at equilibrium, samples were titrated in the customary manner indicating an equilibrium concentration of 0.372 m./l. of benzoic acid (calcd., 0.37 m./l.). Table V contains the experimental data which were substituted into the relevant equation after transformation from pressure into concentration.[3]

TABLE V

ESTERIFICATION OF *i*-BUTENE WITH BENZOIC ACID IN DIOXANE, CONTAINING 0.847 M./L. OF SULFURIC ACID AT 25 ± 0.1°

Hours	p_i, cm.	(*i*-butene), m./l.	Q
0.09	32.77	0.643	7.69
.20	31.14	.611	8.74
.42	29.75	.583	10.2
.70	28.42	.557	11.5
.85	27.40	.536	13.4
1.13	26.42	.518	15.7
1.40	25.54	.500	19.4
1.77	24.47	.480	25.5
2.63	22.85	.459	38
3.00	22.20	.435	99
—	21.5		

The Q term stands for

$$Q = \frac{X + (X_e + c + K_d)}{X - X_e} \qquad (6)$$

to be substituted into the rate equation.[4]

---

(12) Hueckel, Nerdel and Reimer, *J. prakt. Chem.*, **149**, 311 (1937).

(13) Huntress and Mulliken, "Identification of Pure Organic Compounds," John Wiley & Sons, Inc., New York, N. Y., 1941, p. 430.

Summary

The equilibrium and dissociation rate constants are reported for the acid-catalyzed reversible dissociation of seven *t*-butyl esters into the respective carboxylic acids and *i*-butene, in dioxane solution at 25°. The reverse esterification rate constant, determined experimentally in one case, matches the value calculated from the preceding data.

The relationship between these results and the known parent acid ionization constants, viewed in terms of the general problem of structure and reactivity, indicates faster yet less complete esterification for the weaker carboxylic acids. The dissociation rate constants yield to quantitative treatment, and the Hammett reaction constant is calculated graphically for the aromatic esters.

Additional clues for more intimate analysis of the reaction mechanism are interpreted.

Physical constants for three new *t*-butyl esters are presented.

Bronxville 8, N. Y. Received February 24, 1948

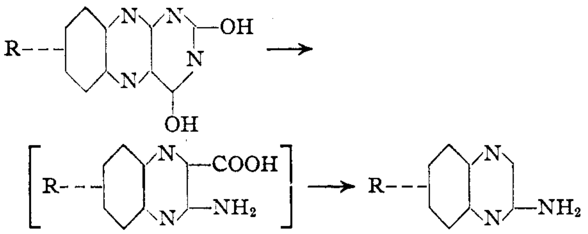
[Contribution from the Research Laboratories of Merck and Co., Inc.]

Substituted Sulfaquinoxalines. II. Some Derivatives and Isomers of 2-Sulfanilamidoquinoxaline[1]

By F. J. Wolf, R. H. Beutel and J. R. Stevens[2]

In view of the promising chemotherapeutic action of sulfaquinoxaline[3,4] as well as its unique pharmacological properties,[5] the preparation of isomers and derivatives was undertaken.

The preparation of 6,7-dimethyl-2-aminoquinoxaline, 6(or 7)-chloro-2-aminoquinoxaline and a mixture of 2(and 3)-amino-5,6-benzoquinoxaline was carried out by degradative cleavage of the corresponding alloxazine under essentially the same conditions as those described in the literature for the cleavage of alloxazine[3] and substituted alloxazines.[6]



Only one of the two possible isomers was obtained when 7(or 8)-chloroalloxazine was cleaved; whereas, cleavage of benzalloxazine yielded 2- and 3-amino-5,6-benzoquinoxaline.

As the above method is not applicable to the preparation of 2-amino-3-alkylquinoxaline compounds, 2-amino-3-methylquinoxaline was prepared from 2-hydroxy-3-methylquinoxaline[7] by chlorination and amination of the resulting chloro compound.

Attempts to convert 2-hydroxy-3-methylquinoxaline into the amine by modifications of the Bucherer reaction were unsuccessful. However, when more rigorous conditions were applied to 2-hydroxyquinoxaline[8] the desired 2-aminoquinoxaline was obtained[9] in low yield.

In addition, the isomeric 5-aminoquinoxaline and 6-aminoquinoxaline[10] were prepared. The former was obtained from the reaction of 2,3-diaminoacetanilide with sodium glyoxal bisulfite followed by hydrolysis of the resulting 5-acetaminoquinoxaline to the desired product.

The amines were converted into the desired sulfonamides by the usual procedures and in addition the *p*-aminobenzoate of 2-aminoquinoxaline was prepared.

Acknowledgment.—The authors are indebted to Dr. R. T. Major and Dr. M. Tishler for their kind encouragement and advice.

Experimental

Alloxazines.—The preparation of 7(or 8)-chloroalloxazine is typical of the method.

7(or 8)-Chloroalloxazine.—A mixture of 60 g. of 4-chloro-2-nitroaniline and 200 g. of iron powder in 300 ml. of ethanol was stirred and refluxed and 12 ml. of 6 *N* hydrochloric acid was added dropwise during the first three hours. After eighteen hours the reaction mixture was filtered and concentrated *in vacuo*. The residue was dissolved in 135 ml. of 2.5 *N* hydrochloric acid and 400 ml. of water, heated to 85° and added to a solution of 50 g. of alloxan monohydrate in 400 ml. of water at 85°. The mixture was stirred for one hour at 85–90° (a yellow precipitate appeared almost instantly) and filtered. The precipitate, after washing with water and ethanol and drying, weighed 75.4 g. (88% yield based on the nitro compound). The product was sufficiently pure for degradation purposes and did not melt when heated at 360°.

2-Amino-6,7-dimethylquinoxaline.—7,8-Dimethylalloxazine[11] (lumichrome) is not attacked by prolonged boiling with 30% sodium hydroxide. It was cleaved to 2-amino-3-carboxy-6,7-dimethylquinoxaline by heating at 170–175° with concentrated aqueous ammonia.

---

[1] For the previous paper in this series see Stevens, Pfister and Wolf, This Journal, **68**, 1035 (1946).

[2] Present address, J. T. Baker Co., Phillipsburg, N. J.

[3] Weijlard, Tishler and Erickson, This Journal, **66**, 1957 (1944).

[4] Smith and Robinson, *Proc. Exptl. Biol. Med.*, **57**, 292 (1944).

[5] Seeler, Mushett, Graessle and Silber, *J. Pharm.*, **82**, 357 (1944).

[6] Weijlard and Tishler, This Journal, **67**, 1231 (1945).

[7] Hinsberg, *Ann.*, **292**, 249 (1896).

[8] Gowenlock, Newbold and Spring, *J. Chem. Soc.*, 622 (1945).

[9] This work was carried out by Mr. Weijlard in this Laboratory.

[10] Hinsberg, *Ann.*, **237**, 345 (1887).

[11] Kuhn and Rudy, *Ber.*, **67**, 1826 (1934).