Comparative Strengths of Aliphatic Acids and Some Other Carboxylic Acids in Benzene at 25°

MARION MACLEAN DAVIS AND MAYA PAABO

National Bureau of Standards, Washington, D. C.

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In continuation of earlier measurements by Davis and Hetzer, the strengths of the following acids (HA) in benzene have been determined: all of the straight-chain aliphatic acids containing from 2 to 20 carbon atoms except the 15- and 19-carbon acids; isobutyric and trimethylacetic (pivalic) acids; and *o*-benzoylbenzoic, *trans*-cinnamic, 2,4- and 2,5-dimethylbenzoic, 2-furoic, and 1- and 2-naphthoic acids. The relative strengths in benzene are expressed as equilibrium constants (K_{BHA}) for 1:1 association of HA with 1,3-diphenylguanidine (B) in the presence of the indicator acid (3′,3″,5′,5″-tetrabromophenolphthalein ethyl ester, "bromophthalein magenta E″). Dimerization constants ($K_{1,2}$) for some of the carboxylic acids have also been deduced from the absorbance data; the values compare favorably with those available from other measuring procedures. The new results conform to linear relationships between log K_{BHA} (benzene, B = DPG) and pK_a (water) derived previously for *meta*- and *ortho*-substituted acids. The significance of the results and other theoretical and experimental aspects of the work are discussed.

This is the fourth paper in a series dealing with the strengths of acids in benzene. The method was developed by Davis and Hetzer, and applied to the determination of the relative strengths of forty acids of the benzoic acid series in benzene at 25°.[1] The strengths of the acids were determined by ascertaining their tendencies to associate with 1,3-diphenylguanidine (DPG) in competition with the phenolic indicator "bromophthalein magenta E" (3′,3″,5′,5″-tetrabromophenolphthalein ethyl ester), as is indicated below.

$$\text{B (reference base)} + \text{HI (indicator)} \rightleftharpoons \text{BHI} \qquad (1)$$

$$\text{B} + \text{HA (carboxylic acid)} \rightleftharpoons \text{BHA} \qquad (2)$$

The strengths were expressed as values of K_{BHA}, the equilibrium constant corresponding to eq 2 (or, alternatively, as values of log K_{BHA}). The second study[2] was performed at 20, 25, and 30°, to determine the comparative behavior of diphenylguanidine and triethylamine as reference bases and obtain approximate values of thermodynamic constants; in this study, HA was benzoic acid. Later,[3] approximate values of thermodynamic constants were calculated for several of the aromatic acids by combining results obtained at 25° with additional data for 30°.

The same method of determining relative acidic strengths in benzene has been extended to 19 aliphatic acids and the following seven acids: *o*-benzoylbenzoic, *trans*-cinnamic, 2,4-dimethylbenzoic, 2,5-dimethylbenzoic, 2-furoic, 1-naphthoic, and 2-naphthoic acids. The aliphatic acids studied were isobutyric, trimethylacetic (pivalic), and all of the straight-chain acids containing from 2 to 20 carbon atoms except the 15- and 19-carbon acids.

Experimental Section

The benzene, diphenylguanidine, and bromophthalein magenta E (BPM) were either the same highly purified materials as before or were similar in origin and treatment.[1-3] In most cases aliphatic acids of high grade were used from freshly opened containers. The 8- and 9-carbon acids were frozen once, the first part to liquefy being discarded. The 10-, 11-, 12-, 16-, and 18-carbon acids were heated in a vacuum oven for two or more hours during which the temperature rose to a few degrees above the melting point. *trans*-Cinnamic acid and the aromatic acids were crystallized at least once from an appropriate solvent, then dried in a vacuum oven. 2-Furoic acid was used as received. Melting points of these seven acids (by the capillary method) were very sharp and in good agreement with values in the literature.

The procedures followed, including precautions to minimize moisture content, conformed to the pattern previously described.[1-3] Throughout, the stoichiometric concentration of the indicator (C_{HI}) was 5×10^{-5} *M*, and the concentrations of base (C_B) and carboxylic acid (C_{HA}) were, respectively, nC_{HI} and $n'C_{HI}$, where *n* and *n′* were usually 1, 2, or 3. Using such dilute solutions and closely equivalent stoichiometric concentrations of the three reactants ensured that other associative reactions (in particular, self-association of the carboxylic acid or association of carboxylic acid with base in 2:1 ratio) would introduce, at most, only very small errors into the results.

Steps in the calculation of association constants and examples of raw data were previously presented in detail.[4] "Correction" of K_{BHA} for benzoic acid by taking the monomer–dimer equilibrium of the acid (eq 3) into consideration was also explained.[5]

$$2\text{HA} \rightleftharpoons (\text{HA})_2 \qquad (3)$$

A similar procedure was used in this work to obtain corrected values of K_{BHA} for nine of the acids (see later discussion).

Benzene solutions of aliphatic acids containing seven or more carbon atoms exhibited poor drainage and a tendency to collect into small droplets on the glass wall above the main body of a solution. This behavior became more pronounced as the number of carbon atoms in the molecule increased, and brought to mind observations made by Langmuir[6] and by Blodgett[7] in

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[1] M. M. Davis and H. B. Hetzer, *J. Res. Natl. Bur. Std.*, **60**, 569 (1958). In this paper K_{BHA} (or K_{assocn}) is substituted for the symbol K″, which was used in most of the earlier work.

[2] M. M. Davis and M. Paabo, *J. Am. Chem. Soc.*, **82**, 5081 (1960).

[3] M. M. Davis and H. B. Hetzer, *J. Res. Natl. Bur. Std.*, **65A**, 209 (1961).

[4] See ref 1, section 3.2.

[5] See ref 1, section 4.1.

[6] I. Langmuir, *J. Franklin Inst.*, **218**, 143 (1934). Speaking of the deposition of stearic acid from a benzene solution, he said, ". . . The molecules of stearic acid in a dilute solution in benzol diffuse one by one onto the glass surface. The first ones that arrive become firmly attached to the glass by their COOH groups. Experiments indicate clearly that at room temperature there is practically no surface mobility of these adsorbed molecules, so that each molecule remains attached to the point at which it first arrived at the surface. After a considerable fraction of the surface is thus covered, newly arriving molecules find increasing difficulty in finding suitable points of attachment on the glass. When the process is complete, there are still many portions of the glass not covered by COOH, but the vacant spaces are too small to permit the entrance of additional COOH groups. We can conclude that the last of the molecules to become attached to the surface are not able to attach themselves firmly to the surface because of the crowding by their neighbors. Such an adsorbed film is therefore nonhomogeneous. Because of the larger spacing than in a close-packed film, the upper surface consists partly of CH_2 . . . If a drop of water is placed on such a film on glass, some of the adsorbed molecules which are crowded by their neighbors and are therefore not held so firmly to the glass can reverse their orientation so that the carboxyl group attaches itself to the water . . ." In the work discussed here, the carboxyl group would become attached to diphenylguanidine rather than to water.

[7] K. B. Blodgett, *J. Am. Chem. Soc.*, **56**, 495 (1934). Blodgett noted that "films (of stearic acid) deposited on glass with the molecules oriented so that only CH_3 groups are exposed at the upper surface form a surface which oil and benzene will not wet. A drop of pure mineral oil, or tetradecane, or benzene placed on a layer that is 1, 2, or 5 . . . molecules deep rolls about on the surface leaving no trace of its path, although stearic acid is soluble in these liquids."

TABLE I

COMPARATIVE VALUES OF LOG K FOR 1:1 ASSOCIATION OF ALIPHATIC ACIDS WITH 1,3-DIPHENYLGUANIDINE IN BENZENE AT 25°[a,b]

Name of acid	No. of carbons	Log K_{assocn}								pK_a, water[c]
		Value of n'								
		1	2	3	2	3	3	4		
		$n = 1$			$n = 2$		$n = 3$		Av	
Acetic	2	4.43	4.37	4.36	4.42	4.38	4.36	4.42	4.39	4.76
Propionic	3	4.28	4.30	4.30	4.32	4.31	4.36	4.28	4.31	4.87
Butyric	4	4.25	4.33	4.29	4.32	4.30	4.33	4.27	4.30	4.82
Isobutyric	4	4.43	4.37	4.37	4.41	4.38	4.43	4.41	4.40	4.86
Valeric	5	4.29	4.34	4.28	4.32	4.30	4.39	4.26	4.31	4.86
Trimethylacetic (pivalic)	5	4.44	4.38	4.38	4.42	4.41	4.42	4.41	4.41	5.05
Hexanoic (caproic)	6	4.29	4.28	4.27	4.30	4.32	4.35	4.32	4.30	4.88
Heptanoic (enanthic)	7	4.30	4.29	4.29	4.34	4.32	4.35	4.31	4.31	4.89
Octanoic (caprylic)	8	4.32	4.28	4.28	4.32	4.30	4.35	4.34	4.31	4.89
Nonanoic (pelargonic)	9	4.35	4.34	4.30	4.36	4.33	4.38	4.34	4.34	4.96
Decanoic (capric)	10	4.35	4.30	4.32	4.34	4.32	4.37	4.36	4.34	
Undecanoic	11	4.37	4.31	4.29	4.36	4.29	4.37	4.32	4.33	
Lauric	12	4.31	4.34	4.30	4.36	4.34	4.35	4.34	4.33	
Tridecanoic	13	4.39	4.29	4.29	4.34	4.32	4.35	4.34	4.33	
Myristic	14	4.34	4.30	4.30	4.34	4.33	4.35	4.31	4.32	
Palmitic	16	4.37	4.33	4.31	4.37	4.32	4.38	4.32	4.34	
Heptadecanoic (margaric)	17	4.32	4.28	4.27	4.32	4.28	4.32	4.31	4.30	
Stearic	18	4.32	4.32	4.32	4.38	4.32	4.39	4.36	4.34	
Arachidic (eicosanoic)	20	4.31	4.29	4.30	4.36	4.30	4.35	4.34	4.32	

[a] Determined by the spectrophotometric method of Davis and Hetzer,[1] in which the aliphatic acid (HA) and the indicator bromophthalein magenta E (HI) compete for diphenylguanidine (B). The stoichiometric concentrations (in moles per liter) were, approximately $C_{\mathrm{HI}} = 5 \times 10^{-5}$; $C_{\mathrm{B}} = nC_{\mathrm{HI}}$; $C_{\mathrm{HA}} = n'C_{\mathrm{HI}}$. Values of n and n' are given in the table. [b] In this paper K_{assocn} and K_{BHA} are used synonymously. Log K_{assocn} was not corrected for dimerization of HA. [c] Determined or cited by J. F. J. Dippy, *J. Chem. Soc.*, 1222 (1938).

TABLE II

"CORRECTED" VALUES OF LOG K FOR 1:1 ASSOCATION OF ALIPHATIC ACIDS WITH 1,3-DIPHENYLGUANIDINE IN BENZENE AT 25°[a]

Acid	Range of n'[b]	No. of expt	Log $K_{1,2}$ giving best fit[c-e]	Log K_{assocn}, cor	Rel std dev of cor K_{assocn}, %
Acetic	1–18	13	2.92	4.45	5.0
Isobutyric	1–5	9	2.77	4.44	4.1
Trimethylacetic	1–20	15	2.85	4.46	2.9
Lauric	1–6[f]	17	2.52	4.35	3.9
Stearic	1–20	22	2.60	4.37	3.2

[a] K is expressed in liters per mole. Experimental details and meaning of symbols are given in the text and in footnote *a* of Table I. [b] Unless otherwise indicated the value of n was 1, 2, or 3. [c] $K_{1,2}$ (in liters per mole) is the equilibrium constant corresponding to the reaction $2\mathrm{HA} \rightleftharpoons (\mathrm{HA})_2$. [d] The following log $K_{1,2}$ values (reduced to molar units) were obtained for dry benzene solutions at 30° by the electric polarization method [see H. A. Pohl, M. E. Hobbs, and P. M. Gross, *J. Chem. Phys.*, **9**, 408 (1941); A. A. Maryott, M. E. Hobbs, and P. M. Gross, *J. Am. Chem. Soc.*, **71**, 1671 (1949)]: acetic acid, 2.57; propionic acid, 2.59; butyric acid, 2.63; trimethylacetic acid, 2.84; stearic acid, 2.72. [e] J. Wenograd and R. A. Spurr [*J. Am. Chem. Soc.*, **79**, 5844 (1957)] obtained the following log $K_{1,2}$ values for dry *carbon tetrachloride* solutions (24°) by infrared spectroscopy: acetic acid, 3.38; propionic acid, 3.39; valeric acid, 3.43; caproic acid, 3.27; lauric acid, 3.29. [f] The value of n was 0.5, 1, 2, or 3.

describing their studies of fatty acid films deposited on glass. It clearly placed limitations on the precision and accuracy attainable in our experiments, but the results (see later discussion) did not reveal any major discrepancies attributable to it.

Results

Aliphatic Acids.—The 19 acids studied are listed in Table I. Columns 3–9 contain "raw" values of log K_{BHA} which were obtained in seven parallel experiments (see footnote *a*). The average value is given in column 10, and the corresponding aqueous pK_a from the literature is in the last column.

Table II contains "corrected" values of log K_{BHA} which were obtained for five of the acids by taking the monomer–dimer equilibrium of the acid (eq 3) into consideration.[5] Experimental values of the dimerization constant ($K_{1,2}$) not being available for benzene solutions at 25°, the values of log $K_{1,2}$ given in column 4 are approximate values fitted to the data (see later discussion).

Other Acids.—Values of log K_{BHA} for the remaining seven acids are presented in Table III. Besides the raw value given for all seven acids (column 5), a corrected value is also given for four of the acids (column 6), together with the estimated value of log $K_{1,2}$ (column 8). Aqueous pK_a values are in the last column.

In Figure 1 the values of log K_{BHA} for the seven acids just mentioned are plotted *vs.* the corresponding pK_a values (see filled circles). Points for acetic, isobutyric, and trimethylacetic acids (see data in Table II) are also included (half-filled circles). Some of the points lie near a line labeled "m-substd. Acids," the equation for which is

$$\log K_{\mathrm{BHA}} = 14.37 - 2.17\mathrm{p}K_a \qquad (4)$$

Equation 4 was obtained in the first investigation[8] by the least-squares method using pK_a and log K_{BHA} values for seven *meta*-substituted benzoic acids (R = Br, Cl, CN, F, I, CH_3, or NO_2). The point obtained for the indicator acid falls on this line; its coordinates are practically identical with those for 2-naphthoic acid.

The remaining points fall close to the line labeled "o-substd. Acids," the equation for which is

$$\log K_{\mathrm{BHA}} = 10.06 - 1.30\mathrm{p}K_a \qquad (5)$$

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(8) See ref 1, section 4.2b.

TABLE III

VALUES OF LOG K FOR 1:1 ASSOCIATION OF AROMATIC AND OTHER CARBOXYLIC ACIDS WITH 1,3-DIPHENYLGUANIDINE IN BENZENE AT 25°[a]

Acid	Range of n	Range of n'	No. of expt	Log K_{assocn} Uncor	Log K_{assocn} Cor	Rel std dev of K_{assocn},[b] %	Log $K_{1,2}$[c]	pK_a, water
o-Benzoylbenzoic	0.5–3	0.5–4	10	6.44		2.5		3.54[d]
trans-Cinnamic	1–3	1–4	8	4.86	4.91	2.1	3.00	4.44[e]
2,4-Dimethylbenzoic	1–3	1–4	15	4.72	4.75	4.4	2.63	4.18[f]
2,5-Dimethylbenzoic	1–2	1–3	4	4.86		3.5		3.98[f]
2-Furoic	0.5–3	0.5–4	9	6.07		4.3		3.17[g]
1-Naphthoic	0.5–3	0.5–4	10	5.31	5.34	3.0	2.96	3.69[f]
2-Naphthoic	0.5–3	0.5–4	9	5.39	5.41	1.2	2.60	4.16[f]

[a] For experimental details and meaning of symbols see text, footnote *a* of Table I, and footnote *d* of Table II. All equilibrium constants are in molar units. In this paper the expressions K_{assocn} and K_{BHA} are used synonymously. [b] For the *corrected* association constant when a correction was applied. [c] Obtained in correcting raw values of K_{assocn}. The $K_{1,2}$ value adopted is the one which gives greatest improvement in the precision of K_{assocn} values. [d] L. G. Bray, J. F. J. Dippy, and S. R. C. Hughes, *J. Chem. Soc.*, 265 (1957). [e] J. F. J. Dippy and R. H. Lewis, *ibid.*, 1008 (1937). [f] J. F. J. Dippy, S. R. C. Hughes, and J. W. Laxton, *ibid.*, 1470 (1954). [g] W. L. German, G. H. Jeffery, and A. I. Vogel, *ibid.*, 1604 (1937).

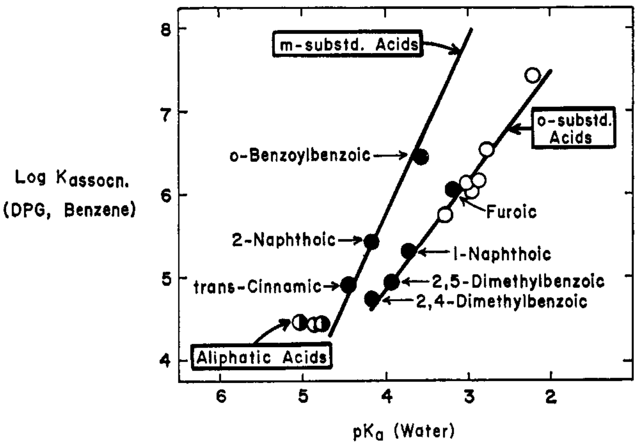

Figure 1.—Relative acidic strengths in benzene and water at 25°. The strength in benzene is expressed as the value of log K for 1:1 association of the acid with 1,3-diphenylguanidine. Equations for the two lines are given in the text. *Open* circles, results from previous work;[1] *half-filled* circles, values for three aliphatic acids (acetic, isobutyric, trimethylacetic), this work (see Table II); *filled* circles, this work (Table III).

A slightly different equation was obtained earlier[9] using coordinates for *six* mono-*ortho*-substituted benzoic acids (R = CH_3, F, Cl, Br, I, or NO_2); the revised equation (eq 5) was obtained by including the coordinates for 2,4-dimethylbenzoic acid (see Table III). The point found earlier[9] for *o*-toluic acid is too close to that for 2,5-dimethylbenzoic acid to be shown in Figure 1.

Discussion

Scales of Acidity and Basicity in Aprotic Solvents.—Systematic experimentation using aprotic solvents such as benzene,[10-12] as well as other solvents of low acid-base character (*e.g.*, acetic acid[13] and acetonitrile[14]) has made it increasingly clear that a *primary acid-base reaction* involves 1:1 association, irrespective of whether the electron acceptor is a Lewis acid or a Brønsted acid. Reactions similar to those denoted by eq 1 and 2 yield *hydrogen-bonded* ion pairs (symbolized by $BH^+ \cdots A^-$) which are quite stable. The separation of BH^+ from A^- does not occur to any significant extent unless competing hydrogen-bonding reactions are made possible. Commonly, this is accomplished by adding a solvent which can hydrogen bond to cations, anions, or both (water and alcohols being, of course, the most familiar examples of such solvents). [A different way of promoting separation of BH^+ from A^- is to add an excess of B or of HA, or a second base B′ or acid HA′, to bring about the formation of "conjugate ions" (BHB^+ or AHA^-) or "heteroconjugate ions" ($B'HB^+$ or $A'HA^-$).[15]] From the new point of view, the separation of BH^+ from A^- is regarded as a *secondary reaction* which occurs more extensively when the tendency toward the primary reaction is great.

Benzene is a too weakly basic solvent to serve as a reference base for practical acidity scales involving acids such as phenols and carboxylic acids—a much stronger base must be selected. So far, either 1,3-diphenylguanidine or triethylamine has generally been used. A set of numerical values of equilibrium constants corresponding to eq 2, obtained using either of these reference bases with a series of acids, constitutes a scale of relative acidities. In the work using diphenylguanidine, most of the values found for K_{BHA} have been in the range 10^4–10^7. The logarithmic equivalent of this scale corresponds to the pK_a scale in water. Obviously, in an aprotic solvent like benzene there will be a different acidity (or basicity) scale for every reference base (or acid) used, not a single acidity scale as in water.

From what has been said, relative acidities expressed on the log K_{BHA} scale will be expected to parallel the equivalent aqueous pK scale, though individual exceptions may occur for steric and other reasons. In this investigation, as in the preceding work,[1] the expected parallelism was observed. Remembering that "pK" values signify *negative* logarithms of aqueous dissociation constants, we find that in accord with expectations the two linear correlations shown in Figure 1 are *numerically* inverse relationships.[16]

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(9) See ref 1, section 4.2d.

(10) M. M. Davis and P. J. Schuhmann, *J. Res. Natl. Bur. Std.*, **39**, 221 (1947).

(11) M. M. Davis and H. B. Hetzer, *ibid.*, **46**, 496 (1951); *ibid.*, **48**, 381 (1952); *J. Am. Chem. Soc.*, **76**, 4247 (1954); also work cited.

(12) A. A. Maryott, *J. Res. Natl. Bur. Std.*, **38**, 527 (1947); **41**, 7 (1948); M. M. Davis and E. A. McDonald, *ibid.*, **42**, 595 (1949).

(13) T. L. Smith and J. H. Elliott, *J. Am. Chem. Soc.*, **75**, 3566 (1953); I. M. Kolthoff and S. Bruckenstein, *ibid.*, **78**, 1 (1956), and later.

(14) J. F. Coetzee and G. P. Cunningham, *ibid.*, **87**, 2534 (1965), with references to earlier related papers.

(15) I. M. Kolthoff and M. K. Chantooni, Jr., *ibid.*, **85**, 2195 (1963).

(16) Two additional linear correlations were obtained in the earlier more extensive investigation—one for *para*-substituted acids and a less precise one for 2,6-disubstituted acids; see ref 1, sections 4.2c and 4.2d.

Like most workers in this area, we have found molarities to be the most useful and convenient units of concentration. Association constants determined over the low ranges of concentration customary in most spectrophotometric procedures are believed to be good approximations to the true values, and it seems satisfactory to regard the *molar concentrations* concerned as not differing measurably from *activities*. As a desirable reminder that—in the most fundamental sense—union, rather than disunion, is the major feature of acid-base interactions, we prefer the term "association constant" to alternative expressions which have been proposed (*e.g.*, "equilibrium quotient"[17] or "ionization constant"[18]).

Recently, Trémillon and associates have performed experiments somewhat analogous to the ones described here (though not including corrections for the monomer–dimer equilibrium of HA).[19] Their results would be numerically identical with values here called "log K_{BHA}" values, but are referred to as "pK" values. Their pK values are obtained in the following manner. (1) The acid–base reaction is formulated as an *association*, with chemical equations similar to our eq 1 and 2. (2) The equilibrium constant for the acid–base reaction is then formulated as a *dissociation*.

$$K = (\mathrm{B})(\mathrm{HA})/(\mathrm{BHA}) \tag{6}$$

(3) Lastly, values of log K_{dissocn}, calculated by eq 6, are converted to the negative logarithms or pK values. We do not see any advantage in extending the use of the symbol "pK" from amphiprotic into aprotic solvents in this way. Confusion may result because the "pK" values of carboxylic acids in *aprotic* solvents (*e.g.*, chloroform) become larger with increasing acidic strength instead of smaller, as in water. A more serious objection is that the clear relationship between 1:1 acid–base association constants obtained in aprotic solvents like benzene and chloroform and the "over-all" acid–base reaction constants obtained in other media[11–15] is in danger of being obscured.

Competing Hydrogen-Bonding Reactions.—As already mentioned, the experiments were designed so as to avoid or minimize errors from any competing associations. Four possibly interfering associations were considered: (1) dimerization of carboxylic acids (eq 3), (2) formation of salts of the general formula $\mathrm{B(HA)_2}$, (3) self-association of diphenylguanidine, and (4) formation of conjugate cations ($\mathrm{BHB^+}$).[11] Reactions 2–4 are not thought to have contributed significant errors.[5] Furthermore, the reference indicator acid HI (which can be regarded as a monobasic, *para*-substituted 2,6-dibromophenol) is not prone to dimerize.[20]

However, dimerization of HA appears to introduce a recognizable error, namely, a slight trend toward lower values of K_{BHA} with increase in n' (that is, in C_{HA}). Such a trend can be detected in Table I and is still more apparent in some of the experiments in which n' exceeded 3 (its most usual maximum value).[4,5] It can be removed by applying a correction for the amount of carboxylic acid calculated to be present as the dimer. There is, unfortunately, a dearth of reliable information about the extent of dimerization of carboxylic acids in aprotic solvents, even though this topic has been studied very extensively. Relatively few of the dimerization constants in the literature are on a comparable basis with respect to solvent and temperature, and most of the reported values are for *wet* solvents, having been obtained by the distribution method. This method has received severe criticism, especially in recent years.[21,22] For example, it has been pointed out that log $K_{1,2}$ values for several aliphatic carboxylic acids in carbon tetrachloride are distinctly higher when obtained (by infrared spectroscopy) using *dry* solvent than by the distribution method[21] (presumably because in water the acid tends to form hydrates at the expense of self-association[23]). Similarly, poor reproducibility of dimerization constants obtained using supposedly dry solvents may be caused by variable moisture content.[22] One apparently reliable generalization is that acids in which -COOH is conjugated with the side chain (*e.g.*, benzoic and cinnamic acids) tend to be more highly dimerized in benzene than aliphatic and other acids lacking such conjugation.[24] Data in the literature also support the conclusion that acids which are weaker in water are the ones more likely to become dimerized in aprotic solvents. Furthermore, there is limited evidence that self-association of benzoic acid is hampered by *ortho* substituents.

Benzoic acid is an example where dimerization constants in benzene which were obtained by several methods, *including* the distribution method, are in good agreement. At 25° most values found for log $K_{1,2}$ are in the range 2.70–2.79. In the first investigation of this series, experiments were performed at values of n' as high as 20, and a dimerization constant for benzoic acid was fitted to the data. The log $K_{1,2}$ value thus obtained was 2.72.[5] A similar fitting procedure was performed in this work for nine of the acids, as indicated in Tables II and III. The values of log $K_{1,2}$ found to best fit the data are all of the expected magnitude. They range between 2.5 and 3.0.

2,4-Dimethylbenzoic acid yielded interesting results in this fitting procedure. A dimerization constant for this acid has not been reported previously, although

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(17) M. W. Hanna and A. L. Ashbaugh, *J. Phys. Chem.*, **68**, 811 (1964); E. J. King, "Acid-Base Equilibria," The Macmillan Co., New York, N. Y., 1965, Sections 1.7 and 11.4.

(18) Kolthoff and associates, in working with solvents like acetic acid and acetonitrile, have determined (overlapping) equilibrium constants for the acid–base association to give BHA (which they refer to as "ionization constants," symbolized as K_{i}) and for the separation of $\mathrm{BH^+}$ from $\mathrm{A^-}$ through solvation (called "dissociation constants" and symbolized by K_{d}); *e.g.*, see ref 13. The expression "ionization" as applied to the acid–base interaction giving BHA is probably an over-simplification, and the term "association" constant (symbolized by K_{assocn} or K_{BHA}) seems preferable when a secondary reaction giving solvated ions is not detectable and a distinction between "ionization" and "dissociation" need not be made.

(19) M. Rumeau and B. Trémillon, *Bull. Soc. Chim. France*, 1049 (1964); A. Rieux, M. Rumeau, and B. Trémillon, *ibid.*, 1053 (1964); B. Trémillon, *ibid.*, 1057 (1964). G. Charlot and B. Trémillon, "Les Reactions Chimiques dans les Solvents et Sels Fondus," Gauthier-Villars, Paris, 1963.

(20) Instead of forming intermolecular hydrogen bonds it probably forms *weak* chelate bonds; see ref 10, section IV.2. In contrast, *o*-nitrophenols, including 2,4-dinitrophenol—one of the most frequently used reference aids—possess *strong* tendencies toward chelation, with consequent lowered reactivity when in aprotic solvents: M. M. Davis, *J. Am. Chem. Soc.*, **84**, 3623 (1962), and unpublished results.

(21) J. Wenograd and R. A. Spurr, *ibid.*, **79**, 5844 (1957).

(22) S. D. Christian, H. E. Affsprung, and S. A. Taylor, *J. Phys. Chem.*, **67**, 187 (1963).

(23) It has also been claimed that moisture *promotes* association of carboxylic acids: W. G. Wright, *J. Chem. Soc.*, 683 (1949).

(24) G. Allen and E. F. Caldin, *Trans. Faraday Soc.*, **49**, 895 (1953); *Quart. Rev.* (London), **7**, 255 (1953).

constants for *o*- and *p*-toluic acids have been determined, by the isopiestic method[25] and by ebullioscopy,[24] respectively. At 25° the log $K_{1,2}$ value reported for *o*-toluic acid is 2.625, and that for *p*-toluic acid is 3.382.[26] A value of log $K_{1,2}$ intermediate between these values might have been expected for the disubstituted acid, but, instead, the value deduced (see Table III) was 2.63—almost identical with the constant reported for *o*-toluic acid. Applying a correction for dimerization caused the relative standard deviation (coefficient of variation) of values of K_{BHA} to drop from 5.7 to 4.4%.

The precision of values of K_{BHA} was improved still more in the other examples given in Table III, the reductions in relative standard deviation (in per cent) being as follows: for *trans*-cinnamic acid, from 6.3 to 2.1; for 1-naphthoic acid, from 5.4 to 3.0; and for 2-naphthoic acid, from 2.5 to 1.2.

The precision of results for five of the aliphatic acids, following "corrections," was also good (see Table II). The dimerization constants inferred for this group range from 2.52 to 2.92 (see fourth column of Table II). *Smaller* dimerization constants were calculated for lauric and stearic acids than for acids of lower molecular weight. The best comparable values in the literature (see footnote *d*), which were obtained for benzene solutions at 30° by the electric polarization method, are similar in magnitude, although the constant obtained for stearic acid at 30° is *larger* than constants obtained for three acids of low molecular weight. Both methods indicate that the branched-chain acid, trimethylacetic (pivalic) acid, is more highly dimerized than are straight-chain acids. Constants which have been reported for several aliphatic acids in carbon tetrachloride at 24° (see footnote *e* of Table II) indicate, not surprisingly, that self-association is more complete in this solvent than in benzene. In agreement with our results, they indicate a slight trend toward less extensive dimerization with increasing carbon content.

It will be noted that in our work more extensive dimerization has been inferred for *trans*-cinnamic acid than for the other acids of its group (Table III). Barton and Kraus obtained analogous results in determining dimerization constants of several carboxylic acids cryoscopically, and they noted that (with a single exception, later explained by Allen and Caldin[24]) the extent of "monomerization" in benzene tends to parallel ionic dissociation in water.[27] Such results suggest that strong tendencies toward self-association by hydrogen bonding can account for the comparatively high $\mathrm{p}K_\mathrm{a}$ values of many carboxylic acids in water.

The dimerization constant deduced for 1-naphthoic acid is higher than expected. The raw association constants obtained for *o*-benzoylbenzoic and 2-furoic acid did not exhibit any detectable trends under the experimental conditions used.

It is recognized that our procedure for calculating dimerization constants and corrected acid–base association constants may prove to be an over-simplified treatment, and we do not consider our method of deducing dimerization constants to yield highly accurate results. However, in all cases where it has been applied it has given results of the expected magnitude which seem at least as good as most of the values now available.

Comparative Strengths of the Acids in Benzene and Water.—The first investigation of this series[1] dealt with numerous *o*-, *m*-, and *p*-substituted benzoic acids and some 2,6-disubstituted acids. When values of log K_{BHA} (B = diphenylguanidine, solvent = benzene) were plotted as a function of aqueous $\mathrm{p}K_\mathrm{a}$ values four linear correlations appeared. Two of these relationships are indicated in Figure 1.[16] The line for *meta*-substituted acids was regarded as a *norm.*[8] Obviously, when points are located below this line the deviating acids may be considered either anomalously weak in benzene, anomalously strong in water, or possibly both. Weakness in benzene could arise from a strong tendency for chelate ring formation. Without doubt, *o*-methoxybenzoic acid is an example of this type. However, it was concluded that most deviations noted arise from peculiarities of acid behavior when in water.

For some years it was believed that *o*-substituted benzoic acids are *invariably* stronger than benzoic acid ($\mathrm{p}K_\mathrm{a}$ = 4.20) since even *o*-toluic acid has an appreciably lower $\mathrm{p}K_\mathrm{a}$ value (3.91)—not merely acids having an electron-attractive group in the *ortho* position. The most satisfactory explanation seemed to be "steric inhibition of resonance" of –COOH with the benzene ring, caused by any adjacent substituent. However, *o*-toluic acid was found[1] to be the weaker acid in benzene: that is, log K_{BHA} was 0.23 less than for benzoic acid (both constants uncorrected). To account for this finding we suggested that steric inhibition of resonance in *ortho*-substituted acids is augmented in water, perhaps because of an added bulkiness of –COOH, resulting from hydration. In support of this conclusion, a study of experimental results of Kilpatrick and co-workers[28] indicates that enhancement of the strengths of *ortho*-substituted acids (compared with their *meta* and *para* isomers) is appreciably less in alcohols than in water, and gradually disappears when dioxane is added to water solutions, until in 36 mole % dioxane (73.5 wt %) it is barely detectable.

Figure 1 shows that the acids included in this investigation (see the *filled* and *half-filled* circles) conform to the earlier derived *meta* relationship or else to the *ortho* relationship. Acids resembling the *meta*-substituted acids studied earlier are *o*-benzoylbenzoic, *trans*-cinnamic, and 2-naphthoic acids. Acetic, isobutyric, and trimethylacetic acids follow the same pattern, though a little less closely. Acids resembling the *ortho*-substituted acids previously studied are 2,4- and 2,5-dimethylbenzoic acids, 1-naphthoic acid, and 2-furoic acid.

It is not surprising to find 1-naphthoic and 2-naphthoic acids fitting, respectively, into the "*ortho*" and "*meta*" relationships, as organic chemists commonly

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[25] F. T. Wall and F. W. Banes, *J. Am. Chem. Soc.*, **67**, 898 (1945).

[26] Values of log $K_{1,2}$ at 25° were calculated from original data reported for three other temperatures. They were reduced to molar units where necessary.

[27] B. C. Barton and C. A. Kraus, *J. Am. Chem. Soc.*, **73**, 4561 (1951).

[28] See ref 1, section 4.3c and literature cited. The enhancement of strength *not* shown by *o*-toluic acid when in benzene seems likely to appear in acids containing a single *o*-alkyl substituent of greater bulk. This possiblity has not been tested. However, the presence of methyl groups in *both* of the *ortho* positions appears to cause augmented strength in benzene, just as in water.[9]

regard them as being in effect an *ortho*- and a *meta*-substituted benzoic acid.[29] Location of the point for 2-naphthoic acid so close to the "*meta*" line indicates that a value of σ, the Hammett substituent constant, as calculated from our acid–base association constants should be very close to the value (0.042) obtained in the conventional way from the aqueous dissociation constants of benzoic and 2-naphthoic acids.[30] In agreement with expectation the value 0.041 is obtained on substituting our (corrected) values of log K, log $K°$, and ρ (which was found[8] to equal 2.17) in the Hammett equation. It seems a little startling at first to find that 1-naphthoic acid, though considerably stronger than its isomer in water, is actually the weaker acid in benzene (see Table III, columns 5 and 6). However, several investigators have noted that the strength of 1-naphthoic acid decreases more rapidly than that of 2-naphthoic acid on changing from water to organic solvents which are still largely aqueous on the mole per cent basis.[31] Furthermore, a similar reversal of strengths was observed for toluic acids:[1] the *ortho* isomer is the strongest of the three isomers in water, but the weakest in benzene.

trans-Cinnamic acid—like its vinylog, benzoic acid—occupies the expected place among the "normal" (*meta*-substituted) acids.

o-Benzoylbenzoic acid, on the other hand, departs from the pattern of behavior (eq 5) shown by most of the *ortho*-substituted acids. The observed value of log K_{BHA} (6.44) is much larger than the value (5.46) calculated from eq 5. Better agreement is obtained with the relation for *meta*-substituted acids (eq 4), and still better agreement on using the equation for *para*-substituted acids.[32] The calculated values using these two equations are, respectively, 6.69 and 6.59. It is noteworthy that *o*-acetylbenzoic acid shows deviant behavior: pK_a values, which have been determined for all three of its isomers, show that the *ortho* isomer is the weakest of the isomers in water.[33]

We offer no explanation for the location of the point for 2-furoic acid very close to the "*ortho*" line. As noted above, this location may signify either that the acid is abnormally weak in benzene or that it is abnormally strong in water. The literature contains differing opinions as to whether 2-furoic acid undergoes chelation or forms dimers. More experimental evidence is needed.

Our principal objective in studying the relative strengths of homologous straight-chain aliphatic acids in benzene was to ascertain whether certain peculiarities in the order of acidities in water would be apparent in benzene. The values of pK_a given in Table I (last column) have been checked in different laboratories, and deviations from a regular sequence of strengths shown by the lowest members of the series have been accepted as real. At first, *n*-butyric acid was considered to have an abnormally low pK value,[34] but after gaps in the pK data had been filled in it was concluded that propionic acid is the deviant (anomalously weak) acid.[35]

The tendency for a tightened, "iceberg" structure to form about a hydrophobic ion is now a well-recognized influence on the behavior of fatty acids in water.[36] Fewer irregularities in behavior might be expected in benzene. Our conclusions must be drawn with caution because of the poor drainage (see Experimental Section), the greater difficulty in achieving absence of moisture when working with liquid, easily volatilized compounds, and uncertainties about the extent of self-association of these acids. Nevertheless, we think that Tables I and II demonstrate a generally uniform behavior of the straight-chain acids with the single exception of acetic acid, which seems a little stronger than its homologs in benzene as well as in water. That is, the raw log K data in Table I, obtained in closely similar experiments, do not indicate any perceptible trends in the acidity (other than those previously attributed to dimerization). Propionic and *n*-butyric acids appear to be equally strong in benzene. Moreover, the results in Table II indicate a close similarity in the acidic strengths of acetic, isobutyric, and trimethylacetic acids in benzene. The points shown for these three acids in Figure 1 do not coincide because of their different aqueous pK values. If lauric and stearic acids are a little weaker and less dimerized in benzene than these three acids of lower molecular weight (as Table II suggests), this reduced reactivity may be attributed to a more extensive screening of the carboxyl groups.

As a group, the aliphatic acids are found to be weaker than aromatic acids in benzene, just as in water. For example, the values of log K_{BHA} and pK_a for hexanoic acid (respectively, $\sim$4.3 and 4.88) may be compared with corresponding values for benzoic acid (5.32, 4.20). Log $K_{1,2}$ for hexanoic acid may be estimated as $\sim$2.6, that is, slightly less than the value for benzoic acid.

Concluding Comments.—The preceding papers of this series contained relevant discussion that will not be repeated here, but several points should be emphasized. (1) Like most other procedures for comparing strengths of Brønsted acids in aprotic solvents this method requires the use of a *standard reference base and a standard indicator acid*, but it differs from other methods in the choice of reference base and reference acid and also in the treatment of data. (2) The comparative strengths of acids are denoted by values of *equilibrium constants*

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(29) More precisely, 1-naphthoic acid is likened to a 2,3-dialkylbenzoic acid, and 2-naphthoic acid, to a 3,4-dialkylbenzoic acid. So far as aqueous pK_a values are concerned, the analogy is a good one for 1-naphthoic acid (pK = 3.69) and 2,3-dimethylbenzoic acid (pK = 3.74). However, the pK_a values for 2-naphthoic acid (4.16) and 3,4-dimethylbenzoic acid (4.41) are substantially different. (Values of pK are from Dippy and co-workers, footnote *f*, Table III.)

(30) The same constant was obtained on averaging values ranging from −0.005 to 0.084, derived in studies of 13 different reactions, and was recommended for adoption as the "normal" value of σ for the 3,4-benzo group [A. Fischer, J. Packer, *et al.*, *J. Org. Chem.*, **24**, 155 (1959)].

(31) As examples, the "pK" of 1-naphthoic acid changes to 4.10 in 10 wt % aqueous acetone ($\sim$97 mole % of water), to 4.53 in 20 wt % aqueous dioxane (95 mole % of water), to 4.74 in 25 wt % aqueous acetone ($\sim$91 mole % of water), and to 5.89 in 47.2 wt % aqueous Butyl Cellosolve (88 mole % of water); the corresponding values for 2-naphthoic acid are 4.47, 4.89, 4.94, and 5.95. See J. O. Halford, *J. Am. Chem. Soc.*, **53**, 2944 (1931); E. Berliner and E. H. Winicov, *ibid.*, **81**, 1630 (1959); A. Fischer, W. J. Mitchell, *et al.*, *J. Chem. Soc.*, 2892 (1963); J. F. J. Dippy, *et al.*, *ibid.*, 1275 (1964).

(32) This relation is log $K_{\mathrm{BHA}} = 12.96 - 1.80\mathrm{p}K_a$ (see ref 1, section IV.2c).

(33) Table III, footnote *d*.

(34) J. F. J. Dippy, *J. Chem. Soc.*, 1222 (1938); G. M. Bennett and A. N. Mosses, *ibid.*, 2364 (1930); H. O. Jenkins and J. F. J. Dippy, *J. Am. Chem. Soc.*, **62**, 483 (1940).

(35) D. H. Everett, D. A. Landsman, and B. R. W. Pinsent, *Proc. Roy. Soc.* (London), **A215**, 403 (1952).

(36) For example, H. S. Frank and M. W. Evans, *J. Chem. Phys.*, **13**, 507 (1945); F. S. Feates and D. J. G. Ives, *J. Chem. Soc.*, 2798 (1956); R. M. Diamond, *J. Phys. Chem.*, **67**, 2513 (1963).

for the *1:1 association* of acid (HA) and reference base (B). The logarithm of K_{BHA} is regarded as the analog of the corresponding pK_{a} value. In the past, a more usual practice has been to express comparative acidities as ratios, taking acetic acid or benzoic acid as the basis for comparison. (3) The reference base adopted, *1,3-diphenylguanidine,* is stronger than the reference bases ordinarily used. For example, it associates readily with carboxylic acids, commonly giving equilibrium constants in the range 10^4–10^7. By comparison, the extent of other hydrogen-bonding reactions under the experimental conditions used is slight and can be neglected. (4) However, slightly more accurate association constants can be obtained by correcting for carboxylic acid present as the dimer, and in the process of correction, a *monomer–dimer equilibrium constant* for the carboxylic acid can be deduced. (Dimerization constants thus deduced compare favorably with results from other methods.) (5) The reference indicator acid, *tetrabromophenolphthalein ethyl ester* (*"bromophthalein magenta E"*), is well suited for determining the strengths of aliphatic and aromatic carboxylic acids in aprotic solvents because it matches them well in strength. (6) The results presented in this paper are in harmony with previous results, whose validity was indicated by clear-cut linear relationships of acidic strengths in benzene with those in water, alcohols, and partly aqueous solvents.[1,37] (7) The method is applicable to varied chemical types of acids.[38] Moreover, it is useful for acids which are difficultly soluble, scarce in amount, or unstable toward moisture. (8) The log K_{BHA} scale is more suitable than the pK_{a} scale for correlations of acid–base behavior in an aprotic solvent.

[37] It should also be noted that Hammett substituent constants calculated from the results for *meta-* and *para-*substituted acids agreed closely with constants derived from many other rate and equilibrium studies using other types of solvents, in particular, with "normal" substituent constants [R. W. Taft, Jr., *et al.*, *J. Am. Chem. Soc.*, **81**, 5343, 5352 (1959); J. E. Leffler and E. Grunwald, "Rates and Equilibria of Organic Reactions," John Wiley and Sons, Inc., New York, N. Y., 1963, Chapter 7].

[38] Exploratory measurements have indicated that the reference acid-base system used here can probably be used in determining the strengths of saccharin, sulfonic acids, and some of the stronger phenols.

Syntheses with Partially Benzylated Sugars. VI.[1] Some Solvolytic Reactions of 2-Acetamido-1-*O*-acyl-2-deoxy-D-glucopyranose and -D-galactopyranose Derivatives

THOMAS D. INCH[2] AND HEWITT G. FLETCHER, JR.

National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, Public Health Service, U. S. Department of Health, Education, and Welfare, Bethesda, Maryland 20014

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2-Acetamido-1-*O*-acyl-3,4,6-tri-*O*-benzyl-2-deoxy-β-D-glucopyranoses and -D-galactopyranoses react readily with methanol to give methyl 2-acetamido-3,4,6-tri-*O*-benzyl-2-deoxy-β-D-glucopyranoside and -D-galactopyranoside. Since 2-acetamido-1-*O*-benzoyl-2-deoxy-β-D-galactopyranose behaves in a similar manner, the benzyl groups do not appear to be involved in the reaction. 2-Acetamido-1-*O*-acyl-3,4,6-tri-*O*-benzyl-2-deoxy-α-D-glucopyranoses and -D-galactopyranoses yield no glycoside when heated with methanol, but undergo simple transesterification with the solvent. 2-Acetamido-1-*O*-acyl-3,4,6-tri-*O*-benzyl-2-deoxy-D-glucopyranoses and -D-galactopyranoses hydrolyze in aqueous dioxane at 50°, the β anomers cleaving more rapidly than the α anomers and β benzoates cleaving more rapidly than a β acetate. The mechanistic features of these reactions are discussed and their potential bearing on the origin of *O*-glycosides in mucoproteins is indicated.

The suggestion that some of the alkali-labile 2-acetamido-2-deoxy-D-galactopyranosyl moieties in ovine submaxillary gland mucoprotein (OSM) may be attached through C-1 with an ester linkage to the non-peptide-bonded carboxyl groups of aspartic and glutamic acids[3] led Harrison and Fletcher[4] to develop a synthetic procedure for the preparation of C-1 esters of 2-acetamido-2-deoxy-D-glucose and of 2-acetamido-2-deoxy-D-galactose. This synthetic procedure has now been improved, several new substances needed for the present research have been prepared, and a study of the solvolytic reactions of some C-1 esters of substituted hexosamines has been carried out. The synthetic aspects of the present work will be discussed first.

Preparation of Substrates

The acetylation of 2-acetamido-3,4,6-tri-*O*-benzyl-2-deoxy-D-glucopyranose (IV) (Scheme I) with acetic anhydride in pyridine affords 2-acetamido-1-*O*-acetyl-3,4,6-tri-*O*-benzyl-2-deoxy-α-D-glucopyranose (V) in 78% yield.[4] In order to obtain the corresponding β 1-*O*-acetyl derivative (VI), IV was acetylated by a variety of procedures which have been reported as suitable for the preparation of β 1-*O*-acyl derivatives of 2-acetamido-2-deoxyhexoses;[5] none of these proved satisfactory. Anderson and Percival[6] found that tritylation of 2-acetamido-2-deoxy-α-D-glucopyranose with trityl chloride in pyridine at 100°, followed by acetylation with acetic anhydride, yielded a substantial proportion of the β anomer of 2-acetamido-1,3,4-tri-*O*-acetyl-6-*O*-triphenylmethyl-D-glucopyranose, a fact that suggests that warm pyridine and the pres-

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[5] C. S. Hudson and J. K. Dale, *J. Am. Chem. Soc.*, **38**, 1431 (1916); B. R. Baker, J. J. Joseph, R. E. Schaub, and J. H. Williams, *J. Org. Chem.*, **25**, 1786 (1954); J. K. N. Jones, M. B. Perry, B. Shelton, and D. J. Walton, *Can. J. Chem.*, **39**, 1005 (1961); M. Stacey, *J. Chem. Soc.*, 272 (1944).

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