monosubstituted tropilidenes, but the band in the 1358–1410 region reported in the earlier series is lacking in these. The present series of compounds do not absorb at 1500 and 1600 cm.$^{-1}$, indicating freedom from aromatic impurity; the only region in which the spectra differ markedly from one another is between 900 and 1100 cm.$^{-1}$.

Eucarvone enol triphenylacetate (I, R = triphenylacetoxy-) was prepared by the method of Corey and Burke[24] from 9.95 g. (32.4 mmoles) of triphenylacetyl chloride[25] and sodio-eucarvone prepared from 1.27 g. (32.4 mmoles) of sodamide and 4.45 g. (29.8 mmoles) of eucarvone in 50 ml. of dioxane. The reaction mixture was treated with Celite and filtered through Celite, concentrated *in vacuo*, and the residue taken up in hot 95% ethanol. There was isolated by fractional crystallization 2.60 g. of light yellow needles, m.p. 95–99°. Chromatography of the solids from the mother liquors of this material gave, from the pentane eluates, an additional 0.30 g. of nearly colorless needles after one additional crystallization from absolute ethanol; m.p. 100.5–102.0°, total yield 23%.

Anal. Calcd. for C$_{30}$H$_{28}$O$_2$: C, 85.68; H, 6.71. Found: C, 85.44; H, 6.63.

Eucarvone Enol diphenylacetate (I, R = Diphenylacetoxy-).—The above procedure, using diphenylacetyl chloride,[26] gave rise to a total of a 39% yield of crude yellow crystals, m.p. 70–77°. A portion of this, after chromatography on alumina and crystallization from 95% ethanol, gave nearly colorless needles, m.p. 79.0–81.0°.

Anal. Calcd. for C$_{24}$H$_{24}$O$_2$: C, 83.69; H, 7.12. Found: C, 83.69; H, 7.12.

Isomerization of 2,3,7,7-Tetramethylcycloheptatriene-1,3,5 to 4-Isopropyl-*o*-xylene. Preparative Run.—A solution of 0.80 g. of *p*-toluenesulfonic acid and 0.50 ml. of the tetramethyltropilidene in 17.0 ml. of glacial acetic acid was allowed to stand at room temperature 17 hours. Pentane and water were added, the water layer discarded and the pentane layer washed with water and bicarbonate solution. Preparative v.p.c. of the concentrated pentane layer on the didecyl phthalate column at 125° afforded a single symmetrical peak which was collected and redistilled at 102° (20 mm.), n^{25}D 1.4972 (lit.[27] $n^{15.5}$D 1.50001, n^{20}D

1.5010). The substance showed infrared absorption appropriate for 4-isopropyl-*o*-xylene: 815 (appropriate for two adjacent H's), 875 (appropriate for one H), 1503, 1611, 3010sh (aromatic absorption) and broad weak bands near 1745 and 1870 cm.$^{-1}$ (appropriate for a 1,2,4-substituted benzene). Nitric acid oxidation[28] gave material, m.p. 164.5–166.0°, 3,4-xylic acid, as expected for the compound with the assigned structure. When this isomerization was attempted in solutions more concentrated in the tropilidene component, considerable proportions of higher boiling materials, presumably olefin dimerization products, were formed.

Kinetic Runs.—A solution of 1.1926 g. of *p*-toluenesulfonic acid hydrate in 25.00 ml. of commercial glacial acetic acid was prepared. Two 5.00-ml. aliquots were transferred to nitrogen-swept serum-capped vials and equilibrated at 25.0° before 137.1 mg. (0.925 mmole) of 2-methylene-3,7,7-trimethylcycloheptadiene-3,5 and 132.5 mg. (0.894 mmole) of 2,3,7,7-tetramethylcycloheptatriene-1,3,5 were introduced into the respective vials by means of a hypodermic syringe. Aliquots (0.33 ml.) were withdrawn from time to time by means of the hypodermic syringe, added to 1.0 ml. of pentane and washed with two portions of water and one of bicarbonate solution. A 0.15-ml. aliquot of the pentane solution served for the v.p.c. sample for a didecyl phthalate column at 125°. The sum of the areas of the three peaks due to the tropilidene, the methylene cycloheptadiene and the *o*-xylene (listed in order of elution) was normalized to 100 and log (100 − area *o*-xylene) was plotted against *t*, measured from the instant of injection of the hydrocarbon samples. The lines obtained in this way (a slight downward curvature and a slight S-curvature appeared, respectively) corresponded to pseudo-first-order rates of 1.07 and 1.14 × 10^{-4} sec.$^{-1}$ (±10%), respectively. The ratio of the areas of the peaks due to the methylene cycloheptadiene and to the tropilidene was determined for each point; this ratio became increasingly uncertain as the areas of the peaks concerned became smaller as the reaction proceeded. During the first half-life of the reactions, the values of the ratio became 12:88 and 8:92, respectively.

(24) E. J. Corey and H. J. Burke. *J. Am. Chem. Soc.*, **78**, 174 (1956).

(25) L. W. Jones and C. D. Hurd, *ibid.*, **43**, 2422 (1921).

(26) M. L. Cohn, L. Hellerman and R. E. Hoen, *ibid.*, **50**, 1716 (1928).

(27) A. Klages and F. Sommer. *Ber.*, **39**, 2306 (1906); Pl. A. Plattner, A. Fürst, L. Marti and H. Schmid. *Helv. Chim. Acta*, **32**, 2137 (1949).

(28) O. Kruber. *Ber.*, **57**, 1008 (1924).

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY, UNIVERSITY OF NEW SOUTH WALES, SYDNEY, AUSTRALIA]

The Ionization Constants of N-(Substituted-phenyl)-glycines

BY A. BRYSON, N. R. DAVIES AND E. P. SERJEANT[1]

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The ionization constants of ten N-(substituted-phenyl)-glycines, RC$_6$H$_4$NHCH$_2$COOH, and their corresponding ethyl esters have been measured, the substituent R being varied throughout the series H, *m*-NO$_2$, *m*-CN, *m*-Cl, *m*-COCH$_3$, *p*-Cl, *m*-OMe, *m*-Me, *p*-Me and *p*-OMe. These values have been used in conjunction with spectral data to calculate the zwitterion equilibrium constants and the constants pertaining to the individual ionization processes. The results invalidate Wegscheider's assumption that the pK_a value of the non-zwitterionic acid pK_B can be equated to the pK_E of the ethyl ester, the expression $pK_B = pK_E + 0.20$ being obtained for the ten substituents. The relations between the individual ionization constants and the zwitterion equilibrium constant lead to inter-related Hammett equations which are compared with the equations applying to *m*-substituted anilines and the phenylglycine esters on one hand and with *m*-substituted phenylpropionic acids on the other. A relation is derived between zwitterion ratios and substituent constants.

As part of a program to determine the relation between the biological activity of N-(substituted-phenyl)-glycines and their metal binding properties it was necessary to determine the effects of ring substituents on the ionizations of the two functional groups in their side chains. This paper records the ionization constants and the ultraviolet absorption spectra of ten of these compounds and their ethyl esters. Interpretation of the experimental pK_a values is complicated by the presence of the zwitterion equilibrium

$$RC_6H_4NHCH_2CO_2H \; \rightleftharpoons \; RC_6H_4NH_2{}^+CH_2CO_2{}^-$$
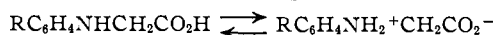
established because of the proximity of the pK_a values of the anilinium and carboxyl groups. The fortuitous choice of the predominantly non-zwitterionic N-(*m*-nitrophenyl)-glycine as the first compound to be investigated revealed that pK_1, the experimental ionization exponent of the reaction

$$m\text{-}NO_2C_6H_4\overset{+}{N}H_2CH_2CO_2H \; \rightleftharpoons \; m\text{-}NO_2C_6H_4NHCH_2CO_2H + H^+$$
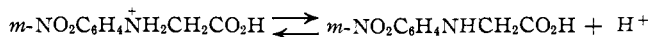
was greater than pK_E for the corresponding ethyl ester. This behavior was subsequently confirmed when the constants for the substituents *m*-CN, *m*-Cl, *m*-COMe and *p*-Cl were obtained. These findings are in conflict with the Ebert–Wegscheider assumption[2] that the effect of a carboxy group can be equated with that of a carboethoxy or carbomethoxy group. This assumption has been widely used[3] in evaluating the zwitterion constants K_Z and the individual ionization exponents pK_A, pK_B, pK_C and pK_D for reactions of the type in eq. 1–4.

(1) Royal Military College, Duntroon. A.C.T., Australia.

(2) L. Ebert. *Z. physik. Chem.*, **121**, 385 (1926); R. Wegscheider. *Monatsh.*, **16**, 153 (1895); **23**, 287 (1902).

(3) J. T. Edsall and M. H. Blanchard. *J. Am. Chem. Soc.*, **55**, 2338 (1933).

Table I

Ultraviolet Spectra of N-(R-Substituted-phenyl)-glycines and their Correspondingly Substituted Ethyl Esters in Water at 25°

Phenylglycine substituent R		Anion[a]		Molecular[b]		Cation[c]	
		, mμ	Log ε	λ_{max}, mμ	Log ε	λ_{max}, mμ	Log ε
m-Nitro	Acid	385, 237	3.08, 4.20	375, 237	3.07, 4.17	257	3.88
	Ester			375, 237	3.11, 4.17	257	3.87
m-Cyano	Acid	323, 255	3.36, 3.91	318, 252	3.36, 3.87	278, 271	2.86, 2.87
	Ester			318, 250	3.37, 3.88	278, 271	2.90, 2.93
m-Chloro	Acid	295, 238	3.29, 3.97	295, 238	3.23, 3.95	Not measured because of
	Ester			295, 238	3.30, 4.00	limited solubility
p-Chloro	Acid	298, 249	3.18, 4.12	298, 249	3.03, 3.97	Not measured because of
	Ester			298, 246	3.17, 4.11	limited solubility
m-Aceto	Acid	345, 235	3.24, 4.38	345, 236	3.18, 4.37	279, 239	2.98, 4.08
	Ester			345, 236	3.25, 4.40	279, 239	299, 4.09
m-Methoxy	Acid	287, 243	3.39, 3.93	278	3.29	272	3.35
	Ester			287, 242	3.38, 3.91	272	3.33
Unsubstd.	Acid	287, 240	3.19, 4.01	287, 238	2.74, 3.87	Not measured because of
	Ester			287, 237	3.19, 4.02	limited solubility
m-Methyl	Acid	289, 242	3.23, 3.99	289, 242	2.74, 3.45	262, 212	2.64, 3.66
	Ester			289, 243	3.23, 3.99	263, 214	2.63, 3.66
p-Methyl	Acid	293, 239	3.20, 4.02	293, 239	2.42, 3.22	259, 212	2.41, 3.80
	Ester			293, 243	3.20, 4.03	258, 214	2.41, 3.81
p-Methoxy	Acid	300, 237.5	3.28, 4.01	272	3.12	278, 272	3.05, 3.13
	Ester			300, 237.5	3.28, 4.01	278, 272	3.00, 3.08

[a] Determined at $pH = pK_{a_2} + 3.0$ [b] Determined for acids at $pH = (pK_1 + pK_2)/2$ and for esters at $pH = pK_a + 3.0$. [c] Determined at $pH = pK_1 - 3.0$ for both acids and esters.

Table II

Ionization and Zwitterionic Equilibrium Constants of N-(Substituted phenyl)-glycines and Esters

Substituent	pK_1	pK_2	K_Z	pK_A	pK_B	pK_C	pK_D	pK_E[a]	$pK_B - pK_E$
m-NO₂	0.06 ± 0.05	3.75 ± 0.01	..	..	0.06	..	3.75	−0.17 ± 0.05	0.23
m-CN	0.28 ± .05	3.78 ± .01	..	..	0.28	..	3.78	.15 ± .05	.13
m-Cl	1.05 ± .03	3.93 ± .02	0.12	2.01	1.10	2.99	3.90	.91 ± .01	.19
m-COCH₃	1.14 ± .02	3.93 ± .03	.14	2.03	1.20	3.05	3.87	1.02 ± .03	.18
p-Cl	1.46 ± .02	4.04 ± .02	.42	1.99	1.61	3.51	3.89	1.39 ± .03	.22
m-OMe	1.68 ± .03	4.14 ± .01	.62	2.09	1.89	3.74	3.95	1.67 ± .03	.22
H	1.83 ± .02	4.41 ± .01[b]	1.82	2.03	2.29	4.22	3.96	2.08 ± .02	.21
m-Me	1.89 ± .02	4.49 ± .01	2.10	2.06	2.38	4.32	4.00	2.19 ± .03	.19
p-Me	1.97 ± .01	4.85 ± .01[c]	5.04	2.05	2.75	4.77	4.07	2.57 ± .03	.18
p-OMe	2.08 ± .02	5.10 ± .01	9.80	2.12	3.11	5.06	4.07	2.85 ± .02	.26
	Proton gained	Proton lost							

[a] These are experimental values for the reaction RPhNH₂⁺CH₂CO₂Et ⇌ RPhNHCH₂CO₂Et + H⁺. [b] Cf. 4.41; A. Walden, Z. physik. Chem., 8, 433 (1891). [c] Cf. 4.86; A. Walden, ibid., 10, 642 (1892).

$$\text{RNH}_2{}^+\text{CH}_2\text{CO}_2\text{H} \underset{K_A}{\rightleftarrows} \text{RNH}_2{}^+\text{CH}_2\text{CO}_2{}^- + \text{H}^+ \quad (1)$$

$$\text{RNH}_2{}^+\text{CH}_2\text{CO}_2\text{H} \underset{K_B}{\rightleftarrows} \text{RNHCH}_2\text{CO}_2\text{H} + \text{H}^+ \quad (2)$$

$$\text{RNH}_2{}^+\text{CH}_2\text{CO}_2{}^- \underset{K_C}{\rightleftarrows} \text{RNHCH}_2\text{CO}_2{}^- + \text{H}^+ \quad (3)$$

$$\text{RNHCH}_2\text{CO}_2\text{H} \underset{K_D}{\rightleftarrows} \text{RNHCH}_2\text{CO}_2{}^- + \text{H}^+ \quad (4)$$

by means of the relations,[4] $K_1 = K_A + K_B$, $1/K_2 = (1/K_C + 1/K_D)$, $K_A/K_B = K_D/K_C = K_Z$, and $K_B = K_E$ where K_1 and K_2 are the measured ionization constants. It became necessary, therefore, to determine the zwitterion constants by an alternative spectrophotometric method and an investigation of the ultraviolet spectra of the N-phenylglycines showed that the data were adequate for the purpose. The basis of this method is well known[5] and depends upon the assumptions that the ultraviolet spectrum of the molecular form of the ethyl ester is identical with or closely related to that of the non-zwitterionic molecular species of the acid, while those of the cations of the ester and the acid are identical with or closely related to that of the zwitterion. Data presented in Table I indicate the validity of these assumptions for the present case.

(4) E. Q. Adams, J. Am. Chem. Soc., 38, 1503 (1916).
(5) S. F. Mason, J. Chem. Soc., 5010 (1957).

It will be observed that the m-nitro- and m-cyanophenylglycines exist predominantly in aqueous solution in the non-zwitterionic form whilst the p-methoxy derivative is largely zwitterionic. The nature of the substituent is therefore the controlling factor in the magnitude of the zwitterion ratio K_Z, values of which can be calculated from the molar absorbance of the ester, cation and molecular species, obtained at a given wave length and temperature as described in the Experimental section. These values can then be used in conjunction with the experimental values of pK_1 and pK_2 to calculate the exponents pK_A, pK_B, pK_C and pK_D without reference to the pK_a value of the ester, pK_E. The constants are shown in Table II and permit a comparison between the values of pK_B and pK_E. It is readily shown that errors of 5% in K_Z in the range 0.2 to 10 lead to errors in pK_A, pK_B, pK_C and pK_D of not more than 0.02 pH unit. Values of pK_A, pK_B, pK_C and pK_D in general are considered to have uncertainties of not more than ±0.04 unit.

Discussion

Non-validity of the Ebert–Wegscheider Hypothesis.— It will be shown later that the quantity in the last column of Table II is expressed by the equation $pK_B - pK_E = 0.20 - 0.04\sigma$. The values are therefore encompassed within the range 0.20 ± 0.03 and thus

appear to be constant within experimental uncertainty. That a CO_2Et group should have a greater $-I$ effect than a CO_2H group is not unexpected, despite the well known $+I$ effect of an ethyl group in replacing H attached to a carbon atom. Jaffé[6] and Van Bekkum, et al.,[7] have shown that the Hammett σ_m-values for CO_2Et and OEt are greater than those for the equivalent CO_2H and OH groups, and the blue shift observed in the B band of the ultraviolet spectrum of anisole with respect to that of phenol[8] indicates a $-I$ effect of the OMe as compared with the OH group. This order, found in ethanolic solution, is reversed in hexane, and suggests an explanation in terms of hydrogen bonding of the phenolic group with the solvent. A similar explanation is likely for the phenylglycines, and indeed for all similar cases where a hydroxyl hydrogen atom can bond to the solvent. Internal hydrogen bonding such as

$$C_6H_5NH—CH_2$$
$$\vdots \qquad | $$
$$HO—C=O$$
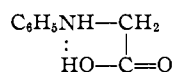
which acts in opposition by stabilizing the base component of the amino acid relative to that of the ester must be of lesser significance.

The significance of equation $pK_B = pK_E + 0.20$ is easily appreciated in the case of N-(m-methoxyphenyl)-glycine, a value of 0.55 for K_Z being obtained by the use of this equation, whereas from the equation $pK_B = pK_E$ the value of K_Z would appear to be zero. Doubt on the validity of the Ebert–Wegscheider assumption arises also from the work of Robinson and Biggs[9] in which an attempted determination of the pK_B value for p-aminobenzoic acid by extrapolation of the pK_a values of a series of esters gave a value which differed from that of the methyl ester itself.

Ionization Exponents of Unsubstituted Phenylglycines and Related Compounds.—Before discussing the relevance of the Hammett equation to the data in Table II we note the following comparisons.

$$
\begin{array}{ll}
NH_3{}^+CH_2CO_2CH_3 & 7.66^3 \\
C_6H_5NH_2{}^+CH_2CO_2CH_3 & 2.08\ (pK_E) \\
\hline
\Delta pK_a & 5.58
\end{array}
$$

$$
\begin{array}{ll}
NH_3{}^+CH_2CO_2{}^- & 9.78^{10} \\
C_6H_5NH_2{}^+CH_2CO_2{}^- & 4.22\ (pK_C) \\
\hline
& 5.56
\end{array}
\qquad
\begin{array}{ll}
NH_3{}^+CH_3 & 10.62^{11} \\
C_6H_5NH_2{}^+CH_3 & 4.85^{12} \\
\hline
& 5.77
\end{array}
$$

These ΔpK_a values which reflect the conversion of the amino group from the aliphatic to the aromatic state indicate that the delocalization of the N lone pair electrons is not appreciably affected by the presence of the side chain with its substantial $-I$ influence, such trends as are evident being in the expected direction.

Other comparisons of interest are

$$
\begin{array}{ll}
CH_3CO_2H & 4.76^{13} \\
CH_3OCH_2CO_2H & 3.53^{14} \\
\hline
\Delta pK_a & 1.23
\end{array}
\qquad
\begin{array}{ll}
CH_3CO_2H & 4.76 \\
C_6H_5OCH_2CO_2H & 3.17^{15} \\
\hline
& 1.59
\end{array}
$$

$$
\begin{array}{ll}
CH_3CO_2H & 4.76 \\
C_6H_5NHCH_2CO_2H & 3.94\ (pK_D) \\
\hline
& 0.82
\end{array}
\qquad
\begin{array}{ll}
CH_3CO_2H & 4.76 \\
C_6H_5CH_2CH_2CO_2H & 4.66^{13} \\
\hline
& 0.10
\end{array}
$$

(6) H. H. Jaffé, Chem. Rev., **53**, 191 (1953).

(7) H. Van Bekkum, P. E. Verkade and W. P. Wepster, Rec. trav. chim., **78**, 815 (1959).

(8) A. Burawoy and J. T. Chamberlain, J. Chem. Soc., 2311 (1952).

(9) R. A. Robinson and A. I. Biggs, Australian J. Chem., **10**, 128 (1957).

(10) E. Michaelis, Biochem. Z., **49**, 248 (1913).

(11) D. H. Everett and W. F. K. Wynne-Jones, Proc. Roy. Soc. (London), **A177**, 499 (1941).

(12) N. F. Hall and R. S. Sprinkle, J. Am. Chem. Soc., **54**, 3469 (1932).

(13) J. F. J. Dippy, Chem. Rev., **25**, 151 (1939).

(14) E. Larsson, Z. anorg. allgem. Chem., **172**, 375 (1928).

(15) N. V. Hayes and G. E. K. Branch, J. Am. Chem. Soc., **65**, 1555 (1943).

The decreasing order of the inductive effects of the isoelectronic phenoxy, anilino and benzyl groups reflects the decreasing nuclear charge in the atom sequence O, N, C. Replacement in methoxyacetic acid to form phenoxyacetic acid causes an increase of $3.53 - 3.17 = 0.36$ unit, while replacement in n-butyric acid to form phenylpropionic acid produces an increase of only $4.82^{13} - 4.66 = 0.16$ unit. The difference reflects the delocalization of the O-electrons in phenoxyacetic acid.

Hammett Relationships.—The values of pK_E, pK_B, pK_C and the corresponding values for substituted anilines all relate to the effects of substituents on the ionization process $RC_6H_4NH_2{}^+R_1 \rightleftharpoons RC_6H_4NHR_1 + H^+$ where R_1 may be $-CH_2CO_2Et$, $-CH_2CO_2H$, $-CH_2CO_2{}^-$ or H. Thus they provide an opportunity for testing the Hammett equation for a series of similar reactions in which substantial changes in the basicity of the nitrogen are produced by charged or polar side chain groups. For the regression analyses we have used meta substituent constants in the first instance since it has been shown that considerable variations may occur when para constants are used even in those cases where no inter-group conjugation can take place.[7] Using the σ_m-values: NO_2, 0.71; Cl, 0.37; CN, 0.61; COMe, 0.34; Me, -0.07; OMe, 0.11, statistical analysis gives the following results for the reaction

$$m\text{-}RC_6H_4NH_2{}^+R_1 \rightleftharpoons m\text{-}RC_6H_4NHR_1 + H^+$$
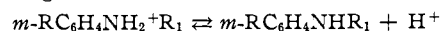
R_1	Equation	n	s^b	Correlation coefficient
H^a	$\Delta pK_a = 2.82\sigma + 0.08$	16	0.04	0.998 (5)
CH_2CO_2Et	$\Delta pK_E = 2.97\sigma + .08$	6	.04	.997 (6)
CH_2CO_2H	$\Delta pK_B = 3.00\sigma + .08$	6	.03$_5$	.996 (7)
$CH_2CO_2{}^-$	$\Delta pK_C = 3.1\sigma + .08$	4	.04$_6$	.996 (8)

[a] Values of N. F. Hall and R. S. Sprinkle, J. Am. Chem. Soc., **54**, 3469 (1932); A. Bryson, ibid., **82**, 4858 (1960).   [b] Standard deviation of experimental pK_a values.

The differences between the reaction constant in 5 and the values in 6 and 7 are statistically significant, but the small sample for reaction 8 ($n = 4$) and the absence of values for the substituents NO_2 and CN makes the value of 3.1 for the phenylglycinate ions less precise. To test the behavior of the p-substituents, we have used equations 5, 6, 7, 8, to calculate substituent constants for the four series of compounds using, in addition to the data from Table II, pK_a values of the following substituted anilines: p-Me, 5.12^{12}; p-Cl, 3.98^{16}; p-OMe, 5.29^{12}, the results being shown in Table III.

TABLE III

CALCULATED σ_p-VALUES

Substituent	Anilines	Phenylglycine esters	Phenylglycines	Phenylglycine ion	Mean	a
p-Me	-0.21	-0.18	-0.19	-0.20	-0.19	-0.17
p-OMe	$-.27$	$-.30$	$-.29$	$-.30$	$-.29$	$-.27$
p-Cl	.19	.18	.20	.20	.19	.23

[a] Values given by H. H. Jaffé, Chem. Rev., **53**, 191 (1953).

It appears that p-substituents behave in a consistent manner in the four series of compounds and the mean values of σ_p in column 6 have been selected for further use.

The significant features of eq. 5 to 8 are: (i) the similarities between the reaction constants and (ii) the presence of positive constant terms in each equation. It is apparent that despite the substantial $-I$ effects of the side chains which lower the pK_a values from 4.59 in aniline to 2.29 and 2.08 in phenylglycine and its ethyl ester, the inductive effects of any one ring substituent remain almost constant, such changes as occur being in the same direction as the $-I$ effects of the side chains.

(16) M. Kilpatrick and C. A. Arenberg, ibid., **75**, 3812 (1953).

This behavior can be explained in terms of the polarization produced at the nitrogen atom. For a closely related series of aromatic amines, ΔpK_a values are considered to be determined chiefly by the differences produced by the substituent in the potential energies of the acid and base components of the system. In the acid the potential energy increment is due to the interaction between the combined substituent dipole and its associated mesomeric dipole with the $\overset{+}{N}H_2R$ pole, and on the basis that the positive pole is associated only with bonding electrons not appreciably displaced by weak fields, it is a reasonable expectation that this term will increase only slightly in the presence of side chain substituents with $-I$ character. In the base the most important but much smaller effect is the interaction between the combined substituent dipoles and the delocalized electrons of the NH_2 group and, as we have seen, the delocalization process is not greatly affected by the presence of the side chain substituent. Hence the potential energy increment produced in the base by a substituent should remain substantially constant throughout the four reaction series under discussion. This is a satisfactory explanation for the phenylglycines and their esters; the high value for the reaction constant of the phenylglycinate ion if significant is difficult to reconcile with this theory.[17]

The constant terms in eq. 7 and 8 could be ascribed to experimental error, for the Hammett linear free energy equation requires that regression lines for ΔpK_a vs. σ correlations pass through the origin. Systematic errors in K_Z would affect K_B, K_C and K_A, K_D in opposite directions and so account in part for the observed constants. That the existence of a constant term in these equations is real, however, is indicated by several considerations. First, while the constant terms in the equations for pK_A and pK_D (eq. 10–13) are admittedly small and within experimental uncertainty, those in eq. 5, 6, 7 and 8 are consistently greater. Moreover eq. 5 and 6 appertain to systems in which considerations of zwitterion formation do not arise, and to the extent that the determination of pK_a values is thus quite straightforward, such results are so much the more reliable. It has been shown, furthermore, that equations of this type apply to other systems; for example, m-substituted phenols obey the relation $\Delta pK_a = 2.23\sigma + 0.08$,[18,19] and investigations of 3-substituted-1-naphthylamines[20] and 3-substituted-1-naphthols[19] have shown that two separate regression lines are necessary to accommodate $-I$, $-M$ and $-I$, $+M$ substituents, the former passing close to the origin and the latter cutting the ΔpK_a axis at a positive value. The Hammett equation is therefore not adequate to explain the observed behavior when functional groups close to the ring are involved. The linear free energy relation rests on the assumption that each substituent (including hydrogen) exerts an effect on all reaction centers which is proportional to its effect on the carboxylic group in benzoic acid. This can be true only if the ratio of the polar (I) and mesomeric (M) components of the inductive effect of any given substituent remains constant for all reaction series, a doubtful assumption. For alkyl groups and

the substituents NO_2, CN, SO_2CH_3, $COOCH_3$, whose respective $+I$, $+M$, and $-I$, $-M$ functions are additive, variations of the I/M ratio from reaction to reaction will not lead to any serious deviation of the regression line from the point representing the unsubstituted compound. On the other hand, changes in the I/M ratio will have significant consequences for the substituents Cl, OCH_3 and NH_2 since $-I$, $+M$ influences are substantial and subtractive. In principle, therefore, if the changes in I/M are sufficiently large, a separate regression line will be required for such substituents, which in general will not pass through the point representing the unsubstituted compound. It appears that such features are observed only when the functional group is close to the ring as in phenols, naphthols, naphthylamines and the aniline series of compounds under discussion. The positive deviations of the regression lines for the latter can thus be attributed to a common cause, viz., the non-proportionality of the polar and mesomeric components of the substituent effect.

The remaining exponents pK_A and pK_D refer to the ionizations of the carboxyl group in the acids RC_6H_4-$NH_2{}^+CH_2CO_2H$ and $RC_6H_4NHCH_2CO_2H$ and reflect the reduced effect of a substituent at a more remote functional group. The equations for pK_A and pK_D can be obtained either from a least squares treatment of the experimental data or from the equations $K_Z = K_A/K_B = K_D/K_C$ using the Hammett equation applying to K_Z values. The expressions found are

		s	Limits of ρ, 95% prob.	
$-\log K_Z$	$= 2.91\sigma - 0.16$	0.048		(9)
ΔpK_A	$= 0.11\sigma - 0.027$		From K_Z and K_B	(10)
	$= 0.12\sigma - 0.028$	0.037	± 0.12	(11)
ΔpK_D	$= 0.29\sigma - 0.02$		From K_Z and K_C	(12)
	$= 0.32\sigma - 0.02$	0.058	± 0.13	(13)

Equation 9 is the first example reported of a relation between zwitterion ratios and Hammett constants. Equations 10 and 11 show that pK_A values are not constant as the experimental values might suggest. Interesting conclusions are reached if the reaction constants for pK_A and pK_D are compared with that for the related β-(substituted-phenyl)-propionic acids RC_6H_4-CH_2CH_2COOH. For the acids $RC_6H_4NH_2{}^+CH_2COOH$ and $RC_6H_4NHCH_2COOH$ the ρ-values are 0.11 and 0.30₅, respectively, while that for the acid $RC_6H_4CH_2$-CH_2COOH is 0.212.[6] This means that inductive effects of ring substituents are transmitted to a carboxyl group with decreasing efficiency through the sequence $NH > CH_2 > NH_2{}^+$ an order to be expected from the polarizabilities of these groups. By contrast we note the following comparisons

$NH_3{}^+CH_2CO_2H$	2.35[10]	$CH_3CH_2CO_2H$	4.87[21]
$C_6H_5NH_2{}^+CH_2CO_2H$	2.03 (pK_A)	$C_6H_5CH_2CH_2CO_2H$	4.66[13]
ΔpK_a	0.32	ΔpK_a	0.21

Here the inductive influence of a phenyl group is apparently transmitted more effectively through an $NH_2{}^+$ group. This difficulty may be overcome by assuming that differential hydrogen bonding effects present in glycine and phenylglycine, but not operative in propionic or phenylpropionic acids, are responsible for the enhanced increment in the former pair.

Experimental

Preparation of the Compounds.—The phenylglycine esters were prepared by heating the m- or p-substituted aniline (0.1 mole) with ethyl bromoacetate (0.1 mole) in the presence of sodium acetate (0.1 mole) and a small amount of ethanol for 5 hours under reflux.[22] The reaction mixture was poured into water and allowed to stand overnight. The solidified product was recrystallized from 90% ethanol. The phenylglycines

(17) Statistical analysis of all data using the σ_p-values selected gives the following results.

	n	s	Limits of ρ, 95% confidence level
$\Delta pK_E = 2.98\sigma + 0.07_2$	10	0.04_0	± 0.09
$\Delta pK_B = 3.02\sigma + 0.07_3$	10	$.03_8$	$\pm .09$
$\Delta pK_C = 3.20\sigma + 0.07_7$	8	$.04_3$	$\pm .14$
$pK_B - pK_E = 0.20 - 0.04\sigma$			

Thus it is doubtful if the differences in the ρ-values are significant.

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TABLE IV
N-(R-SUBSTITUTED-PHENYL)-GLYCINES AND THEIR ETHYL ESTERS

R equals		Melting point, °C. Found	Literature	Yield,[a] %	Purification	Formula	Analysis, % Calcd. C	H	N	Found C	H	N
m-NO₂	Ester	87	87–88²²	63	Ex. EtOH							
	Acid	160–161	158–159²³	72	Ex. H₂O							
m-CN	Ester	90	...	42	Ex. EtOH	$C_{11}H_{12}N_2O_2$	64.7	5.9	13.7	65.4	6.0	14.0
	Acid	126	...	51	As described	$C_9H_8N_2O_2$	61.4	4.6	15.9	61.6	4.4	16.0
m-COMe	Ester	65	...	71	Ex. EtOH	$C_{12}H_{15}NO_3$	65.1	6.8	6.3	65.4	6.8	6.4
	Acid	140	...	72	Ex. 50% EtOH–H₂O	$C_{10}H_{11}NO_3$	62.2	5.7	7.25	61.9	5.8	7.3
m-Cl	Ester	110	108²⁵	80	Ex. EtOH							
	Acid	98	93²⁴	72	Ex. cyclohexane							
p-Cl	Ester	94	88²⁵	68	Ex. EtOH							
	Acid	144	141²⁴	69	Ex. benzene							
m-OMe	Ester	38–39	39–40²²	67	Distilled 205° (20 mm.)							
	Acid	84	85²²	60	Ex. 50% EtOH–H₂O							
m-Me	Ester	71	68²⁶	73	Ex. EtOH							
	Acid	97	...	82	Ex. 60% EtOH–H₂O	$C_9H_{11}NO_2$	65.5	6.7	8.5	65.3	6.8	8.8
p-Me	Ester	51	52²⁷	66	Ex. EtOH							
	Acid	123	121²⁸	76	Ex. 60% EtOH–H₂O[b]							
p-OMe	Ester	59	...	62	Ex. EtOH	$C_{11}H_{15}NO_3$	63.1	7.2	6.7	63.3	7.0	6.9
	Acid	145	...	66	Ex. 66% EtOH–H₂O[b]	$C_9H_{11}NO_3$	59.7	6.1	7.8	59.3	5.9	7.9

[a] The yield of the ester was based upon the weight of substituted aniline taken. The yield of the acid was based upon the weight of ester taken.   [b] The temperature during purification was not allowed to exceed 45°.

were obtained in all but one case by heating the esters with 1.5 equivalents of sodium hydroxide (2.5 N containing 10% ethanol) under reflux for 20 minutes. The acids were precipitated with 5 N hydrochloric acid (1.5 equivalents) and recrystallized as shown in Table IV. N-(m-Cyanophenyl)-glycine was obtained by refluxing a mixture of m-aminobenzonitrile (5.5 g.), chloro-acetic acid (5 g.) and sodium acetate (5 g.) in 10 ml. of ethanol plus 5 ml. of water for 5 hours. Water (20 ml.) was added to the cooled mixture to dissolve the sodium chloride; the solution was treated with sodium bicarbonate solution and extracted with ether. The aqueous phase was adjusted to pH 3, and the dark colored oil produced crystallized on standing overnight at 5°. The product was dried, dissolved in a small volume of boiling cyclohexanol, decolorized with charcoal and filtered into boiling cyclohexane. On cooling, white needles of m.p. 126° were obtained (yield 4.2 g., 56%). All the compounds were dried at room temperature over concentrated sulfuric acid in vacuo (5 mm.) for 16 hours.

Determination of pKₐ₂ Values of the Acids.—The constants describing the "proton lost" ionizations were determined potentiometrically using a Cambridge pH meter in conjunction with a glass electrode (type GG 33, Electronic Instruments Ltd., Richmond, Surrey) and a saturated calomel electrode fitted with a sintered plug. The temperature of the solutions was maintained at 25.00 ± 0.01° by performing the titrations in a water-jacketed beaker.²⁹ To prevent hysteresis effects³⁰ the electrodes were stored at this temperature for 16 hours before the commencement of a titration. The compound (0.0005 mole) in 50 ml. of ion-free water was titrated under nitrogen with carbonate-free sodium hydroxide (0.100 N) delivered from a 5-ml. microburet in 0.10-equivalent portions until 0.90 equivalent had been added. The titrations were then continued with smaller additions until the potentiometric end-point was reached. If this deviated by more than 0.5% from the theoretical equivalent, the compound was either repurified or dissolved without heating. Solutions were not heated above 50° owing to the risk of decarboxylation which was demonstrated by refluxing a 0.01 M aqueous solution in an atmosphere of nitrogen for 30 minutes. The extent of decarboxylation (%) found was: m-NO₂, 2.5; m-OMe, 13.0; p-OMe, 42.0. The dissolution of the p-chloro derivative at 40° for about 10 minutes resulted in an 8% decomposition. This compound was therefore dissolved in one equivalent of alkali and back-titrated with acid. Since there is the possibility of error due to the proximities of the pKₐ₁ and pKₐ₂ values, the latter were determined from the last seven points of the titration curve by the method of successive approximations described by Albert and Serjeant³¹ and corrections applied for ionic strength in the usual way.

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Determination of the "Proton Gained" Exponents pK_{a_1} of the Acids by Spectrophotometry.—The ionization exponents of the esters lie in the range −0.2 to 2.0, and estimates based on potentiometric titrations involve uncertain corrections for ionic strength. For ionizations of the type $RNH_3^+ \rightleftarrows RNH_2 + H^+$ this problem can be overcome by measuring the optical densities in solutions of known hydrochloric acid strength, the concentrations of the compound being so low that the H^+ concentration is virtually unaffected. The thermodynamic exponent is given by the equation

$$pK_{a_1} = -\log (H^+) + \log \frac{\epsilon_M - \epsilon}{\epsilon - \epsilon_C} \qquad (14)$$

where (H^+) is the calculated hydrogen ion concentration, ϵ_M and ϵ_C are the molar absorbances of solutions containing the compounds in the molecular and cationic forms and ϵ is the molar absorbance of the hydrochloric acid solution of the compound.

The same method was used for the determination of the pK_{a_1} values of the phenylglycines where, however, the calculations are complicated by the fact that the measured optical density d_M at the isoelectric point does not give a true estimate of the molar absorbance ϵ_M of the molecular form since it includes contributions from the anionic and cationic species present. Corrections for these can, however, be readily made. A potentiometric titration gives the approximate pK_{a_1} from which the isoelectric point can be estimated. At this pH the fractions present as anion F_A, and cation F_C are $K_{a_2}/([H^+] + K_{a_2})$ and $[H^+]/([H^+] + K_{a_1})$, respectively. Moreover, the observed optical density $d_M^0 = d_M + d_C + d_A$, where d_M, d_C and d_A are the contributions from the molecular, cationic and anionic species present, and if C_t is the total phenylglycine concentration

$$\epsilon_M^0 C_t = \epsilon_M(1 - F_C - F_A)C_t + \epsilon_C F_C C_t + \epsilon_A F_A C_t$$

ϵ_M, ϵ_C and ϵ_A being the corresponding molar absorbances and ϵ_M^0 the observed molar absorbance of the molecular species.
Hence

$$\epsilon_M = \frac{\epsilon_M^0 - \epsilon_C F_C - \epsilon_A F_A}{1 - F_C - F_A} \qquad (15)$$

The corrected value of ϵ_M can then be used in eq. 14 to obtain a closer approximation to pK_{a_1}, and the process repeated until no change occurs in successive estimates. Note that the use of eq. 14 involves the assumption that a negligible amount of the anion is present in the solution at the pH range used to measure ϵ. This is justified since the highest pH value used was in no case less than 2.5 units below pK_{a_2}. Optical densities were measured in matched 4-cm. cells at a temperature of 25.0 ± 0.1°, the wave length in most cases being at the peak of the long wave length band of the molecular species. The exceptions were the m-nitro and m-cyano derivatives which exhibited solvent–solute interactions at these wave lengths. The values for these compounds were obtained from measurements at 235 and 250 mμ, respectively.

Determination of the Zwitterion Equilibrium Constant K_Z.—Values of K_Z were calculated by the equation

$$K_Z = \frac{\epsilon_{ester} - \epsilon_M}{\epsilon_M - \epsilon_{cation}}$$

the molar absorbances of the ester, cation and molecular species being determined at a given wave length and temperature, the value of ϵ_M being corrected as described above. The wave lengths chosen were located at the peaks of the long wave length bands where the values of ϵ_{cation} are small. It was found practical to substitute the value ϵ_{anion} for ϵ_{ester} in a number of cases where the esters were very slightly soluble in water.

Summary

We have reached the following conclusions: 1. The Wegscheider assumption that the inductive effect of a COOH group is equal to that of a $COOC_2H_5$ group is invalid for substituted phenylglycines. Zwitterion ratios based on this assumption are suspect and should be checked by alternate criteria. 2. The proportion of zwitterions in aqueous solution is governed mainly by the effect of the substituent on the pK_a of the anilinium group, and can vary from a small fraction up to 90% in changing the substituent from m-NO_2 to p-OCH_3. 3. The presence of side chains with substantial $-I$ character attached to the nitrogen atom has little influence on the intensity of m- and p-substituent effects on the $-NH_2R^+$ ionization, the Hammett reaction constants being similar for four reaction series in which R may be H, CH_2COOH, CH_2COOEt and CH_2-COO^-. 4. The presence of a positive constant term in the Hammett equations relating to the NH_2R^+ ionization is considered to indicate a different I/M ratio of the components of the substituent effect in anilines as compared with that in benzoic acids. 5. The transmission of the inductive effects of ring substituents to functional groups via side chains is related to the polarizabilities of the intervening groups, the efficiency decreasing in the sequence $NH > CH_2 > NH_2^+$.

Anchimerically Accelerated Bond Homolysis. III.[1] Polar and Geometric Factors Influencing the Radical Decomposition of t-Butyl o-Phenylthioperbenzoate

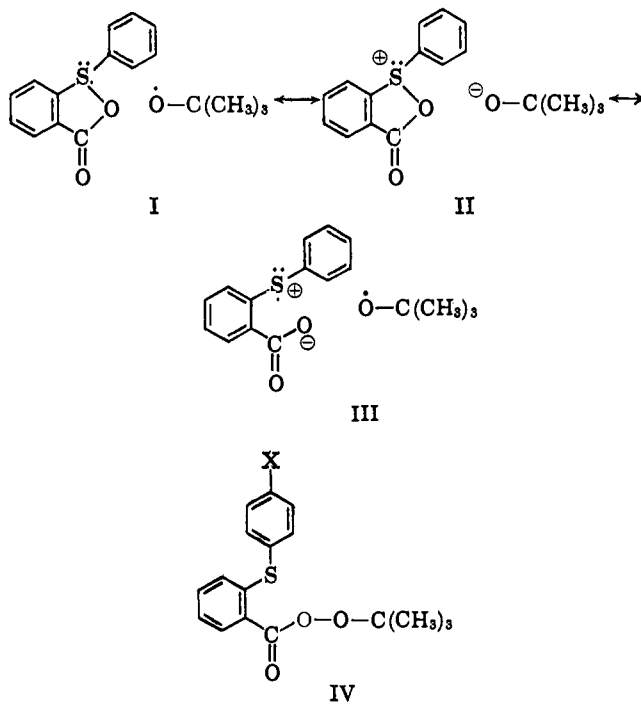BY D. L. TULEEN,[2] W. G. BENTRUDE[2] AND J. C. MARTIN

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The susceptibility of the rate of thermal decomposition of t-butyl o-phenylthioperbenzoate to the effects of substituents, solvent ionizing power and added salt indicates that a large contribution to the transition state for this homolysis is made by dipolar structures in which sulfur bears a positive charge. Further evidence is presented that the products of this decomposition are free radicals. Rates of decomposition of geometrically restricted model compounds indicate that homolytic decomposition may be anchimerically assisted by neighboring sulfur only when it is possible for the groups attached to sulfur to attain an approximately tetrahedral configuration. The results are compatible with a transition state, described rather well by structure II, in which the bonding to sulfur is very similar to that in a sulfonium ion.

Many radical reactions resemble heterolytic processes to a considerable degree.[3] The effects of m- and p-substituents upon the rates of the thermal decomposition of benzoyl peroxides,[4,5] t-butyl perbenzoates[6] and phenylperacetates[7] are, for example, correlated by the Hammett σ-ρ relationship. Even for reactions showing appreciable polar substituent effects the separation of charge in the transition states is usually not large enough to be reflected in an unambiguous dependence of rate on solvent polarity. Rates of certain radical reactions have, indeed, been shown[8-10] to vary markedly with solvent. A clear-cut correlation with solvent ionizing power has not, however, been made prior to this work.

It has been proposed[1] that the transition state for the anchimerically assisted homolysis of t-butyl o-phenylthioperbenzoate may be represented by structures I and II. The importance to the transition state of the contribution made by dipolar structure II, or the closely analogous structure III, has been evaluated by an examination of the response of the rate of decomposition of this perester to the effects of substituents, of the ioniz-

ing power of the solvent, of added salt and of geometric restraint (in closely related series of model compounds). In a previous communication[11] we presented evidence that this decomposition is sensitive to changes in the ionizing power of the solvent. In this paper results are presented which confirm and extend this view.

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(2) Taken from the Ph.D. Theses of D. L. Tuleen, Univ. of Ill., July, 1962, and W. G. Bentrude, Univ. of Ill., June, 1961.

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