Two distinctly negative results were obtained, which are interesting in that they are in harmony with the theory proposed. No reaction for an oxidase was obtained with aqueous extracts from two varieties of cultivated roses. German otto of rose contains a very small proportion of citral and a trace of nonyl aldehyde. The extracted oil may contain as much as 75 per cent. phenylethyl alcohol[1] but it is not known to contain phenylacetaldehyde or phenylacetic acid.

Negative results were also obtained with *Andropogon schoenanthus*, which yields palma rosa oil. This oil may contain as high as 93 per cent. of geraniol in addition to citronellol and dipentene. This is in marked contrast with the very closely related *Andropogon* grasses which yield lemon grass and citronella oils, both of which contain citral and citronellal as their major constituents. These species will be examined when the material is available.

The presence of an oxidase probably accounts for the fact that the perfumes of certain flowers deteriorate rapidly after picking, particularly if bruised, as is the case with champaca and gardenia flowers. The author ventures the opinion that flowers showing marked reactions for oxidases are not treated to the best advantage by the enfleurage method.

The action of oxidases from various sources on terpene alcohols will be taken up in the second paper on this subject.

GÖTTINGEN, GERMANY.

[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY, UNIVERSITY OF ILLINOIS.]

CORRELATION OF IONIZATION AND STRUCTURE. II. NEGATIVELY SUBSTITUTED BENZOIC ACIDS.

BY C. G. DERICK.

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1. Introduction.

In a previous article,[2] the author has shown that the free energy of ionization for negatively substituted monobasic paraffin acids in water solution at 25° is made up additively of the separate effects of each atom within the molecule. Because of this fact, it was shown that the position of a negative substituent in a paraffin acid could be determined with certainty if its α place factor and the ionization constant of this nega-

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[1] v. Soden, *J. prakt. Chem.*, [2] 69, 265 (1904).

[2] THIS JOURNAL, 33, 1181 (1911).

tively substituted paraffin acid were known. The advantages of this method for the determination of structure over methods that use physical properties were pointed out. In the first place, no high degree of purity is necessary if the substituent is in the α, β, γ or δ positions, which is usually the case. A second advantage is due to the fact that no expensive apparatus and no exceptional skill are required to measure the ionization constant within the necessary limits. On the other hand, it was shown that in the calculation of the ionization constants from structure a much greater accuracy in the measurements of the ionization constants is required. Tables were given showing that the ionization constants for negatively substituted paraffin acids could be calculated with a degree of accuracy equal to that obtained in the measured values. This last fact constituted a rigid test of the statement that the free energy of ionization is made up additively of the separate influence of each atom in the molecule. Finally, it was shown that for the non-ionizing negative radicals, Cl, Br, I, OH and C_6H_5, the place factors for the positions α, β, γ, δ, etc., possessed the following simple relationship α, $\alpha/3$, $\alpha/9$, $\alpha/27$, etc., respectively. It was also shown that even though a negative radical did not obey this "rule of thirds," its effect upon the free energy of ionization was still additive and from the experimentally determined place factors for the different positions of substitution, structures and ionization constants for such negatively substituted paraffin acids could be determined.

2. Place Factors for Negative Radicals in Aromatic Acids.

It is the purpose of this paper to show that the additive relationship in the free energy of ionization holds for the complex benzene derivatives of the aromatic series. It is therefore possible to determin the structure or ionization of negatively substituted benzoic acids if the ortho, meta and para place factors are known for each negative radical.

In the calculation of the place factors, the influence of all of the atoms in the molecule upon the ionization was defined as proportional to $1/\log K$, where K is the mass law constant. Hence this influence is inversely proportional to the free energy of ionization according to the expression $A = RT \log K$ where A is the free energy of ionization, for R and T (since all measurements are made at 25°) are constant. In order to determin the place factor for the given negative radical or atom in a given negatively substituted benzoic acid it becomes necessary to determin the effect of all the other atoms in this acid. This is accomplished as follows. In salicylic acid, the ortho hydroxyl place factor is desired. Leaving out of consideration this hydroxyl group, the other atoms in the molecule of salicylic acid differ from the corresponding unsubstituted benzoic acid, by a single hydrogen atom. The influence of all the atoms in benzoic acid is defined as proportional to $1/\log K$ and this may be taken as the summation of the influences of the atoms in salicylic acid, excepting the influence of the ortho hydroxyl group, thereby neglecting the influence of a single hydrogen atom, which is justifiable, if it has a small value, since it occurs additively in the above. The ratio of the influence upon the ionization of the atoms in salicylic acid to the atoms in benzoic acid is then determined as follows:

$$\frac{\text{Salicylic}}{\text{Benzoic}} = \frac{1}{\text{Log K (salicylic)}} : \frac{1}{\text{Log K (benzoic)}} = \frac{-4.17457^{1}}{-2.98297} = \frac{1.399}{1}.$$

The influence of the ortho hydroxyl group upon the ionization or its *place factor* is therefore 1.399 — 1.000 = 0.3990. The value for the ionization constant of benzoic acid is taken as 6.69×10^{-5} and is the average of three determinations reported by Lunden in his pamphlet, "Affinitätmessungen on schwachen Sauren und Basen."

In Table I are given the ortho, meta, and para place factors for different negative radicals and atoms for benzoic acid, calculated in the same man-

TABLE I.—PLACE FACTORS OF THE NEGATIVE RADICALS IN MONOBASIC AROMATIC ACIDS.

Aromatic acid.			Radical.		
Name.	K_a.	Log K_a.[1]	Formula.	Position.	Place factor.
o-Acetohydroxybenzoic	3.33×10^{-4}	—3.47756	CH_3CO_2—	*o*	0.200
m-Acetohydroxybenzoic	9.9×10^{-5}	—4.00436	CH_3CO_2—	*m*	0.0425
p-Acetohydroxybenzoic	4.2×10^{-5}	—4.37675	CH_3CO_2—	*p*	0.0462
Phthalaldehydic	3.6×10^{-5}	—4.44370	HCO—	*o*	—0.0606
o-Benzoylbenzoic	3.7×10^{-4}	—3.43180	C_6H_5CO—	*o*	+0.216
o-Bromobenzoic	1.45×10^{-3}	—2.83863	Br—	*o*	0.471
Phthalic	1.21×10^{-3}	—2.91721	CO_2H—	*o*	0.431
Isophthalic	2.9×10^{-4}	—3.53760	CO_2H—	*m*	0.180
Terephthalic	1.5×10^{-4}	—3.82391	CO_2H—	*p*	0.092
Methyl phthalate	6.56×10^{-4}	—3.18310	CO_2CH_3—	*o*	0.311
Ethyl phthalate	5.51×10^{-4}	—3.25885	$CO_2C_2H_5$	*o*	0.281
o-Chlorobenzoic	1.32×10^{-3}	—2.87943	Cl—	*o*	0.450
m-Chlorobenzoic	1.55×10^{-3}	—2.80967	Cl—	*m*	0.486
p-Chlorobenzoic	9.3×10^{-5}	—4.03156	Cl—	*p*	0.0355
m-Cyanobenzoic	1.99×10^{-4}	—3.70115	CN—	*m*	0.128
m-Fluorobenzoic	1.4×10^{-4}	—3.85387	F—	*m*	0.0832
**o*-Hydroxybenzoic	1.04×10^{-3}	—2.98297	(OH)—	*o*	0.399
m-Hydroxybenzoic	1.04×10^{-3}	—4.07935	(OH)—	*m*	0.0233
p-Hydroxybenzoic	2.9×10^{-5}	—4.53760	(OH)—	*p*	—0.0800
o-Iodobenzoic	1.37×10^{-3}	—2.86328	I—	*o*	0.458
m-Iodobenzoic	1.6×10^{-4}	—3.79588	I—	*m*	0.0997
Methylsalicylic	8.1×10^{-5}	—4.09151	CH_3O—	*o*	0.0204
**o*-Nitrobenzoic	6.3×10^{-3}	—2.20066	NO_2—	*o*	0.897
**m*-Nitrobenzoic	3.44×10^{-4}	—3.46344	NO_2—	*m*	0.205
p-Nitrobenzoic	4.0×10^{-4}	—3.39794	NO_2—	*p*	0.229
o-Methylolbenzoic	1.5×10^{-4}	—3.82391	CH_2OH—	*o*	0.0917

[1] Log K is expressed as a negative logarithm.

* Acids so marked have been measured by two or more investigators.

ner as illustrated with the ortho hydroxyl place factor. The data are taken from Lunden's work just referred to. From the experimental study now in progress in this laboratory it is evident that in most cases the third figure in these place factors is doubtful, but no final word can be said on this point until a thorough study of the field has been completed.

3. Calculated Ionization Constants of Substituted Benzoic Acids.

From the place factors, given in Table I, the calculated ionization constants for the substituted benzoic acids, given in Table II, were computed. The method of calculation is the reverse of that just given under "Place Factors for Negative Radicals in Aromatic Acids." From the algebraic sum of the place factors representing the substituents in the acid whose ionization constant is desired, the above ratio of substituted benzoic acid to benzoic acid is determined and solved for the negative logarithm of the desired ionization constant, from which the algebraic value of the constant is determined.

In all the acids, the calculated and experimental value for the ionization constant fall within the same order. In twelve out of the twenty acids considered, the first significant figure in the calculated and experimental values are identical. It is very doubtful if the experimental results are known with an accuracy beyond this figure in the majority of cases, as will be shown in the experimental study of these place factors. In the cases where the experimental ionization constants have been measured by two or more investigators, the agreement with the calculated values is much closer. Such acids have been marked by an asterisk in Table II, from which we find the difference between the experimental and calculated values to be 7.4%, 1.7%, 33%, 12% and 9.9%. In all but one of the cases, the difference is well within the experimental error and the additive relationship of the place factors seems to be clearly established. On the other hand, the place factors representing a single hydrogen must be very small, since it was neglected in the calculation of the place factors for other radicals. However, the final word can be said only after a careful experimental determination of the above place factors.

4. Determination of Structure of Substituted Benzoic Acids from their Ionization Constants by Means of Place Factors.

The problem of determining the structures of negatively substituted acids from their ionization constants is much more complex than in the corresponding substituted paraffin acids. In the first place the rule of thirds does not apply, nor is there any apparent simple relationship between the place factors for a given group for the ortho, meta and para position. Hence the experimental ortho, meta and para place factors for each negative radical must be determined. These values, once ac-

TABLE II.—CALCULATED IONIZATION CONSTANTS OF POLYSUBSTITUTED BENZOIC ACIDS.

Aromatic acid.		Ionization constant.	
Name.	Substituent.	Calculated.	Measured.
o-Chloro-*m*-nitrobenzoic	*o*-Cl, *m*-NO_2—	3.0 × 10^{-3}	6 × 10^{-3}
m-Chloro-*o*-nitrobenzoic	*m*-Cl, *o*-NO_2—	1.7 × 10^{-2}	1.5 × 10^{-2}
p-Chloro-*m*-nitrobenzoic	*p*-Cl, *m*-NO_2—	4.3 × 10^{-4}	4.6 × 10^{-4}
p-Chloro-*o*-nitrobenzoic	*p*-Cl, *o*-NO_2—	7.0 × 10^{-3}	1.0 × 10^{-2}
α-Methyl 3,6-dichlorophthalate	*m*-Cl, *o*-Cl, *o*-$COOCH_3$	1.3 × 10^{-2}	1.5 × 10^{-2}
*2,5-Dihydroxybenzoic	*o*-(OH), *m*-(OH)	1.16 × 10^{-3}	1.08 × 10^{-3}
*2,3-Dihydroxybenzoic	*o*-(OH), *m*-(OH)	1.16 × 10^{-3}	1.14 × 10^{-3}
*2,4-Dihydroxybenzoic	*o*-(OH), *p*-(OH)	6.8 × 10^{-4}	5.1 × 10^{-4}
*3,4-Dihydroxybenzoic	*m*-(OH), *p*-(OH)	3.7 × 10^{-5}	3.3 × 10^{-5}
*3,5-Dihydroxybenzoic	*m*-(OH), *m*-(OH)	1.0 × 10^{-4}	9.1 × 10^{-5}
2-Methyl 4-hydroxyphthalate	*p*-(OH), *m*-(CO_2CH_3)	4.0 × 10^{-4}	2.0 × 10^{-4}
Pyrogallol carboxylic (1 : 2 : 3 : 4)	*o*-(OH), *m*-(OH), *p*-(OH)	7.7 × 10^{-4}	5.5 × 10^{-4}
5-Nitro-2-aldehydobenzoic	*o*-(HCO), *m*-(NO_2)	2.2 × 10^{-4}	1.0 × 10^{-4}
1-Ethyl 4-nitrophthalate	*m*-(NO_2), *o*-$(CO_2C_2H_5)$	1.5 × 10^{-3}	3.0 × 10^{-3}
2-Ethyl 4-nitrophthalate	*p*-(NO_2), *o*-$(CO_2C_2H_5)$	1.7 × 10^{-3}	5.2 × 10^{-3}
1-Methyl 3-nitrophthalate	*o*-NO_2, *o*-(CO_2CH_3)	1.3 × 10^{-2}	1.6 × 10^{-2}
2-Methyl 3-nitrophthalate	*m*-NO_2, *o*-(CO_2CH_3)	1.8 × 10^{-3}	2.1 × 10^{-3}
o-Nitrosalicylic	*o*-(OH), (NO_2)	1.52 × 10^{-2}	1.57 × 10^{-2}
p-Nitrosalicylic	*o*-(OH), *p*-(Cl)	2.7 × 10^{-5}	8.9 × 10^{-5}
m,m-Dinitrobenzoic	*m*-(NO_2), *m*-(NO_2)	1.1 × 10^{-3}	1.6 × 10^{-3}

*Acids so marked have been measured by two or more investigators.

curately determined, make it possible to calculate from the ionization constant, the structure of polysubstituted benzoic acids, where the substituent is a negative radical. The method will be illustrated as follows: A polyhydroxy benzoic acid has been prepared and its ionization constant has been measured. From its molecular weight and reaction with acetyl chloride, two hydroxyl groups are known to be present. We are, therefore, dealing with a dihydroxybenzoic acid. Theoretically, the following six are possible: $CO_2H : OH : OH = 1:2:3$; $1:2:4$; $1:2:5$; $1:2:6$; $1:3:4$; $1:3:5$.

The algebraic sum of the place factors, corresponding to the hydroxyl group in each of the possible dihydroxybenzoic acids above, are, from Table I, respectively:

$$\begin{array}{ccc}
(1) & (2) & (3) \\
o\text{-(OH)} = 0.399 & o\text{-(OH)} = 0.399 & o\text{-(OH)} = 0.399 \\
m\text{-(OH)} = 0.023 & p\text{-(OH)} = -0.080 & m\text{-(OH)} = 0.023 \\
\hline
o + m = 0.422 & o + p = 0.319 & o + m = 0.422 \\
 & & \\
(4) & (5) & (6) \\
o\text{-(OH)} = 0.399 & m\text{-(OH)} = 0.023 & m\text{-(OH)} = 0.023 \\
o\text{-(OH)} = 0.399 & p\text{-(OH)} = -0.080 & m\text{-(OH)} = 0.023 \\
\hline
o + o\text{-(OH)} = 0.798 & m + p = -0.057 & m + m\text{-(OH)} = 0.046
\end{array}$$

The ionization constant of the unknown dihydroxybenzoic acid is found to be 3.3×10^{-5}, from which the experimental place factor, representing the algebraic sum of the place factors for the two hydroxyl groups, is calculated to be -0.068. Obviously the hydroxyl groups must be in the meta and para position and the unknown acid is 3,4-dihydroxybenzoic acid, since the only combination of two place factors for two hydroxyl groups whose algebraic sum will give the experimental value, -0.068, is that represented by acid (5) above.

It is interesting to note that the para hydroxyl group behaves like a positive radical, decreasing the hydrogen ionization and therefore having a negative place factor in this consideration.

In the formation of new poly-substituted benzoic acids, this method for the determination of structure may be used very effectively to determin whether or not a molecular rearrangement has occurred within the molecule as well as to assign structure.

5. Limitations in the Use of Place Factors for the Determination of Structure in the Aromatic Series.

If the place factor for a given group in the ortho, meta or para position differ but little, it will be difficult to assign the structure for a given aromatic acid unless extreme accuracy in the measurement of the ionization constant is possible for the given acid. A study of Table I shows, however, that this difficulty is not likely to interfere, seriously, in the majority of cases.

A far greater difficulty is presented by the fundamental conception of this work, namely, that the factor, representing the influence upon the ionization of all the atoms in the molecule (inversely proportional to the free energy of ionization), is made up *additively* of the separate influences of each atom. This means that each atom or radical exerts its influence upon the ionization independent of the other atoms or radicals and that the influence upon the ionization from a carboxyl group of a given radical will always be the same if it is the same distance from the ionizing group. For example, in 2,3- and 2,5-dihydroxybenzoic acids, the two hydroxyl groups are ortho and meta to the carboxyl group in both acids. This means, if the above additive relationship in the place factors is correct, that each should have the same ionization constant, since in each acid the hydroxyl groups are the same distance from the ionizing carboxyl group according to the hexagon formula for benzene. Experimentally the ionization constants for 2,3- and 2,5-dihydroxybenzoic acids are 1.06×10^{-3} and 1.14×10^{-3}, respectively. In other words, the substituent in position 3 will exert the same influence as in position 5 upon the carboxyl group in position 1 independent of the substituent in position 2 or 6. This fact is a peculiarity of the meta position for disubstituted benzoic acids. It is supported by many calculations in Table II where the value of the place factor of a given group is taken for the ortho, meta or para positions without regard to the other substituents in the molecule.

But Kekulé's "Atomic Linking Theory" predicts a difference between the 2,3- and 2,5-dihydroxybenzoic acids and this difference has been proven experimentally. Obviously, if the additive relationship in the place factor is true, as the above work has shown it to be, then the difference between the two acids is one of space relationship, since the relative distances between the groups in the 2,3- and the 2,5-dihydroxybenzoic acids must be the same. Ionization cannot, therefore, be used to determin this difference in structure, *i. e.*, it will not distinguish between the 3- and 5-positions in disubstituted benzoic acids, as it does not between the same positions in the mono-substituted benzoic acids.

6. A New Proof of the Equivalence of the Positions 3 and 5 with Respect to Position 1 in the Benzene Ring.

Hübner and Peterman[1] first proved that for a given position in the benzene ring there are two pairs of positions which with respect to this given position are equivalent. They observed "that ordinary bromobenzoic acid gives, on nitration, two isomeric nitrobromobenzoic acids. The latter, on reduction, yield the same aminobenzoic acid, *i. e.*, anthranilic

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[1] *Ann.*, 149, 129 (1869). Also Cohen's "Organic Chemistry for Advanced Students," pages 438-444.

acid, which is related to salicylic acid." In other words in the pair 2–6, the positions 2 and 6 in the benzene ring with respect to 1 are equivalent. Later Noelting proved the same fact, as have numerous other investigators. These proofs have all been based upon the assumption that no molecular rearrangement occurs after the new radical has entered the molecule.

The additive relationship in the place factors for the negative substituents in substituted benzoic acids offers us a new proof of the symmetry of the benzene molecule. It offers us a means of detecting whether or not a molecular rearrangement follows the introduction of a new radical into the molecule.

In the previous section, it was shown that the positions 3 and 5 with respect to the position 1 in the benzene molecule are equivalent, independent of the substituents in the positions 2 and 6. This may be taken as a new proof of the equivalency of the pair of positions 3 and 5 with respect to position 1. But fortunately another proof is possible; for if we substitute a given radical into position 3 and the same radical into position 5, the algebraic sum of the place factors for these two positions must be just twice that for the single group in the meta position. For example, the place factor for the hydroxyl group in the meta position, taken from Table I, is equal to 0.023. The algebraic sum of the place factors for the two hydroxy groups in 3,5-dihydroxybenzoic acid, if the positions 3 and 5 are equivalent with respect to 1, is $2 \times 0.023 = 0.046$ from which we obtain the calculated ionization constant 1.0×10^{-4}. The experimental ionization constant for this acid is 9.1×10^{-5} and agrees with the calculated value within 10%, which is within the experimental error. Similarly the calculated value for the ionization constant of *m,m*-dinitrobenzoic acid, calculated on the assumption of the equivalency of positions 3 and 5 with respect to 1, is 1.1×10^{-3}, while the experimental value is 1.6×10^{-3}. These two examples, as well as the acids mentioned under the previous sections, prove clearly that the positions 3 and 5 with respect to position 1 in the benzene ring are equivalent from an energy standpoint, since the place factor is inversely proportional to the free energy of ionization.

7. Summary.

(1) The place factors for benzoic acid for the radicals acetohydroxy carboxyl, chlorine, hydroxyl, and nitro, for the ortho, meta and para positions; aldehyde, benzoyl, bromine, carboxymethyl, carboxyethyl iodine and methoxy for the ortho position; and cyanogen, fluorine and iodine for the meta position have been determined.

(2) No simple relationship exists between the ortho, meta, and para place factors for the same radical substituted in benzoic acid.

(3) The calculated ionization constants for twenty polysubstituted

benzoic acids have been compared with their experimental ionization constants and found to agree fairly accurately in all but four cases. For those acids whose ionization constants have been measured by two or more investigators, the agreement between the calculated and experimental values is within the limit of the experimental error in all but one acid.

(4) A method for the determination of the structure of polysubstituted benzoic acids from their ionization has been developed.

(5) Ionization will not distinguish the difference in structure of 2,3- and 2,5-disubstituted benzoic acids where the substituents in 3 and 5 are the same and the substituent in 2 is also the same in both acids.

(6) The equivalency of the positions 3 and 5 with respect to position 1 in the benzene ring has been proven in terms of the free energy of ionization.

(7) The assumption that the free energy of ionization is made up additively of the separate influence of each atom in the molecule of an acid has received further substantiation.

URBANA, ILL.

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF MICHIGAN.]

THE FORMATION OF PYRIMIDINES BY USE OF NITROMALONIC ALDEHYDE.[1]

BY WILLIAM J. HALE AND HARVEY C. BRILL.

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When either acetone or one of its mono- or symmetrical di-substitution products is allowed to act upon nitromalonic aldehyde, a condensation readily takes place. The course of these condensations was thoroughly investigated by Hill and his coworkers.[2] In all of the cases studied, the acetone nucleus was involved with the two aldehyde groups conjointly, and resulted in the formation of six-membered ring compounds—derivatives of benzene. Derivatives of acetone higher than the symmetrical di-substitution products could not be made to enter into the reaction. There arose, therefore, the necessity of explaining these results through the formation of an intermediate product—a derivative of dihydrobenzene. This latter, by the elimination of water, readily underwent a transformation to the benzene type. Two free hydrogen atoms upon either end of the acetone nucleus are thus shown to be a prerequisite for this condensation with nitromalonic aldehyde.

Substances possessing amino groups, and thereby two free hydrogen

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[1] The work described in this article formed part of a thesis presented to the Faculty of the Department of Literature, Science and the Arts of the University of Michigan for the degree of Doctor of Philosophy, by Harvey C. Brill.

[2] *Am. Chem. J.*, **22**, 89 (1899); **24**, 1 (1900); **33**, 1 (1905).