255. *The Additive Effect of Substituents on the Strength of Benzoic Acid.*

By J. SHORTER and F. J. STUBBS.

The change in the free energy of ionisation caused by two or more substituents in benzoic acid has been shown in a number of cases to be very nearly the algebraic sum of the effects of the individual groups.

STUBBS and HINSHELWOOD (this vol., p. S 71) have shown that the velocity of benzoylation of 21 disubstituted anilines can be predicted quite accurately from those of the corresponding monosubstituted anilines. Each substituent, at a given position in the aniline, alters the free energy of activation ($-\boldsymbol{R}T \ln k$) by a characteristic amount independent of the presence of another substituent. Thus the effect on the free energy of activation of two substituents in the same nucleus is very closely the sum of their individual effects.

In the present work, this principle of additivity has been examined for the free energies of *ionisation* ($-\boldsymbol{R}T \ln K$) of substituted benzoic acids.

The free-energy data in the tables are calculated from classical dissociation constants taken from the International Critical Tables and the " Tabellen " of Landolt–Börnstein. Table I contains the values for benzoic acid and its mono-substituted derivatives, and the fourth column gives the *change* in the free energy of ionisation [$\Delta(-\boldsymbol{R}T \ln K)$] caused by the various substituents.

TABLE I.

Acid.	10^5K_{25}.	$-\boldsymbol{R}T \ln K$ (cals./mole).	$\Delta(-\boldsymbol{R}T \ln K)$ (cals./mole).
Benzoic	6·69	5690	0
o-Chlorobenzoic	132	3930	−1760
m-Chlorobenzoic	15·5	5200	− 490
p-Chlorobenzoic	9·3	5500	− 190
o-Bromobenzoic	145	3870	−1820
m-Bromobenzoic	13·7	5270	− 420
p-Bromobenzoic	10·7	5420	− 270
o-Nitrobenzoic	620	3010	−2680
m-Nitrobenzoic	36	4690	−1000
p-Nitrobenzoic	38	4660	−1030
o-Hydroxybenzoic	106	4050	−1640
m-Hydroxybenzoic	8·33	5570	− 120
p-Hydroxybenzoic	2·90	6190	+ 500
o-Methoxybenzoic	8·3	5570	− 120
m-Methoxybenzoic	8·8	5540	− 150
p-Methoxybenzoic	3·2	6120	+ 430
o-Toluic	12·5	5320	− 370
m-Toluic	5·60	5800	+ 110
p-Toluic	4·30	5960	+ 270

From the results given in Table I the change in the free energy of ionisation for the polysubstituted benzoic acids can be predicted as in the following examples.

4-*Nitro*-3-*methylbenzoic acid.*

	$\Delta(-\boldsymbol{R}T \ln K)$.
4-Nitro	−1030
3-Methyl	+ 110
Predicted value	− 920

2 : 3-*Dinitro*-5 : 6-*dimethoxybenzoic acid.*

	$\Delta(-\boldsymbol{R}T \ln K)$.
2-Nitro	−2680
3-Nitro	−1000
5-Methoxy	− 150
6-Methoxy	− 120
Predicted value	−3950

Table II gives for 73 polysubstituted benzoic acids the observed values of $\Delta(-\boldsymbol{R}T \ln K)$ and those predicted on the assumption of a strictly additive effect.

Discussion.—The results given in Tables I and II are based on investigations by a large number of different workers employing a variety of experimental methods. Many are of considerable antiquity, the concentration ranges employed vary greatly, and in certain cases the compounds may have been of questionable purity. Consequently, some of the free energies of ionisation quoted may be in error by 100 cals. or more. Therefore without performing an unduly elaborate and tedious analysis of the data, it is not possible to do more than investigate the validity of the additivity principle to within a few units %.

An examination of Table II shows that the predicted and observed values of $\Delta(-\mathbf{R}T \ln K)$ are frequently in close agreement. Occasionally, as with 2 : 4-dinitro- and 3-chloro-6-nitro-benzoic acids, the agreement is remarkable, while in others such as 2 : 4-dibromo- and 2-hydroxy-4-methyl-benzoic acids there is agreement to within 5%. When the total effect of the substituents is comparatively small, considerable discrepancies reckoned as percentages are only to be expected, although in examples such as 3 : 5-dimethyl- and 3-hydroxy-2-methyl-benzoic acids, the discrepancy in calories is quite small.

There are, however, certain cases in which the total effect of the substituents is considerable, and the additivity principle is seriously violated. These are worthy of more detailed consideration.

Compounds containing two groups ortho to the carboxyl group often show serious discrepancies; *e.g.*, 2 : 6-dimethyl-, 2 : 6-dinitro-, and 2 : 6-dihydroxy-benzoic acids. Others, however, *e.g.*, 2 : 4 : 6-tribromobenzoic acid, do not. Some, at any rate, of these discrepancies are probably real and not due to gross experimental error. Rather convincing evidence for this view exists in a few of the examples. If the effect be real, an improved prediction for a trisubstituted benzoic acid containing two *ortho*-groups should be possible from the experimental value for the 2 : 6-disubstituted-benzoic acid, *e.g.*, a new value of $\Delta(-\mathbf{R}T \ln K)$ for 2 : 4 : 6-tri-hydroxybenzoic acid may be derived from the results for 2 : 6-dihydroxy- and *p*-hydroxy-benzoic acids. Some illustrations of this procedure are given in Table III.

TABLE II.

		$\Delta(-\mathbf{R}T \ln K)$, cals./mole :	
Substituted benzoic acid.	10^5K_{25}.	Observed.	Predicted.
2 : 4-Dibromo-	200	−2010	−2090
2 : 3-Dinitro-	1300	−3110	−3680
2 : 4-Dinitro-	3500	−3700	−3710
2 : 5-Dinitro-	2400	−3480	−3680
2 : 6-Dinitro-	7450	−4150	−5360
3 : 4-Dinitro-	150	−1840	−2030
3 : 5-Dinitro-	160	−1870	−2000
2 : 3-Dihydroxy-	114	−1680	−1760
2 : 4-Dihydroxy-	50·5	−1190	−1140
2 : 5-Dihydroxy-	108	−1640	−1760
2 : 6-Dihydroxy-	500	−3920	−3280
3 : 4-Dihydroxy-	3·3	+ 420	+ 380
3 : 5-Dihydroxy-	9·1	− 180	− 240
3 : 4-Dimethoxy-	3·54	+ 380	+ 280
2 : 4-Dimethyl-	9·0	− 170	− 100
2 : 5-Dimethyl-	12	− 340	− 260
2 : 6-Dimethyl-	62	−1310	− 740
3 : 5-Dimethyl-	4·8	+ 200	+ 220
2-Chloro-3-nitro-	870	−2880	−2760
2-Chloro-4-nitro-	1000	−2960	−2790
2-Chloro-5-nitro-	620	−2580	−2760
3-Chloro-2-nitro-	440	−2470	−3170
3-Chloro-5-nitro-	74·1	−1420	−1490
3-Chloro-6-nitro-	1400	−3170	−3170
4-Chloro-2-nitro-	1000	−2960	−2870
4-Chloro-3-nitro-	46	−1130	−1190
2-Chloro-3-hydroxy-	136	−1780	−1880
2-Chloro-5-hydroxy-	138	−1790	−1880
3-Chloro-4-hydroxy-	5·6	+ 110	+ 10
5-Chloro-2-hydroxy-	195	−1990	−2130
2-Chloro-5-methoxy	130	−1750	−1910
2-Bromo-3-nitro-	1200	−1710	−2820
2-Bromo-5-nitro-	910	−2910	−2820
3-Bromo-2-nitro-	300	−2250	−3100
3-Bromo-6-nitro-	1400	−3170	−3100
4-Bromo-3-nitro-	42	−1080	−1270
5-Bromo-2-hydroxy-	240	−2120	−2060
3-Nitro-2-hydroxy-	1500	−3210	−2640

TABLE II (*continued*).

Substituted benzoic acid.	10^5K_{25}.	$\Delta(-RT \ln K)$, cals./mole Observed.	Predicted.
5-Nitro-2-hydroxy-	780	−2810	−2640
3-Nitro-4-methoxy-	19	− 620	− 570
4-Nitro-3-methyl-	31	− 900	− 920
4-Hydroxy-3-methoxy-	2·94	+ 490	+ 350
2-Hydroxy-3-methyl-	100	−1600	−1530
2-Hydroxy-4-methyl-	72	−1410	−1370
2-Hydroxy-5-methyl-	86	−1500	−1530
2-Hydroxy-6-methyl-	104	−1630	−2010
3-Hydroxy-2-methyl-	16·6	− 530	− 490
2-Methoxy-4-methyl-	4·04	+ 300	+ 150
2-Methoxy-5-methyl-	6·65	+ 10	− 10
4-Methoxy-2-methyl-	5·2	− 150	− 60
4-Methoxy-3-methyl-	3·4	− 410	− 540
2 : 4 : 6-Tribromo-	390	−3770	−3910
2 : 4 : 6-Trihydroxy-	2100	−3400	−2780
2 : 3 : 4-Trimethyl-	3·3	+ 410	+ 10
2 : 4 : 5-Trimethyl-	9·5	− 210	+ 10
2 : 4 : 6-Trimethyl-	37	−1010	− 470
2 : 6-Dichloro-3-hydroxy-	2100	−3400	−3640
3 : 5-Dichloro-2-hydroxy-	450	−2490	−2620
2-Chloro-6-bromo-3-hydroxy-	2200	−3430	−3700
2-Chloro-6-bromo-5-hydroxy-	200	−2010	−3700
2-Nitro-3 : 4-Dimethoxy-	79	−1460	−2400
2-Nitro-4 : 5-dimethoxy-	320	−2290	−2400
3-Nitro-2 : 5-dimethoxy-	170	−1910	−1270
4-Nitro-2-hydroxy-5-methoxy-	1000	−2960	−2820
5-Nitro-2-hydroxy-3-methoxy	900	−2890	−2790
5-Nitro-3-hydroxy-4-methoxy-	270	− 820	− 690
5-Nitro-4-hydroxy-3-methoxy-	170	− 550	− 650
2 : 6-Dihydroxy-4-methyl-	4100	−3790	−3010
2 : 3 : 4 : 5-Tetramethyl-	6·0	+ 70	+ 120
2 : 3 : 4 : 6-Tetramethyl-	10	− 230	− 360
2 : 3 : 5 : 6-Tetramethyl-	30	− 890	− 520
2 : 3-Dinitro-5 : 6-dimethoxy-	4400	−3830	−3950
2 : 3-Dinitro-4-hydroxy-5 : 6-dimethyl-	4600	−3860	−3440

TABLE III.

Substituted benzoic acid.	$\Delta(-RT \ln K)$, cals./mole : Observed.	New predicted.	Old predicted.
2 : 4 : 6-Trihydroxy-	−3400	−3420	−2780
2 : 4 : 6-Trimethyl-	−1010	−1040	− 470
2 : 6-Dihydroxy-4-methyl-	−3790	−3650	−3010
2 : 3 : 5 : 6-Tetramethyl-	− 890	−1100 *	− 520

* From 2 : 6- and 3 : 5-dimethylbenzoic acids.

The great improvement in the predictions seems to show that for 2 : 6-dimethyl- and 2 : 6-dihydroxy-compounds at least, the effect is real and takes the form of an enhancement of the influence of the groups. This " di-*ortho* " effect for 2 : 6-dinitro- and 2-hydroxy-6-methyl compounds would be of the nature of a " saturation effect ".

It is interesting to note that Stubbs and Hinshelwood (*loc. cit.*) found no violation of the additivity principle for free energy of activation in the benzoylation of 2 : 6-dimethylaniline.

If one of a given pair of substituents be placed in the *ortho*-position and the other in either of the two *meta*-positions, the two compounds should, according to the additivity principle, have the same value of $\Delta(-RT \ln K)$. For certain pairs, *e.g.*, 2 : 3- and 2 : 5-dihydroxybenzoic acids, and 2-hydroxy-3-methyl- and 2-hydroxy-5-methyl-benzoic acids, this holds. In others, however, *e.g.*, 2 : 3- and 2 : 5-dinitro-, and also 3-chloro-2-nitro- and 3-chloro-6-nitro-benzoic acids, the " 2 : 3 " compound shows a serious discrepancy.

It may be concluded, therefore, that while the additivity principle holds for free energies of ionisation of a number of polysubstituted benzoic acids, marked discrepancies occur with certain 2 : 6- and 2 : 3-compounds.

[*Added in proof.*] Since this paper was written, it has come to our notice that Wegsheider (*Monatsh.*, 1902, **23**, 288) examined the effect of substituents on strength for a number of aromatic acids (mainly monoesters of phthalic acids) in terms of "factors," a procedure which is analogous to that employed above. He found the effect of groups to be very approximately additive, except for certain 2 : 6- and 2 : 3-compounds.

PHYSICAL CHEMISTRY LABORATORY, OXFORD UNIVERSITY. [*Received, November* 11*th*, 1948.]