S 13. *The Benzoylation of Substituted Anilines. An Investigation into the Additive Effects of Substituents.*
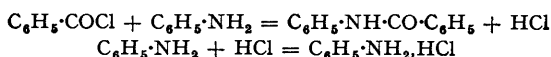
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It has been shown, for the benzoylation of twenty-one disubstituted anilines, that the resultant effect on the activation energy of two substituents in the same benzene nucleus is very closely the sum of their individual effects. The entropy of activation remains very nearly constant for *o*- as well as *m*- and *p*-substituted derivatives. Reactivity of mono-derivatives is quantitatively correlated both with polarity, and with the dissociation constant of the amine.

THE study of organic reactions has shown that a substituent in the benzene nucleus affects the reactivity by altering the availability of electrons at the point of reaction. Most of the kinetic studies on aromatic compounds have been concerned with the influence of a single substituent in the nucleus, and little systematic work seems to have been carried out on the resultant effect of two or more substituents. The question whether this resultant effect is

less than, equal to, or greater than the sum of the individual effects is of considerable interest, and the present paper deals primarily with this problem. The results of Bradfield and Jones indicate that in the chlorination of phenolic ethers, $R \cdot O \cdot C_6H_4X$, the effects of R and X are additive (see Watson, "Modern Theories of Organic Chemistry," Oxford, 1941, p. 78) so that the existence of a more general additive effect is not improbable.

The reaction chosen for the investigation was the benzoylation of aniline in benzene solution, which had been studied previously by Williams and Hinshelwood (*J.*, 1934, 1079). The reaction is simple and complete, taking place quantitatively according to the equations

$$C_6H_5 \cdot COCl + C_6H_5 \cdot NH_2 = C_6H_5 \cdot NH \cdot CO \cdot C_6H_5 + HCl$$
$$C_6H_5 \cdot NH_2 + HCl = C_6H_5 \cdot NH_2, HCl$$

no by-products being formed. Reaction occurs at one point only in the molecule, the carbon of the –COCl uniting with the nitrogen of the –NH_2 group and HCl being eliminated.

The previous work was a general kinetic study of the reaction, and included measurement of the effect of *m*- and *p*-substituents both in the aniline and in the benzoyl chloride. Within the limits of error for activation energy determination, changes in reaction velocity caused by the various substituents were found to be wholly accounted for by changes in the activation energy, the entropy of activation remaining very nearly constant.

The present investigation was confined to a study of the effect of substituents in the amine itself. The effect of various individual groups in positions *o*-, *m*-, and *p*- with respect to the –NH_2 group was first determined, and with this knowledge the resultant effect of different combinations of two substituents in the same nucleus could be compared with the sum of the individual effects. Twenty-one di-substituted anilines were investigated, including all six isomeric xylidines.

EXPERIMENTAL.

The hydrogen chloride formed as a product of the reaction combines with excess of aniline to give a precipitate of aniline hydrochloride. This was filtered off and dissolved in water, the chloride being then estimated by Volhard's method. The experimental details have already been described (Grant and Hinshelwood, *J.*, 1933, 1351; Williams and Hinshelwood, *loc. cit.*).

The reaction was again shown to be strictly quantitative. All reagents were mixed at the temperature of the experiment, and all concentrations corrected for the thermal expansion of the solvent. All apparatus was calibrated.

The concentrations of reagents used in all experiments were : benzoyl chloride, M/200; aniline, M/100.

Where there was no reason to expect any possible abnormality in the activation energy–entropy relation, the rate measurements were made at 25·0° only. Various direct activation energy determinations were, however, made over the range 15—60°. (The thermostats could be regulated to $\pm 0.02°$.)

Benzoyl chloride, aniline, and the various aniline derivatives were purified to constant m. p. or b. p. by recrystallisation or fractionation. "AnalaR" Benzene was used as solvent in all reactions.

The velocity constants determined covered a 50,000-fold range. The experimental method proved to be satisfactorily precise, and the results with all derivatives were readily reproducible.

The course of the reaction is expressed by the usual bimolecular formula, as shown by the typical results in Table I, where t is the time in minutes, x the % change, and k the velocity constant (g.-mols./l./sec.); a is the initial concentration of the acid chloride, and b that of the amine in g.-mols./l. $a = b/2 = 0.005$.

Hence
$$k = \frac{1}{2 \times 60t}\left\{\frac{1}{100 - x} - \frac{1}{100}\right\} \times \frac{100}{a}.$$

The summarised results are given in Tables II—V; those for *o*-, *m*-, and *p*-nitroaniline have been taken from the work of Hinshelwood, Newling, and Staveley (*Trans. Faraday Soc.*, 1934, **30**, 597).

TABLE I.

Velocity constants at 25·0°.

2 : 4-Dimethylaniline.			*p*-Chloroaniline.			5-Chloro-2-methylaniline.		
x.	t.	$k \times 10^2$.	x.	t.	$k \times 10^2$.	x.	t.	$k \times 10^2$.
40	9·7	11·54	20	27·0	1·56	20	290	0·145
50	14·3	11·79	30	46·4	1·55	30	488	0·148
60	22·5	11·20	40	70·7	1·58	40	740	0·152
70	35·5	11·04	50	108·0	1·56	50	1160	0·151
	Mean 11·4		60	162·0	1·56	60	1640	0·154
			70	244·0	1·61		Mean 0·150	
				Mean 1·57				

TABLE II.

Compound.	$(k_{25} \times 10^2)$.	Activation energy (E).*	Compound.	$(k_{25} \times 10^2)$.	Activation energy (E).*
Aniline	7·48	7600	o-Chloroaniline	0·0486	10,100
o-Toluidine	2·81	8300	o-Nitroaniline	0·00030	13,800
2 : 6-Dimethylaniline	0·908	9000			

* From temperature coefficient.

TABLE III.

Compound.	$(k_{25} \times 10^2)$.	$\log_{10}$ $(k_{25} \times 10^2)$.	E'.*	Compound.	$(k_{25} \times 10^2)$.	$\log_{10}$ $(k_{25} \times 10^2)$.	E'.*
Aniline	7·48	0·8739	7,600	m-Bromoaniline	0·396	$\bar{1}$·5977	9,340
o-Toluidine	2·81	0·4487	8,180	o-Anisidine	9·07	0·9576	7,490
m-Toluidine	13·8	1·1399	7,240	o-Nitroaniline	0·00030	$\bar{4}$·4771	13,600
p-Toluidine	31·6	1·4997	6,750	m-Nitroaniline	0·0444	$\bar{2}$·6474	10,640
o-Chloroaniline	0·0486	$\bar{2}$·6866	10,580	p-Nitroaniline	0·00421	$\bar{3}$·6243	12,030
m-Chloroaniline	0·436	$\bar{1}$·6395	9,270				
p-Chloroaniline	1·57	0·1955	8,530				

* Calculated from log k_{25} with non-exponential factor equal to that for aniline.

TABLE IV.

Substituent group.	$\Delta E'$.	Substituent group.	$\Delta E'$.
H	0	m-Br	+1740
o-CH$_3$	+ 580	o-OCH$_3$	− 110
m-CH$_3$	− 360	o-NO$_2$	+6000
p-CH$_3$	− 850	m-NO$_2$	+3040
o-Cl	+2980	p-NO$_2$	+4430
m-Cl	+1670		
p-Cl	+ 930		

TABLE V.

| Compound.	$k_{25} \times 10^2$.	E'.	Predicted E'.	$\Delta E'$.	Predicted $\Delta E'$.
Aniline	7·48	7,600	7,600	0	0
2 : 3-Dimethylaniline	5·31	7,800	7,820	+ 200	+ 220
2 : 4-Dimethylaniline	11·4	7,350	7,330	− 250	− 270
2 : 5-Dimethylaniline	3·76	8,010	7,820	+ 410	+ 220
2 : 6-Dimethylaniline	0·908	8,850	8,760	+1250	+1160
3 : 4-Dimethylaniline	54·0	6,430	6,390	−1170	−1210
3 : 5-Dimethylaniline	23·4	6,920	6,880	− 680	− 720
2 : 4-Dichloroaniline	0·00960	11,540	11,510	+3940	+3910
2 : 5-Dichloroaniline	0·00202	12,470	12,250	+4870	+4650
3 : 5-Dibromoaniline	0·0289	10,890	11,080	+3290	+3480
3-Chloro-2-methylaniline	0·206	9,730	9,850	+2130	+2250
4-Chloro-2-methylaniline	0·692	9,010	9,110	+1410	+1510
5-Chloro-2-methylaniline	0·150	9,920	9,850	+2320	+2250
3-Chloro-4-methylaniline	2·09	8,360	8,420	+ 760	+ 820
4-Nitro-2-methylaniline	0·00149	12,650	12,610	+5050	+5010
5-Nitro-2-methylaniline	0·0159	11,250	11,220	+3650	+3620
2-Nitro-4-methylaniline	0·00112	12,810	12,750	+5210	+5150
4-Chloro-3-nitroaniline	0·00902	11,580	11,570	+3980	+3970
5-Chloro-2-methoxyaniline	0·472	9,260	9,160	+1660	+1560
5-Bromo-2-methoxyaniline	0·431	9,290	9,230	+1690	+1630
4-Nitro-2-methoxyaniline	0·00425	12,030	11,920	+4430	+4320
5-Nitro-2-methoxyaniline	0·0351	10,770	10,530	+3170	+2930
α-Naphthylamine	1·04	8,770	—	—	—
β-Naphthylamine	5·12	7,830	—	—	—

DISCUSSION.

(1) *Constancy of the Entropy of Activation.*—For *p*-substituents, the entropy of activation (non-exponential term) has already been shown to be constant within the limit of experimental error. In view of the behaviour of *o*-substituted compounds in general, it was thought desirable to make direct measurements of the activation energies for the benzoylation of some of

the *o*-substituted anilines. The results are given in Table II, and in Figure 1. The experimental values of E are plotted against $\log_{10} (k_{25} \times 10^2)$. The line of slope $-2 \cdot 303RT$ is drawn through the point representing the benzoylation of unsubstituted aniline. All four points lie close to the theoretical line, showing that even for *o*-substituted compounds the entropy of activation is very nearly constant. (In this consideration we are neglecting changes in the collision frequency Z, which in fact varies slightly from one reaction to another according to the expression $Z = \text{constant} \sqrt{\dfrac{1}{M_A} + \dfrac{1}{M_B}}$, where M_A and M_B are the molecular weights of the reacting molecules. Benzoyl chloride was one reagent throughout, so that M_A is constant. M_B varies slightly, but calculation shows the difference between the highest and lowest values of Z is so very small that the variations may be disregarded.)

We therefore take the entropy of activation to be constant throughout, within the limits of error involved in direct determinations of E.

FIG. 1.
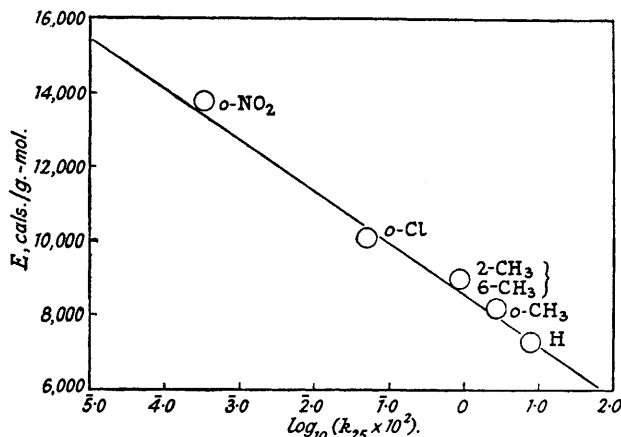
Plot of experimental E *against* $log_{10}(\text{k}_{25} \times 10^2)$ *for* o-*compounds.*

(2) *Additive Effects of Substituents.*—The velocity constants for the whole series of mono- and di-substituted derivatives are given in Tables III and V. The resultant effect of two substituents in the same nucleus can now be compared with the sum of the individual effects.

Since changes in log *k* itself can be determined more accurately than changes in experimentally measured values of E, we work in the first instance with the former. Results expressed in terms of log *k* being, however, less convenient for discussion than those translated into energies, we express them as changes in the free energy of activation, $(-RT \ln k)$. If the entropy of activation is in fact constant, then changes in the free energy of activation are changes in the activation energy itself. With the observed value of E for the benzoylation of aniline as a reference point all values of $\log_{10} k_{25}$ can now be translated into values of an activation energy, E'. (Changes in E' are only changes in the true activation energy in so far as the non-exponential factor is in fact constant, but are always changes in the free energy of activation.)

The experimental error in determining velocity constants in this work was about $\pm 2 \cdot 5\%$ which corresponds in terms of activation energy changes to about ± 25 cals. The values of E' are therefore given to the nearest 10 cals., but only limited significance is to be attached to the last figure before the zero. The error involved in the direct determination from temperature coefficient measurements of changes in E is greater, being about ± 100 cals. Thus variations in the free energy of activation (or E') will be known more accurately than those in E itself.

Table III contains the values of E', calculated from log *k* for the mono-substituted derivatives of aniline. These values may be compared with those found from temperature coefficients for E (in Table II) and show quite good agreement.

From the results given in Table III, the *change* in E' ($\Delta E'$) caused by the various substituents can be determined and these are given in Table IV.

The resultant effect of two substituents in the same nucleus proves to be simply the sum of their individual effects. From the results given in Table IV, the values of the activation energy for all the di-substituted aniline derivatives can be predicted, as in the following examples :

$$2 : 3\text{-Dimethylaniline} \quad 7,600 + 580 - 360 = 7,820$$
$$3\text{-Chloro-4-methylaniline } 7,600 - 850 + 1,670 = 8,420$$

Table V gives for the twenty-one di-substituted anilines investigated the values of E' obtained from log k and those predicted on the assumption of a strictly additive effect. There is in fact good agreement in all cases, such discrepancies as occur being probably insignificant. The values of E' from log k, are correct to about ± 25 cals. but the additively computed values since they depend upon two determinations are only correct to ± 50 cals. The possible divergences of the two sets are therefore about 75 cals. The last two columns of Table V record the observed and predicted *changes* in E' caused by the introduction of the substituents into aniline. The agreement between the two sets of values is shown more clearly in this way. Practically none of the divergences significantly exceeds that estimated as the experimental error.

In the benzoylation of twenty-one di-substituted anilines, therefore, the resultant effect of two substituents is very closely the sum of their individual effects.

This result applies primarily and directly to what are essentially changes in the free energy of activation. The evidence that the entropy of activation remains constant was already available for various *m*- and *p*-substituted anilines, and has now been provided for some of the *o*-compounds. Thus the additivity applies to the activation energies themselves.

A comment on this last statement should be made. The degree of accuracy with which the changes in the free energy of activation ($\Delta E'$) have been shown to be additive exceeds that with which they can be shown experimentally to equal the changes in the activation energy itself. The question arises, therefore, whether the additivity does in fact apply less closely to the latter than to the former. Coherence arguments suggest that this is improbable. Changes in E are sometimes correlated with changes in the entropy term, and when such a correlation occurs it is systematic. Now in the present examples there is no systematic correlation of E and the non-exponential term over wide ranges of the former. It is very unlikely, therefore, that small irregular changes would be so compensated as to lead to a more precise additivity among free energies of activation than among the E values themselves. The precise additivity of the free energy values combined with the less precisely verifiable but still quite definite constancy of the entropy term, thus makes it probable that the additivity shown by the change in free energy of activation ($\Delta E'$) does in fact merely reflect a corresponding additivity in the values of ΔE.

(3) *Halogen Substituents.*—The results of Table IV show that a *p*-methyl group has a greater effect than a *m*-methyl group, and also that a *p*-nitro-group has a greater effect than a *m*-nitro-group. In the chloroanilines, however, the *p*-chlorine atom has a smaller effect than the *m*-chlorine atom (cf. the slightly anomalous position of the *p*-Cl in Fig. 2).

This fact appears to be intimately connected with the anomaly encountered in aromatic substitution reactions, that a halogen atom, although it deactivates the nucleus, is *o*–*p*-directing. This is commonly attributed to the fact that whereas in the normal state a halogen substituent attracts electrons, thereby deactivating the nucleus at all points ($-I$), the approach of a reagent causes an electromeric effect ($+T$). These two effects are in opposition, but since the latter produces activation at the *o*- and *p*-positions, substitution occurs there in spite of the general deactivation. In the present example the $-I$ effect increases the activation energy. The $+T$ effect tends to neutralise the increase if the halogen is in the *p*-position to the amino-group, but not if it is in the *m*-position.

It is interesting to note, moreover, that in spite of the existence of the anomaly referred to, the E–log k relations for the halogens fit in perfectly well with those for other substituents. The abnormal behaviour of the halogens might have been expected to reveal itself in an abnormal entropy of activation. No such discrepancy is found. Although the approach of the reagent sets up an induced electromeric moment, this is reflected simply in a changed activation energy, the non-exponential factor remaining unchanged.

It is also interesting to note that the effect of bromine is almost identical with that of chlorine.

(4) *Relation between* E *and Polarity.*—Figure 2 is a plot of E' (calculated from log k) against the polarity of the substituent group (as measured by the dipole moment of the compound
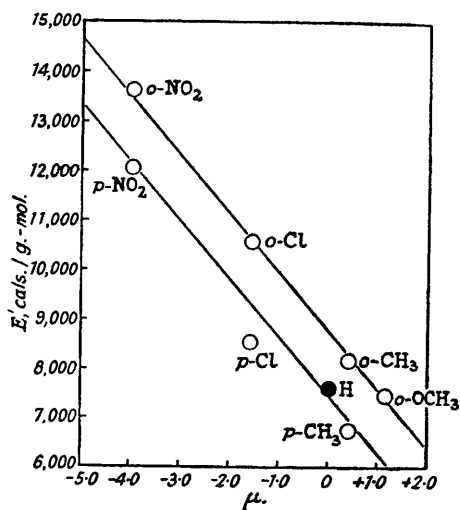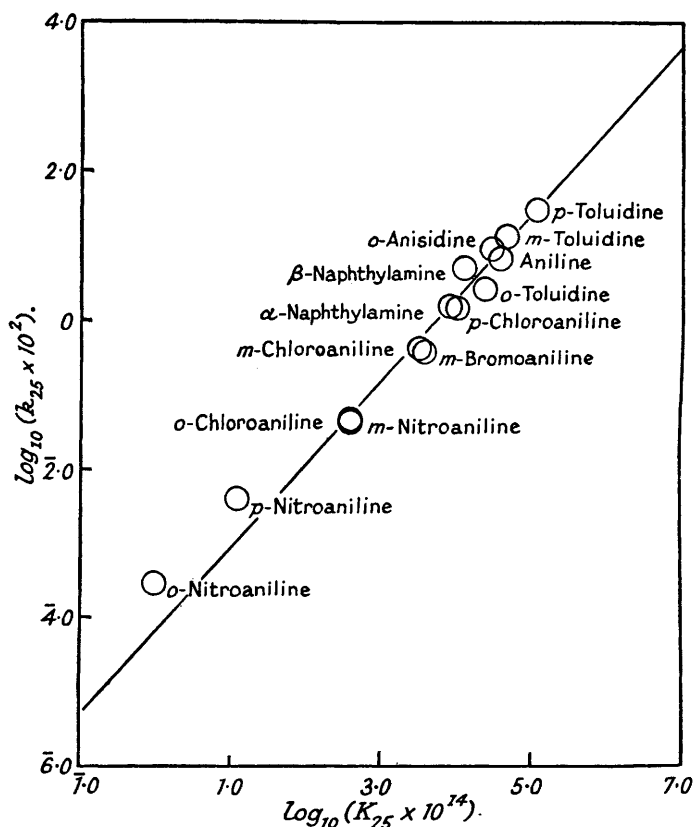
Fig. 2.

Plot of E' against polarity.

Fig. 3.

Plot of $\log_{10}(k_{25} \times 10^2)$ against the logarithm of the dissociation constant.

C_6H_5X) for some *p*-compounds and for the four *o*-compounds studied. The points lie approximately on straight lines, showing that there is a general relationship between the reactivity of the nucleus and the polarity of the substituent.

(5) *Relation between Velocity Constant and Dissociation Constant.*—Figure 3 is a plot of log *k* for the benzoylation of various substituted anilines and two naphthylamines against the logarithm of their dissociation constants. There is a definite linear relationship. This is readily explained, since both the basic strength of the aniline and its rate of benzoylation depend upon the availability of the unshared pair of electrons on the nitrogen atom. This result again reflects the correlation between reactivity and polarity.

(6) *The " Ortho-effect ".*—Victor Meyer attributed the " ortho-effect " to geometrical steric hindrance. If this were correct the magnitude of the effect would be dependent upon the size of the substituent. No such simple relationship has ever been found. Moreover, a purely geometrical effect might well tend to cause a low velocity by reducing the non-exponential term rather than by increasing *E*.

In the benzoylation of anilines the non-exponential term remains constant, even for *o*-substituted derivatives. This fact is in contrast with what some investigators have found in other reactions (Evans, Watson, and Williams, *J.*, 1939, 1348; Evans, Gordon, and Watson, *J.*, 1937, 1430).

If the " ortho-effect " is due to some interaction between adjacent groups in the aromatic nucleus (such as the formation of hydrogen bonds), anomalies might be expected in the results for those di-substituted derivatives where the two substituents are in adjacent positions. Compounds of this type are 2 : 3-dimethylaniline, 3 : 4-dimethylaniline, 3-chloro-2-methylaniline, 3-chloro-4-methylaniline, and 4-chloro-3-nitroaniline. With all these compounds, however, the results throughout the present work are perfectly normal. The substituent in the position *o*- to the amino-group appears somehow to interact with the unshared pair of electrons on the nitrogen atom in such a way that the latter are subjected to an extra constraint. This constraint leads to a change in the energy of activation only, and not to a change of entropy. Fig. 2 shows that there is an increased energy of activation for all *o*-compounds of roughly 1500 cals.

(7) *Naphthylamines.*—It was thought worth while to compare the reactivity of α- and β-naphthylamine respectively with 2 : 3-dimethyl- and 3 : 4-dimethyl-aniline. From Table V it is obvious that there is no similarity between the respective values. In fact, both α- and β-naphthylamine are less reactive than aniline. General experience shows that β-naphthylamine is more reactive than α-naphthylamine and this is found to be so here.