# Dissociation Constants of Mono- and Poly-substituted Benzoylacetanilides

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The dissociation constants of benzoylacetanilides of general formula $XC_6H_4\cdot CO\cdot CHZ\cdot CO\cdot NH\cdot C_6H_4Y$ have been evaluated at 25° in aqueous solution containing <1% of organic solvent. The acidity constants of monosubstituted compounds ($Y \neq H, X = Z = H$) are in agreement with the classical Hammett equation, with $\rho_Y = 0{\cdot}79$. For the polysubstituted compounds ($Y \neq H$, $X \neq H$, $Z = H$) the equation $\log (K_{XY}/K_0) = \rho_X\rho_Y(\sigma_X/\sigma_Y + \sigma_Y/\rho_X)$ was found to hold with $\rho_X = 2{\cdot}5$. The substituent constants for o-Cl, o-Br, o-OMe, $o\text{-}NEt_2$, $p\text{-}NEt_2$, $p\text{-}SO_2C_6H_4Me$, $p\text{-}SO_2C_6H_4NO_2$, and $p\text{-}OSO_2Ph$ have been determined. The effect of the presence of a halogen atom in position Z is also discussed.

DYE formation by reaction of benzoylacetanilides with *p*-benzoquinone di-imines,[1] *p*-nitrosoanilines,[2] and *p*-benzoquinone monoimines,[3] has been investigated owing to the use of these compounds in colour photographic processes.

In order to elucidate the effect of substituents on the kinetics of this reaction, it seemed to be advisable to prepare some substituted benzoylacetanilides of general formula $XC_6H_4\cdot CO\cdot CHZ\cdot CO\cdot NH\cdot C_6H_4Y$. The present paper reports the preparation of these compounds and the correlation of their dissociation constants with the Hammett equation.

TABLE 1

Structures, m.p.s, and analytical data of the benzoylacetanilides $XC_6H_4\cdot CO\cdot CHZ\cdot CO\cdot NH\cdot C_6H_4Y$ (1)—(25)

| | | | | | | N (%) | | Other elements (%) * | |
|---|---|---|---|---|---|---|---|---|---|
| Compound | Y | X | Z | M.p. (°C) | M.p. (°C) (lit.) | Found | Calc. | Found | Calc. |
| (1) | H | H | H | 105—106 | 106—108 [a] | 5·8 | 5·85 | | |
| (2) | o-Cl | H | H | 139—140 | 135—137 [a] | 5·2 | 5·1 | 12·9 [c] | 12·95 |
| (3) | o-Br | H | H | 127—128 | 123—125 [a] | 4·35 | 4·4 | 24·3 [d] | 25·1 |
| (4) | $m\text{-}CO_2Me$ | H | H | 128—130 | | 4·7 | 4·7 | | |
| (5) | $m\text{-}NO_2$ | H | H | 134—135 | 136—138 [a] | 10·05 | 9·85 | | |
| (6) | m-COMe | H | H | 126—127 | 121—123 [a] | 4·9 | 5·0 | | |
| (7) | m-CN | H | H | 161—162 | 158—159 [a] | 10·65 | 10·6 | | |
| (8) | p-COMe | H | H | 167—168 | 163—165 [a] | 5·15 | 5·0 | | |
| (9) | $p\text{-}NEt_2$ | H | H | 147—148 | | 9·15 | 9·05 | | |
| (10) | p-OH | H | H | 160—161 | | 5·4 | 5·5 | | |
| (11) | $p\text{-}CO_2H$ | H | H | 230—232 | | 4·85 | 4·95 | | |
| (12) | $p\text{-}SO_2NH_2$ | H | H | 190—191 | | 8·85 | 8·8 | 10·15 [e] | 10·05 |
| (13) | $p\text{-}SO_2C_6H_4Me$ | H | H | 222—224 | | 3·3 | 3·55 | 8·25 [e] | 8·15 |
| (14) | $p\text{-}SO_2C_6H_4NO_2$ | H | H | 178—180 | | 6·7 | 6·6 | 7·45 [e] | 7·55 |
| (15) | $p\text{-}OSO_2Ph$ | H | H | 153—154 | | 3·5 | 3·55 | 8·2 [e] | 8·1 |
| (16) | H | $2,4,6\text{-}Me_3$ | H | 94—96 | 97 [a] | 5·05 | 5·0 | | |
| (17) | H | H | Cl | 116—118 | | 5·05 | 5·1 | 12·9 [c] | 12·95 |
| (18) | o-Cl | o-Cl | H | 99—101 | | 4·6 | 4·55 | 23·0 [c] | 23·0 |
| (19) | o-Cl | o-Cl | Cl | 121—123 | | 4·15 | 4·1 | 31·1 [c] | 31·05 |
| (20) | o-OMe | o-Cl | H | 80—82 | | 4·5 | 4·6 | 11·75 [c] | 11·65 |
| (21) | o-OMe | o-Cl | Cl | 132—134 | | 4·05 | 4·15 | 20·95 [c] | 20·95 |
| (22) | $m\text{-}NO_2$ | p-OMe | H | 177—178 | 172—173 [b] | 9·0 | 8·9 | | |
| (23) | m-CN | p-OMe | H | 144—145 | | 9·65 | 9·5 | | |
| (24) | p-OMe | p-OMe | H | 162—163 | | 4·55 | 4·7 | | |
| (25) | $o\text{-}NEt_2$ | p-OMe | H | 98—99 | | 8·25 | 8·25 | | |

* For some compounds C and H were determined: C was within ±0·3 and H ±0·1% of the calculated value.

[a] See ref. 1. [b] See ref. 4. [c] Cl. [d] Br. [e] S.

Van Brandt *et al.*[4] investigated some mono- and poly-substituted benzoylacetanilides in ethanol–aqueous buffer (3 : 2). Our work was performed in water containing no more than 1% organic solvent.

Table 1 lists the compounds investigated, their m.p.s, and the analytical data. The dissociation constants of *N*-cyclohexyl-*p*-methoxybenzoylacetamide (26) and 2-*o*-hydroxybenzoylacetophenone (27) were also evaluated.

$$\text{cyclo-}C_6H_{11}\cdot NH\cdot CO\cdot CH_2\cdot CO\cdot C_6H_4\cdot OMe\text{-}p \qquad (26)$$

$$o\text{-}HO\cdot C_6H_4\cdot CO\cdot CH_2\cdot COPh \qquad (27)$$

## EXPERIMENTAL

*Benzoylacetanilides.*—Compounds (1)—(16), (18), (20), and (22)—(25) were prepared by methods already described.[5]

*Anilines.*—Except for 3-cyanoaniline which was prepared by reduction of the corresponding nitroaniline,[6, 7] the remaining anilines were commercial.

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[1] G. H. Brown, J. Figueras, R. J. Gledhill, C. J. Kibler, F. C. McCrossen, S. M. Parmenter, P. W. Vittum, and A. Weissberger, *J. Amer. Chem. Soc.*, 1957, **79**, 2919; E. Pelizzetti and G. Saini, forthcoming paper.

[2] P. Van Brandt and A. Bruylants, *Bull. Soc. chim. belges*, 1964, **73**, 843.

[3] E. Pelizzetti, C. Verdi, and G. Saini, *J. Chem. Soc.* (*B*), 1972, 1243.

[4] P. Van Brandt, E. De Hoffmann, and A. Bruylants, *Bull. Soc. chim. belges*, 1964, **73**, 782.

[5] C. J. Kibler and A. Weissberger, *Org. Synth.*, 1945, **25**, 7.

[6] F. Beilstein and A. Kuhlberg, *Annalen*, 1868, **146**, 336.

[7] A. W. Hoffmann, *Ber.*, 1868, **1**, 196.

4-*Aminophenyl* 4-*Methylphenyl Sulphone* [*See Compound* (13)].—Sodium *p*-methylsulphinate (1·5 mol) was dissolved in ethane-1,2-diol (125 ml) and mixed with *p*-chloronitrobenzene (1·5 mol) dissolved in ethane-1,2-diol (125 ml). The mixture was kept at 165° for 8 h and then poured into water. The crude product was recrystallized from ethanol, m.p. 173—174°. 4-Nitrophenyl 4-methylphenyl sulphone (114 g) was then converted to the corresponding amine, by reduction with iron (300 g) in refluxing *p*-dioxan (1350 ml) and 50% acetic acid (850 ml) for 60—80 min. The mixture was filtered and poured into water; the product was recrystallized from ethanol, m.p. 183—184°.

4-*Aminophenyl* 4-*Nitrophenyl Sulphone* [*See Compound* (14)].—A mixture of sodium *p*-acetylaminobenzenesulphinate (1 mol) and *p*-chloronitrobenzene (1 mol) was dissolved in dimethyl sulphoxide (350 ml) and heated at 140° for 20 h. The mixture was poured into water and ice and the crude product was filtered and recrystallized from a mixture of ethanol and dimethylformamide (5 : 1 v/v), m.p. 227—230°. A solution of the product (100 g) ethanol–*p*-dioxan (270 ml) (3 : 1 v/v) was treated with concentrated HCl (15 ml) and kept at reflux for 4 h; after a further addition of concentrated HCl (8 ml) and another 4 h of heating under reflux, the solution was neutralized with a slight excess of sodium carbonate before the mixture was poured into water and ice. The crude product was filtered and recrystallized from ethanol, m.p. 169—171°.

p-*Aminophenylbenzenesulphonate* [*See Compound* (15)].—This compound was prepared by a published procedure.[8]

NN-*Diethyl*-o-*phenylenediamine* [*See Compound* (25)].—*NN*-Diethyl-*o*-nitroaniline (0·7 mol) (technical grade) dissolved in *p*-dioxan–water (1·2 l) (5 : 1 v/v) was reduced with iron (400 g) and 60% acetic acid (900 ml), during 5 h heating under reflux. The solvent was then evaporated under reduced pressure and the residue was dissolved in diethyl ether, which was shaken with an aqueous solution of sodium carbonate. The ether was evaporated and the amine was distilled, b.p. 173—175° at 18 mmHg.

*Substituted Ethyl Benzoylacetates*.—The products were obtained by mixing the corresponding benzoyl chloride and ethyl acetoacetate in the presence of sodium ethoxide.[9]

The acid chlorides were commercial, with the exception of 2,4,6-trimethylbenzoyl chloride [see compound (16)] which was prepared from 2,4,6-trimethylbenzoic acid and thionyl chloride.[10]

*Syntheses of Compounds* (17), (19), and (21).—These products were prepared from compounds (1), (18), and (20) respectively; the corresponding benzoylacetanilide (0·1 mol) was dissolved in anhydrous chloroform (300 ml) and mixed with an equimolar amount of $SO_2Cl_2$, at 18—20°. After stirring for 3 h, the chloroform was evaporated and the crude product was recrystallized from ethanol.

*Synthesis of Compound* (26).—Compound (26) was prepared from ethyl *p*-methoxybenzoylacetate and cyclohexylamine according to the procedure used for compound (1), m.p. 141—143° (Found: C, 69·6; H, 7·75; N, 5·0. Calc. for $C_{16}H_{21}NO_3$: C, 69·8; H, 7·7; N, 5·1%).

*Synthesis of Compound* (27).—Compound (27) was prepared by stirring a heated solution of *o*-benzoyloxyacetophenone (1 mol) in pyridine (900 ml), with KOH (1·5 mol) at 50° for 15 min; during this time a precipitate of the yellow potassium salt of compound (27) was formed. The mixture was cooled and acidified with 10% acetic acid (750 ml). The insoluble diketone was filtered and recrystallized from ethanol, m.p. 119—120° (lit.,[11] 117—120°) (Found: C, 74·9; H, 5·15. Calc. for $C_{15}H_{12}O_3$: C, 74·8; H, 5·05%).

*Spectrophotometric Evaluation of Dissociation Constants*.—The acid dissociation constants of benzoylacetanilides were evaluated spectrophotometrically using either a Hitachi EPS3T or an Optica CF 4 spectrophotometer at 25 ± 1°.

A solution of the benzoylacetanilide in methanol or in ethane-1,2-diol was diluted with an aqueous buffer so that the final solution had a concentration in the range 1·0—4·0 × $10^{-5}$M, and did not contain more than 1% organic solvent.

The benzoylacetanilide was dissolved in a buffered acid solution to ensure that all the solute was in the undissociated form and in a solution of 0·1M-NaOH in order to give complete dissociation of the solute. Other solutions were made in buffers whose pH were near to the p$K_a$ of the compound. By measuring the absorbance of the above solutions (with the same total concentration of the solute) at the wavelength of maximum absorbance of the dissociated form, and taking into account that at this λ the molar absorptivity of the undissociated form was in general small or negligible, the p$K_a$ was calculated by use of equation (1)

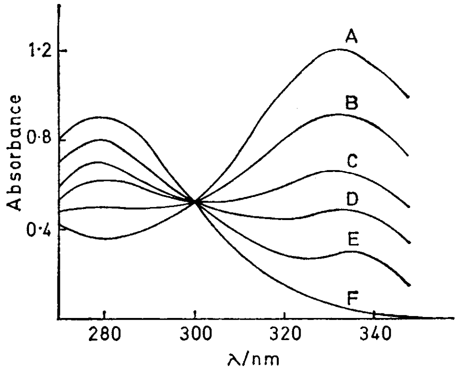

FIGURE 1 Absorption spectra of compound (22) at different pH values. [(22)] 4·0 × $10^{-5}$M; 25°. pH: A, *ca.* 12; B, 10·0; C, 9·6; D, 9·3; E, 9·0; F, *ca.* 6

$$\mathrm{p}K_a = \mathrm{pH} - \log \frac{(D_{[\mathrm{H}^+]} - D_{\mathrm{A}})}{(D_{\mathrm{B}} - D_{[\mathrm{H}^+]})} \qquad (1)$$

where $D_{[H^+]}$ is the absorbance of the buffered solution at pH ≈ p$K_a$ and $D_A$ and $D_B$ are the absorbances of the solutions containing the solute in the undissociated and dissociated form, respectively.

Figure 1 shows the collected spectra of compound (22) at different pH values. In the range 8—11, borax buffers were used,[12] while for pH >11 or <8, phosphate buffers were adopted.[12]

The p$K_a$, $\lambda_{max.}$, and log ε values of the dissociated forms of the benzoylacetanilides are listed in Table 2.

## DISCUSSION

The benzoylacetanilides can exist in solution in more than one tautomeric form. In aqueous solution they

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[8] C. D. Nenitzescu and A. Balaban, *Chem. Ber.*, 1958, **91**, 2109.

[9] C. Bulow and H. Hailer, *Ber.*, 1902, **35**, 915.

[10] A. I. Vogel, 'Chimica Organica Pratica,' C.E.A., Milano, 1967.

[11] T. S. Wheeler, *Org. Synth.*, 1952, **32**, 72.

[12] L. Meites, 'Handbook of Analytical Chemistry,' McGraw-Hill, London, 1963, section 11-7.

do not show absorption in the enol range (3500—3700 cm$^{-1}$)[13] and the keto-form seems to be predominant. Besides it seems that this tautomeric equilibrium does not interfere with the acid–base equilibrium investigated.[4]

TABLE 2

Dissociation constants and spectrophotometric data of compounds (1)—(27)

| Compound | $\lambda_{max.}$/nm | log $\varepsilon_{max.}$ | p$K_a$ |
|---|---|---|---|
| (1) | 327 | 4·35 | 9·4 |
| (2) | 332 | 4·35 | 8·9 |
| (3) | 332 | 4·36 | 8·7 |
| (4) | 328 | 4·38 | 9·2 |
| (5) | 329 | 4·37 | 8·9 |
| (6) | 328 | 4·38 | 9·2 |
| (7) | 330 | 4·41 | 8·9 |
| (8) | 354 | 4·58 | 9·1 |
| (9) | 332 | 4·35 | 9·8 |
| (10) | 327 | 4·26 | 10·2 |
| (11) | 338 | 4·39 | 9·4 |
| (12) | 335 | 4·36 | 8·8 |
| (13) | 347 | 4·60 | 8·9 |
| (14) | 355 | 4·53 | 8·8 |
| (15) | 332 | 4·36 | 9·2 |
| (16) | 303 | 4·36 | 8·3 |
| (17) | 317 | 4·34 | 8·1 |
| (18) | 309 | 4·35 | 7·4 |
| (19) | 315 | 4·25 | 5·0 |
| (20) | 314 | 4·29 | 7·8 |
| (21) | 322 | 4·34 | 5·4 |
| (22) | 333 | 4·48 | 9·6 |
| (23) | 334 | 4·53 | 9·8 |
| (24) | 330 | 4·36 | 10·4 |
| (25) | 333 | 4·45 | 10·3 |
| (26) | 312 | 4·32 | 11·2 |
| (27) | 363 | 4·21 | 8·8 |

The p$K_a$ data for benzoylacetanilides substituted in the aniline ring (Y $\neq$ H, X = Z = H) agree with the Hammett equation in the form (2) where $K_0$ is the

$$\log (K_Y/K_0) = \rho\sigma \qquad (2)$$

dissociation constant of unsubstituted benzoylacetanilide (1). In Figure 2 only the compounds with reliable σ values are reported.[14] Using the least-squares method a value of $\rho_Y = 0{\cdot}79$ was found (correlation coefficient $r$ 0·982). The value of $\rho_Y$ can be used to derive σ values for the substituents of compounds (2), (3), (13)—(15), by means of equation (2); these values are collected in Table 3.

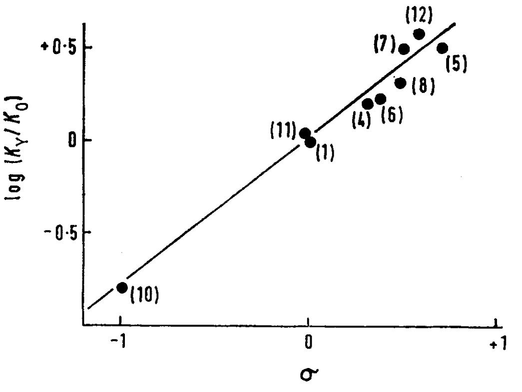

FIGURE 2 log ($K_Y/K_0$) as a function of substituent effect for the monosubstituted (Y $\neq$ H, X = Y = H) benzoylacetanilides

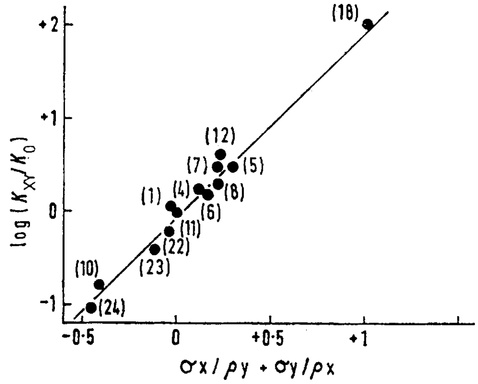

FIGURE 3 Combined effect of substituents on p$K_a$ of benzoylacetanilides. The points are the experimental data and the straight line has a slope $\rho_X\rho_Y = 2{\cdot}00$ (to calculate the abscissa values, $\rho_Y = 0{\cdot}79$ and $\rho_X = 2{\cdot}5$ were adopted)

TABLE 3

Substituent constants

| *ortho*-Substituent | $\sigma_o$ |
|---|---|
| Cl | 0·63 |
| Br | 0·88 |
| OMe | 0·04 |
| $NEt_2$ | −0·28 |
| *para*-Substituent | $\sigma_p$ |
| $NEt_2$ | −0·51 |
| $SO_2C_6H_4Me$ | 0·63 * |
| $SO_2C_6H_4NO_2$ | 0·76 |
| $OSO_2Ph$ | 0·25 |

* A value of 0·71 is reported for *p*-$SO_2Ph$ by C. D. Ritchie and W. F. Sager, *Progr. Phys. Org. Chem.*, 1964, **2**, 323; B. J. Lindberg and B. Schoder, *Acta Chem. Scand.*, 1970, **24**, 3089.

For the polysubstituted benzoylacetanilides a generalized Hammett equation (3) can be used. In Figure 3

$$\log K_{XY}/K_0 = \rho_X\sigma_X + \rho_Y\sigma_Y \qquad (3)$$

log ($K_{XY}/K_0$) is reported as function of ($\sigma_X/\rho_Y + \sigma_Y/\rho_X$) and a good fit was obtained with $\rho_X = 2{\cdot}5$ ($r$ 0·998). In Figure 3 the values of monosubstituted compounds are reported for comparison.

From the p$K_a$ values of compounds (20) and (25), the σ values for *o*-OMe and *o*-$NEt_2$ can be calculated: they are also collected in Table 3. Many values for *ortho*-substituents are given in the literature. Data for *o*-Cl, *o*-Br, *o*-OMe, and *o*-$NR_2$ are surveyed in refs. 15 and 16.

The p$K_a$ value of compound (16) is lower than expected from taking into account only the inductive effect of the three methyl groups. This may be caused by an alteration of the planarity of the molecule (owing

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[13] L. Hevesi, P. Van Brandt, and A. Bruylants, *Bull. Soc. chim. France*, 1970, **11**, 3971.

[14] J. Hine, ' Physical Organic Chemistry,' Holt, New York, 1959.

[15] M. T. Tribble and J. G. Traynham, *J. Amer. Chem. Soc.*, 1969, **91**, 379.

[16] A. C. Farthing and B. Nam, in ' Steric Effects in Conjugated Systems,' ed. G. C. Gray, Butterworths, London, 1958, p. 131.

to the *ortho*-methyl groups) which could modify the methylene acidity.

The benzoylacetanilides with a hydrogen atom of the methylene group substituted by chlorine (Z = Cl) have p$K_a$ lower by *ca.* 1·5—2 units than the corresponding unsubstituted compounds.

Compound (26) has a high p$K_a$ (11·2) owing to the substitution of a phenyl by a cyclohexyl ring, and (27) a lower value (8·8) than the parent compound, probably because the electron-releasing effect of *o*-OH offsets only in part the withdrawing power of the benzoyl group relative to the anilide.

Some p$K_a$ data for these compounds have already been measured by Van Brandt *et al.*[4] for ethanol–water (3 : 2 v/v); they are 0·6 ± 0·2 units lower than ours.

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