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# ACIDITY CONSTANTS OF BENZAMIDE AND SOME *ORTHO*-SUBSTITUTED DERIVATIVES

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**Acidity constants of benzamide and seven *ortho*-substituted derivatives were determined. Except for *o*-nitrobenzamide, all the amides exhibit medium effects. The data were treated by vector analysis. *o*-Aminobenzamide displays two protonation equilibria. The second acidity constant was determined by vector analysis and by the excess acidity function, since the acid strength provided by perchloric acid is insufficient for complete protonation. Different acidity functions and the *ortho* substituent effect on ionization of the amide group are compared.**

## INTRODUCTION

We have previously obtained[1,2] the acidity constants of weak bases from UV–visible measurements: the spectral curves recorded as a function of acidity showed well defined isosbestic points. Measurements of ionization ratios $I = C_{BH^+}/C_B$ from the absorbance readings and derivation of the corresponding acidity constants followed. However, unreliable ionization ratios may arise from direct measurements for bases with spectral curves distorted by medium effects, such as benzamide and some *ortho*-substituted derivatives. Several corrections for medium effects on spectral curves have been proposed.[3] According to factor analysis,[4,5] the absorbance of many carbonyl compounds is expressed as an average absorbance, $\bar{A}$, corrected by two characteristic vectors, $v_1$ and $v_2$:

$$A = \bar{A} + c_1 v_1 + c_2 v_2 \qquad (1)$$

In this work, the weighing factors $c_1$ and $c_2$ were determined for the absorbances of benzamide, *o*-ethoxybenzamide, salicylamide, *o*-chlorobenzamide, *o*-bromobenzamide, *o*-toluamide, *o*-nitrobenzamide, *o*-aminobenzamide and *o*-fluorobenzamide. The sets of spectral curves for these bases, averaged curves and first characteristic vectors were obtained. Using the resulting sets of $c_1$ values, ionization ratios were measured for each perchloric acid concentration, and applied to the calculation of $pK_{BH^+}$ values. Only *o*-nitrobenzamide exhibited no medium effects; its ionization ratios were measured using direct readings of absorbances. Only *o*-aminobenzamide displayed two protonation equilibria; protonation of the amine group, which occurred within the pH range 1·1–5·6, showed no medium effects and its $pK_{BH^+}$ value was obtained as described previously.[2,6,7] The acid strength of perchloric acid is insufficient for completion of the second protonation. Hence, direct calculation of the absorbances and $c_1$ factors is impossible; however, they can be determined by a simple procedure. Acidity constants of equilibria occurring at high acidity levels were calculated by means of Hammett–Deyrup[8], Cox–Yates[9] and Marziano *et al.*[10] equations.

## RESULTS AND DISCUSSION

Medium effects were displayed by all the amides investigated except *o*-nitrobenzamide. *o*-Aminobenzamide undergoes two acid–base equilibria; the first acidity constant stems from absorbance readings at 208 nm[6] (Figure 1). Figure 2 shows the spectral curves corresponding to the second equilibrium. Figure 3 shows the results of vector analysis of the same spectral curves. Table 1 gives ionization ratios for *o*-nitrobenzamide, together with the $c_1$ factors at different acidities for the other amides, from which ionization ratios were measured. Acidity constants were calculated from the following equations:

Hammett–Deyrup:[8]

$$\log I = -mH_A + pK_{BH^+} \qquad (2)$$

Corrected Hammett–Deyrup:[1]

$$\log I = -mH_A + mpK_{BH^+} \qquad (3)$$

Cox–Yates:[9,10]

$$\log I - \log C_{H^+} = m^*X + pK_{BH^+} \qquad (4)$$

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Marziano and co-workers:[11,12]

$$\log I - \log C_{H^+} = -n_B M_c + pK_{BH^+} \quad (5)$$

where $C_{H^+}$ is the molar concentration of solvated protons, $X$ is the excess acidity function, $m$, $m^*$ and $n_B$ are the slope parameters and $K_{BH^+}$ is the dissociation constant of the conjugated acid of base B. The acidity function $H_A$ was used as defined for amides and calculated by Attiga and Rochester[13] and Yates *et al.*[14] The $pK_2$ value for *o*-aminobenzamide was also estimated with unsatisfactory results using the acidity function $H^+$ defined by Lowell *et al.*[15] for cationic amides. The acidity constants calculated by means of equation (3) using $H_A$ are in close agreement with those calculated by means of equations (4) and (5), regardless of which acidity function is used (Table 2).

According to Levi *et al.*'s assumption of solvation,[16] $m = 1$ for bases with the same solvation requirements as Hammett's protonated indicators: $m > 1$ if solvation of the first indicator is higher, and $m < 1$ in the opposite case. Table 2 reveals that $m < 1$ using $H_A$ only for benzamide, indicating that benzamide is more solvated than the *ortho*-substituted derivatives; values of $m < 1$ have also been reported for amides other than *ortho*-

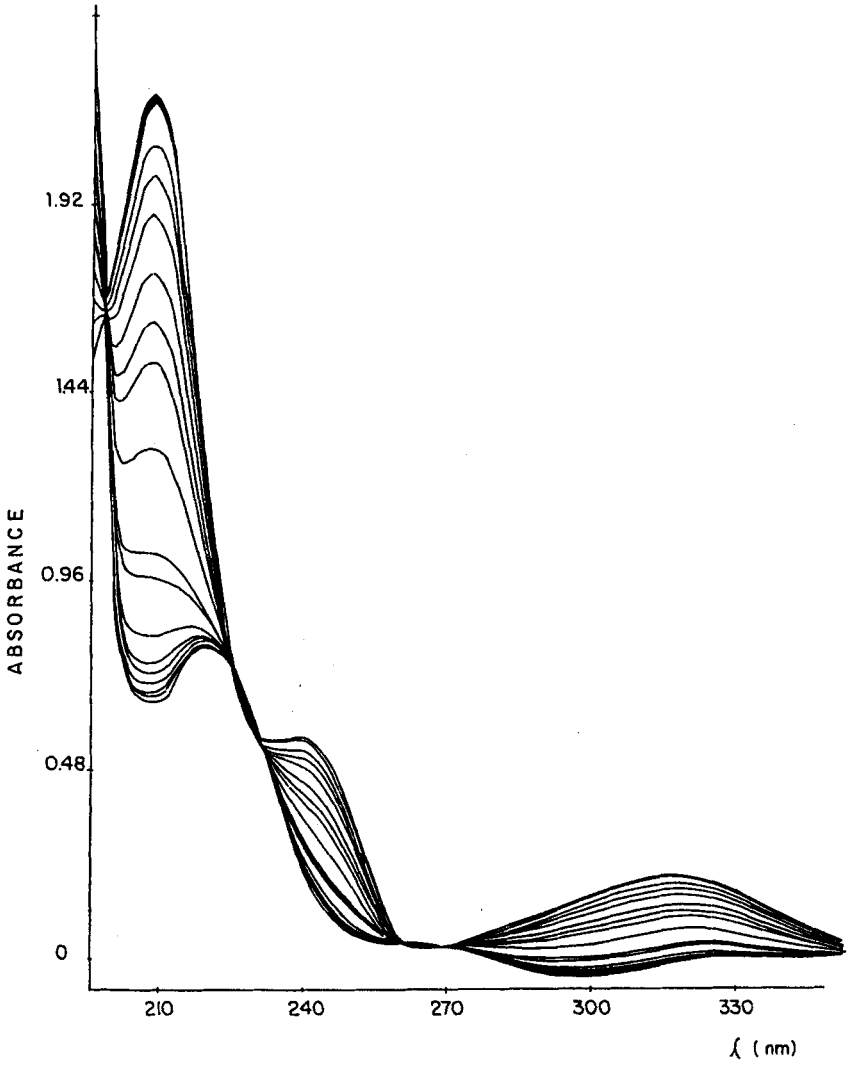


Figure 1. Ultraviolet absorption spectra of *o*-aminobenzamide as a function of medium acidity between pH 5·59 and 1·08 (from top to bottom) between 200 and 340 nm

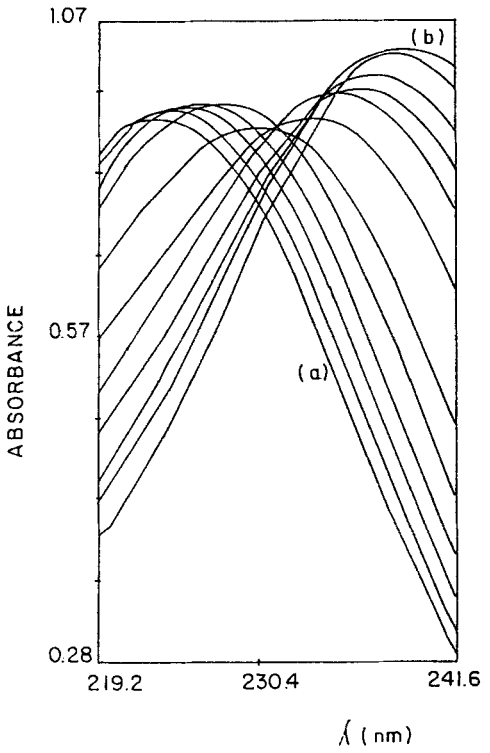


Figure 2. Experimental absorbances of *o*-aminobenzamide as a function of medium acidity: from bottom to top on the right, 1·00, 3·02, 5·03, 6·04, 7·05, 8·06, 9·06, 9·57, 9·82, 10·07, 10·32 and 10·57 M $HClO_4$

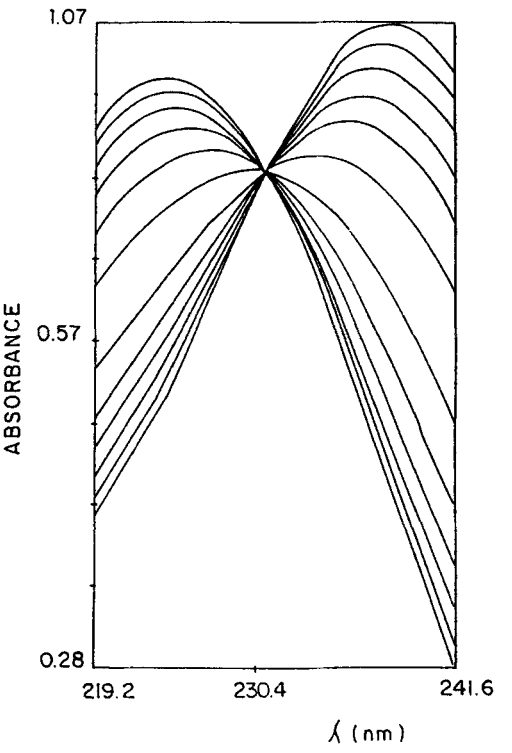


Figure 3. Reconstituted absorbances of *o*-aminobenzamide. For details, see Figure 2

substituded benzamides.[5,17] Also listed in Table 2 are the average values of $pK_{BH^+}$ calculated with $H_A$ and the excess functions $X$, $X_0$ and $M_c$. The value of $pK_{BH^+} = -1{\cdot}65$ reported for benzamide in sulphuric acid[5] is in good agreement with the value of $-1{\cdot}60$ in perchloric acid calculated in this work.

Introduction of the ionization ratios calculated by vector analysis for *o*-aminobenzamide into equations (2)–(5) did not give a linear relationship, because full protonation was not achieved at 10·67 M $HClO_4$: hence the value for $c_1$ calculated at this acid molarity is not reliable for the measurements of ionization ratios. In fact, plots of $A$ vs $H_A$ should give sigmoid curves;[18] however, only a single curve was obtained, which lacked the highest acidity value; this effect was observed only with *o*-aminobenzamide (Figure 4). This difficulty was recently overcome by Zalewski and Geribaldi,[19] who used principal component analysis (PCA) for the correction of the medium effects. Accordingly, absorbances at a wavelength λ for the *n*th spectrum may be represented as:

$$A_{n,p} = c_{1,p}L_{n,1} + c_{2,p}L_{n,2} \quad (6)$$

where $c$ represents the principal components for wavelength $p$ and $L$ the loading for the *n*th spectrum. Hence the values for $c$ calculated in this work by means of equation (1) are independent of the wavelength chosen, depend on the medium acidity only and have a more distinct meaning than $c$ as defined by equation (6).

A simpler method is suggested here for determining the coefficients $c_1$ and/or the experimentally inaccessible absorbances of the protonated bases. The protonation of the base B may be represented by

$$B + H^+ \rightleftharpoons BH^+ \quad (7)$$

We introduce the additivity of absorbances of the base B and the conjugate acid $BH^+$ at a wavelength λ:

$$A = A_B + A_{BH^+} \quad (8)$$

and define the total concentration $C_t$ as the sum

$$C_t = C_B + C_{BH^+} \quad (9)$$

Rearrangement of equation (4) in the form

$$K_{BH^+} = (C_B C_{H^+} C_{BH^+}) \times 10^{m^* X} \quad (10)$$

Leads to the straight-line equations

$$1/A = 1/A_B + (1/A_B K_{BH^+})[C_{H^+}(A - A_{BH^+})_* \times 10^{m^* X}/A] \quad (11)$$

Table 1. Weighting factors of the characteristic vector $v_1$ as a function of perchloric acid concentration

| Benzamide | | *o*-Toluamide | | Salicylamide | | *o*-Chlorobenzamide | | *o*-Bromobenzamide | | *o*-Aminobenzamide | | *o*-Ethoxybenzamide | | *o*-Nitrobenzamide | | *o*-Fluorobenzamide | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| $HClO_4$(M) | $c_1$ | $HClO_4$(M) | $c_1$ | $HClO_4$(M) | $c_1$ | $HClO_4$(M) | $c_1$ | $HClO_4$(M) | $c_1$ | $HClO_4$(M) | $c_1$ | $HClO_4$(M) | $c_1$ | $HClO_4$(M) | Log $I$ | $HClO_4$(M) | Log $I$ |
| 0·000 | −0·333 | 0·000 | −0·330 | 0·000 | −0·333 | 0·000 | −0·301 | 0·000 | −0·333 | 1·007 | −0·401 | 0·000 | −0·311 | 2·355 | −1·211 | 0 | −0·289 |
| 0·883 | −0·313 | 1·613 | −0·305 | 1·163 | −0·304 | 1·983 | −0·278 | 1·983 | −0·319 | 4·030 | −0·367 | 0·294 | −0·290 | 3·532 | −0·755 | 0·9 | −0·283 |
| 1·472 | −0·293 | 1·745 | −0·283 | 1·745 | −0·283 | 2·645 | −0·258 | 3·306 | −0·286 | 5·031 | −0·324 | 0·589 | −0·283 | 4·121 | −0·567 | 1·8 | −0·272 |
| 2·060 | −0·267 | 2·327 | −0·253 | 2·327 | −0·261 | 3·306 | −0·241 | 3·967 | −0·256 | 6·042 | −0·265 | 1·177 | −0·258 | 4·709 | −0·413 | 2·7 | −0·262 |
| 2·649 | −0·231 | 2·909 | −0·211 | 2·909 | −0·228 | 3·967 | −0·222 | 4·628 | −0·210 | 7·051 | −0·186 | 1·776 | −0·224 | 5·298 | −0·245 | 3·6 | −0·234 |
| 3·238 | −0·186 | 3·491 | −0·149 | 3·491 | −0·177 | 4·628 | −0·177 | 5·289 | −0·170 | 8·062 | −0·072 | 2·060 | −0·199 | 5·886 | −0·053 | 4·5 | −0·185 |
| 3·826 | −0·129 | 4·073 | −0·092 | 4·073 | −0·119 | 5·289 | −0·120 | 5·950 | −0·094 | 9·065 | 0·097 | 2·355 | −0·171 | 6·475 | 0·115 | 5·4 | −0·097 |
| 4·415 | −0·063 | 4·655 | −0·021 | 4·655 | −0·042 | 5·950 | −0·056 | 6·612 | −0·013 | 9·570 | 0·197 | 2·943 | −0·105 | 7·064 | 0·376 | 6·3 | −0·012 |
| 5·003 | 0·014 | 5·236 | 0·061 | 5·236 | 0·041 | 6·612 | 0·039 | 7·273 | 0·087 | 9·821 | 0·254 | 3·532 | −0·025 | 7·820 | 0·769 | 7·2 | −0·136 |
| 5·592 | 0·090 | 5·818 | 0·151 | 5·857 | 0·119 | 7·273 | 0·136 | 7·934 | 0·182 | 10·078 | 0·311 | 3·826 | 0·018 | 8·192 | 0·885 | 8·1 | −0·234 |
| 6·181 | 0·167 | 6·400 | 0·229 | 6·400 | 0·205 | 7·934 | 0·226 | 8·595 | 0·258 | 10·321 | 0·356 | 4·415 | 0·104 | 8·751 | 1·299 | 9·0 | −0·318 |
| 6·769 | 0·229 | 6·982 | 0·313 | 6·982 | 0·268 | 8·595 | 0·317 | 9·256 | 0·329 | 10·577 | 0·392 | 5·003 | 0·180 | | | 10·4 | −0·424 |
| 7·358 | 0·274 | 7·564 | 0·395 | 7·564 | 0·322 | 9·917 | 0·450 | 9·917 | 0·389 | – | 0·864 | 5·592 | 0·224 | | | 11·1 | −0·491 |
| 8·006 | 0·317 | 8·727 | 0·495 | 8·175 | 0·364 | 10·578 | 0·485 | 10·578 | 0·437 | | | 6·181 | 0·295 | | | | |
| 8·564 | 0·346 | | | 9·309 | 0·427 | | | | | | | 6·769 | 0·331 | | | | |
| 9·309 | 0·376 | | | | | | | | | | | 7·064 | 0·347 | | | | |
| | | | | | | | | | | | | 7·358 | 0·362 | | | | |

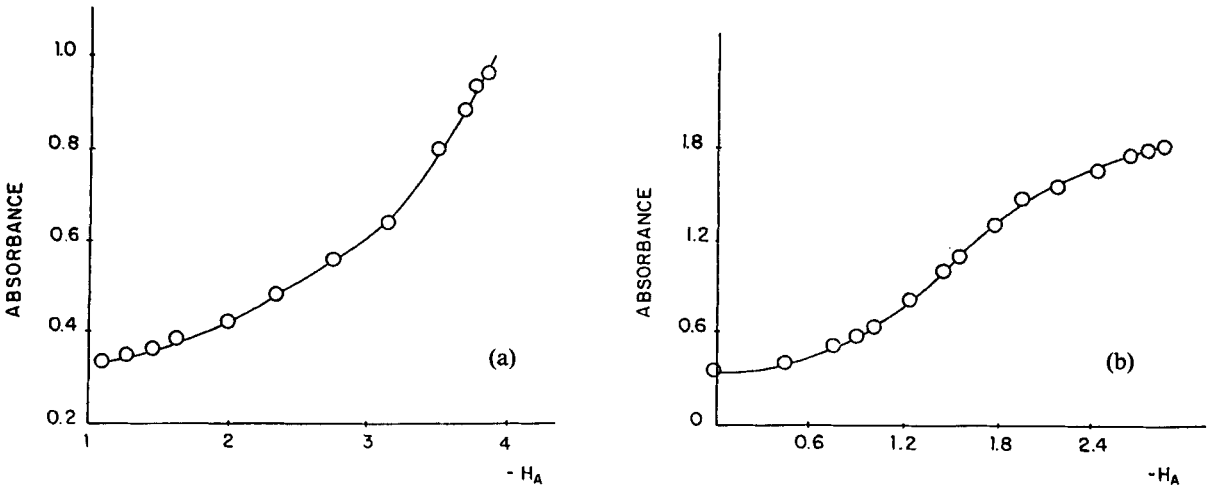


Figure 4. Variation of absorbances as a function of perchloric acid acidity, $-H_A$: (a) *o*-aminobenzamide at 240 nm and (b) *o*-ethoxybenzamide at 248 nm

Table 2. Values of acidity constants calculated with different acidity functions reported for $HClO_4$

| | $H_A^{13}$ | | | $H_A^{14}$ | | |
|---|---|---|---|---|---|---|
| Amide | $m$ | $-pK^a$ | $-pK^b$ | $m$ | $-pK^a$ | $-pK^b$ |
| Benzamide | 0·90 | 1·45 ± 0·03 | 1·61 ± 0·03 | 0·88 | 1·48 ± 0·05 | 1·68 ± 0·04 |
| *o*-Toluamide | 1·11 | 1·45 ± 0·03 | 1·61 ± 0·03 | 1·12 | 1·88 ± 0·04 | 1·68 ± 0·04 |
| Salicylamide | 1·10 | 1·85 ± 0·03 | 1·68 ± 0·03 | 1·12 | 1·89 ± 0·01 | 1·69 ± 0·02 |
| *o*-Chlorobenzamide | 1·08 | 2·16 ± 0·04 | 2·00 ± 0·03 | 1·10 | 2·27 ± 0·03 | 2·06 ± 0·03 |
| *o*-Bromobenzamide | 1·01 | 2·28 ± 0·05 | 2·26 ± 0·04 | 1·11 | 2·53 ± 0·08 | 2·28 ± 0·08 |
| *o*-Nitrobenzamide | 1·08 | 2·00 ± 0·06 | 1·85 ± 0·06 | 1·16 | 2·16 ± 0·09 | 1·86 ± 0·08 |
| *o*-Ethoxybenzamide | 1·28 | 1·72 ± 0·03 | 1·34 ± 0·02 | 1·18 | 1·64 ± 0·03 | 1·39 ± 0·04 |
| *o*-Aminobenzamide[d] | 1·09 | 3·00 ± 0·05 | 2·76 ± 0·04 | 1·11 | 3·18 ± 0·19 | 2·86 ± 0·10 |
| *o*-Fluorobenzamide | 1·00 | 2·05 ± 0·07 | 2·05 ± 0·09 | 1·01 | 2·13 ± 0·10 | 2·13 ± 0·09 |

| | $X$ with equation (4) | | $X_0$ with equation (4) | | $-M_c$ with equation (5) | | |
|---|---|---|---|---|---|---|---|
| | $m^*$ | $-pK$ | $m^*$ | $-pK$ | $n_B$ | $-pK$ | $-\overline{pK}^c$ |
| Benzamide | 0·45 | 1·57 ± 0·01 | 0·51 | 1·55 ± 0·02 | 0·31 | 1·59 ± 0·01 | 1·60 ± 0·02 |
| *o*-Toluamide | 0·46 | 1·64 ± 0·03 | 0·51 | 1·60 ± 0·02 | 0·31 | 1·67 ± 0·02 | 1·65 ± 0·03 |
| Salicylamide | 0·48 | 1·66 ± 0·01 | 0·50 | 1·58 ± 0·02 | 0·32 | 1·68 ± 0·01 | 1·66 ± 0·02 |
| *o*-Chlorobenzamide | 0·43 | 2·11 ± 0·01 | 0·43 | 1·98 ± 0·02 | 0·28 | 2·09 ± 0·02 | 2·05 ± 0·02 |
| *o*-Bromobenzamide | 0·47 | 2·26 ± 0·04 | 0·46 | 2·11 ± 0·02 | 0·30 | 2·23 ± 0·03 | 2·23 ± 0·04 |
| *o*-Nitrobenzamide | 0·49 | 1·90 ± 0·06 | 0·50 | 1·79 ± 0·04 | 0·32 | 1·90 ± 0·05 | 1·86 ± 0·06 |
| *o*-Ethoxybenzamide | 0·58 | 1·32 ± 0·02 | 0·70 | 1·36 ± 0·03 | 0·41 | 1·40 ± 0·02 | 1·36 ± 0·03 |
| *o*-Aminobenzamide[d] | 0·30 | 2·65 ± 0·01 | 0·40 | 2·68 ± 0·08 | 0·15 | 2·65 ± 0·02 | 2·72 ± 0·05 |
| *o*-Fluorobenzamide | 0·37 | 1·98 ± 0·05 | 0·35 | 1·83 ± 0·06 | 0·24 | 1·95 ± 0·05 | 1·99 ± 0·07 |

[a] $pK$ calculated with equation (2).
[b] $pK$ calculated with equation (4).
[c] Calculated with average $H_A$, $X$, $X_0$ and $-M_c$.
[d] $pK = pK_2$.

and

$$1/A = 1/A_{BH^+} + (K_{BH^+}/A_{BH^+})(A - A_B)/(C_{H^+}A \times 10^{m^*X}) \quad (12)$$

where the absorbances $A_B$ and $A_{BH^+}$ may be replaced by absorptivities $\varepsilon_B$ and $\varepsilon_{BH^+}$, provided that Beer's law is obeyed. An iterative procedure permits the determination of the unknown $A_{BH^+}$ by introducing an initial value of $m^*$ into equation (12); the intercept of the straight-line plot of $1/A$ vs $(A - A_B)/(C_{H^+}A \times 10^{m^*X})$ provides $A_{BH^+}$, which, in turn, is introduced into equation (11), leading to a straight line of intercept $1/A_B$. If this value does not match the experimental $A_B$, the process is iterated, this time introducing another $m^*$ until convergence is achieved; $m^*$, $A_{BH^+}$ and $K_{BH^+}$ must be self-consistent. This procedure is reliable assuming that the acidity function used is valid; nevertheless, the validity of the excess acidity functions used here has been widely recognized in the study of both thermodynamic and kinetic processes at high acidity levels. For bases susceptible to medium effects, it is advisable to replace the experimental absorbances by corrected absorbances ($A_C = A + c_1v_1$); this allows the ionization ratios to be obtained starting from the $A_C$ values provided by the method.

As $c_1$ is independent of the wavelength chosen, a more convenient modified procedure consists in determining $c_1$ for $BH^+$, which yields similar results. Table 1 gives the $c_1$ values of totally protonated *o*-aminobenzamide; the results for $m^*$ and $pK_{BH^+}$ determined with equations (11) and (12) and those in Table 2 calculated with the excess acidity $X$ are in good agreement. Cox and Stewart[20] suggested that a variation in $m^*$ of $\pm 0{\cdot}1$ units is needed between the bases for a series of compounds to form a suitable acidity function set; they reported[21] a value of $m^* = 0{\cdot}51 \pm 0{\cdot}07$ for amides in perchloric acid, and calculated the $pK_{BH^+}$ values with equation (4) assuming that $-H_A - \log C_{H^+} = m^*X$. The $m^*$ values reported in this work fall within the $\pm 0{\cdot}1$ interval, except for *o*-aminobenzamide.

## EXPERIMENTAL

All the benzamides investigated were commercially available in high purity (Aldrich, Merck and Fluka), and were further purified by sublimation in a vacuum line; melting points were in agreement with literature values. Doubly distilled, deionized water was used as the solvent throughout, over which nitrogen was bubbled before use. Freshly prepared solutions were always used. Spectral curves were recorded with a Milton Roy 3000 diode-array spectrophotometer; this permits standard and multiple expansion scales for both absorbances ($\pm 0{\cdot}001$) and wavelengths ($\pm 0{\cdot}1$) and also differential modes for measurements; it is furnished with a temperature cell holder adapter for 1 nm cells, electrically regulated and controlled by computer. The absorbance–wavelength data pairs provided by the equipment were stored in ASCII files, and used directly for vector analysis. Twenty-five wavelengths were introduced for all the matrix analyses carried out and the number of absorbances was never less than twelve.

Stock solutions were prepared in perchloric acid of acidity between the limits within which ionizations occur, and with a sufficient amide concentration that the final solutions give a suitable acidity and adequate absorbances. Volumetric manipulations were made with solutions thermostated at $25 \pm 0{\cdot}01\,^{\circ}C$ with a Grant LTD 6 circulator. The reference cell contained the same solvent as the sample under measurement, and control of ionic strength was not necessary since this factor is included in the excess acidity function method, pH readings ($\pm 0{\cdot}01$) were made with a Crison 501 pH meter. The stability of the solutions utilized and the absence of hydrolysis of benzamides during the time needed for the experiments was assessed. A table with the variations of absorptivities of the benzamides with medium acidity is stored in a supplemental data registry.

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