

## **CALORIMETRIC ANALYSIS OF THE PROTONATION PROCESS FOR 3-ARYLIMINO-3H-INDOLE N-OXIDES AND N,N'-DIOXIDES IN ACETONITRILE**

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### **ABSTRACT**

Calorimetric analysis on two series of indole derivatives (both previously studied from the calorimetric and electrochemical points of view) has been carried out. Both series show a single protonation process, but only for one series does the electron charge distribution enable the site of protonation to be recognized.

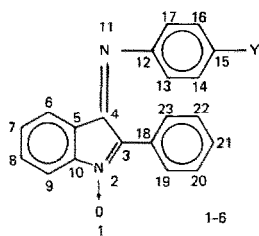
### **INTRODUCTION**

A comparison between electro-oxidation, electro-reduction and protonation processes for a series of compounds with similar structures has been the subject of research in our laboratory [1–3].

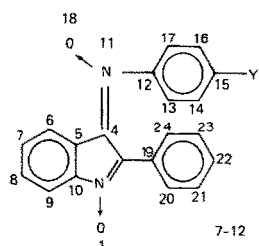
A linear regression analysis of the proton transfer and electron transfer data in acetonitrile has led to the hypothesis that the same substituents affect the protonation and the electro-oxidation processes in the same way, while for the electro-reduction and protonation processes the contrary is true. This analysis, together with the electron charge distributions of molecules and anions of the series studied, also showed how these molecules undergo a single protonation process.

The aim of this work was to ascertain whether a calorimetric analysis, by itself, is able to supply information about the protonation processes of two series of compounds with similar structures and about the influence of substituents on the same processes.

The compounds studied are the 2-phenyl-3-arylamino-3H-indole *N*-oxide derivatives **1–6** and the 2-phenyl-3-arylamino-3H-indole *N,N'*-dioxide derivatives **7–12**



- 1:** Y = Br  
**2:** Y = Cl  
**3:** Y = H  
**4:** Y = Me  
**5:** Y = OMe  
**6:** Y = N(Me)<sub>2</sub>



- 7:** Y = Br  
**8:** Y = Cl  
**9:** Y = H  
**10:** Y = Me  
**11:** Y = OMe  
**12:** Y = N(Me)<sub>2</sub>

It may be expected that if substituents at position 15 affect the protonation of the derivatives **1–12** in the same way, then the enthalpic values of protonation of the two series would follow a linear relationship. However, it is more convenient to compare both series with compounds studied previously by electrochemical and thermodynamic approaches [3].

For this purpose, a monoparametric linear regression analysis can be used. Total standard deviation, standard deviations of the slope and of the intercept, correlation coefficient values and their Student *t*-test results supply the precise form of the mathematical function relating the two variables and test how the experimental results support the theoretical relationship within the limits of the experimental error of measurements [4–9]. However, the significance level of these relationships only allows the experimental results to be compared and explained in terms of probability.

## EXPERIMENTAL AND PROCEDURE

All compounds were prepared as indicated in ref. 10. A Tronac calorimeter (Model 458) was used. The calorimeter vessel was a rapid-response glass vacuum Dewar of maximum capacity 25 cm<sup>3</sup>; the burette volume was 2 cm<sup>3</sup> and the measured titrant delivery rate was 0.49373 cm<sup>3</sup> min<sup>-1</sup>. The thermostat was maintained at 298.15 ± 0.0002 K by employing a Tronac P.T.C. 41 precision temperature controller.

Potential vs. time measurements were made using a Fluka Model 88100. The imbalance (V) of the bridge of the calorimeter was fed into a Hitachi 561-10002/p strip-chart recorder and into a digital voltmeter, which, in turn,

was connected to an Olivetti M24 computer. Data acquired by the computer via a data acquisition system were subsequently read and converted into enthalpy values using a BASIC program [11].

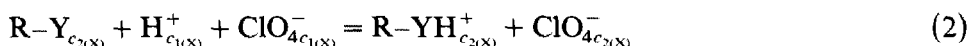
Data obtained using the chart recorder may be slightly different from those obtained using the computer and they also give the slope of the reaction curve. Acetonitrile (Carlo Erba RS for UV-IR) and perchloric acid (Merck 12.49 M) were used. Acid concentration was checked by potentiometric titration. 25 ml of derivatives **1-12**, in solutions ranging from  $5.64 \times 10^{-4}$  M to  $1.51 \times 10^{-3}$  M, were placed in the vessel. Acid solution containing an excess of  $\text{HClO}_4$  (10-100% equivalents) was subsequently added via a precision burette.

The protonation process of the derivatives **1-12** (R-Y) in acetonitrile solutions can be represented as



The partial molar enthalpy of protonation,  $\Delta\bar{H}_1$ , was obtained from the following experimental measurements:

(a) the partial molar enthalpy of reaction,  $\Delta\bar{H}_2$ , of R-Y derivatives dissolved in acetonitrile at concentration  $C_2$  with  $\text{HClO}_4$  (also dissolved in acetonitrile) at concentration  $C_1$



(b) the partial molar enthalpy of dilution,  $\Delta\bar{H}_3$ , of  $\text{HClO}_4$ , at concentration  $c_{1(x)}$ , dissolved in 25 ml of acetonitrile



so that the molar enthalpy of process (1) can be obtained by subtracting  $\Delta\bar{H}_3$  from  $\Delta\bar{H}_2$ .

For each solution the  $\Delta\bar{H}_1$  values refer to the reaction of one mole of R-Y and one mole of protons, both dissolved at infinite dilution in 1000 g of solvent, yielding one mole of  $\text{R-YH}^+$  diluted in the same amount of solvent.

In processes (1) and (2), concentrations ranging from  $5.6 \times 10^{-3}$ - $1.56 \times 10^{-3}$  M were used. Therefore the  $\Delta\bar{H}$  values related to these processes were assumed to be equal to  $\Delta H^0$  [12].

Regarding the subtraction of  $\Delta H_3^0$  from  $\Delta H_2^0$ , the following considerations must be taken into account.

Consider the equation

$$Q_o = Q_p + Q_d$$

where  $Q_o$  is the overall heat term,  $Q_p$  the heat term due to the protonation and  $Q_d$  the dilution heat term. The equation can be written in the form

$$Q_o = n_1 \Delta H_1^0 + n_2 \Delta H_3^0$$

where  $n_1$  and  $n_2$  are the moles, respectively, of derivatives **1–12** and of perchloric acid, and  $\Delta H_1^0$  and  $\Delta H_3^0$  (as previously shown) are the partial molar enthalpies of the protonation and dilution processes, respectively. Bearing in mind that  $n_2 = n_1(1 + \beta)$ , where  $\beta$  is the excess percentage of  $n_2$  with respect to  $n_1$ , one can write

$$Q_o = n_1 \Delta H_1^0 + n_1(1 + \beta) \Delta H_3^0$$

and finally the enthalpy values of protonation  $\Delta H_1^0$  can be obtained as

$$\Delta H_1^0 = Q_o/n_1 - (1 + \beta) \Delta H_3^0$$

where  $Q_o/n_1$  represents the partial molar enthalpy of the overall heat term with respect to the derivatives **1–12** ( $\Delta H_2^0$ ).

A constant value for  $\Delta H_1^0$  is obtained on varying  $\beta$  from 10–100%. This fact implies that only one proton process occurs. A useful contribution to evaluating the site of the protonation process is given by the Hückel–McLachlan charge density distribution calculated by a computer program with the following values [13]

$$\begin{aligned} h_{\text{N}} &= 0.5; K_{\text{CN}} = 1; K_{\text{C-N}} = 0.8; K_{\text{CC}} = 1; K_{\text{C-C}} = 0.8; K_{\text{C-Me}} = 0.7; \\ h_{\text{Me}} &= 2.00; K_{\text{C-OMe}} = 0.8; h_{\text{OMe}} = 2.00; K_{\text{C-Cl}} = 0.4; h_{\text{Cl}} = 2.00; \\ K_{\text{C-Br}} &= 0.3; h_{\text{Br}} = 1.5; K_{\text{C-N(Me)}_2} = 0.8; h_{\text{N(Me)}_2} = 1.5; K_{\text{N-O}} = 0.2; \\ h_{\text{O}} &= 1; h_{\text{N}^+} = 2; \end{aligned}$$

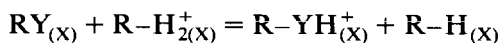
where  $h$  is the coulomb integral increment in  $\beta^0$  and  $K$  is the bond integral which represents the energy of interaction of two atomic orbitals; C–N symbolizes a single bond, C=N a double bond and CN an aromatic bond.

## RESULTS AND DISCUSSION

Table 1 lists the enthalpy values for the protonation of **1–12** and also the *para*-substituent values [14]. For the sake of comparison it is convenient to express the protonation enthalpy values,  $\Delta H_1^0$ , as the differences between their values and that of the reference compounds **3** and **9** ( $Y = \text{H}$ ) so that

$$\delta \Delta H_1^0 = \Delta H_{Y_1}^0 - \Delta H_{\text{H}_1}^0$$

refers to the proton transfer process



These values show (Table 2) how the protonation process for derivatives which bear electron-withdrawing substituents are endothermic with respect to the reference compound, while for derivatives with electron-donating substituent groups the reverse is true.

The Hückel–McLachlan molecular orbital calculation method shows (Table 3) that in molecules **1–6** (the 2-phenyl-3-arylimino-3H-indole *N*-oxides)

TABLE 1

Enthalpy values for the protonation processes of 2-phenyl-3-aryl-3H-indole-*N*-oxide derivatives 1–6 and 2-phenyl-3-aryl-3H-indole *N,N'*-dioxide derivatives 7–12 in acetonitrile, plus substituent values

Compound	Y	$\Delta H_1^0$ (kcal mol <sup>-1</sup> )	$\sigma_p$
1	Br	5.31	0.23
2	Cl	4.54	0.23
3	H	0.53	0.00
4	Me	0.52	-0.17
5	OMe	-1.12	-0.27
6	N(Me) <sub>2</sub>	-38.02	-1.27
7	Br	5.70	
8	Cl	2.93	
9	H	2.70	
10	Me	1.43	
11	OMe	0.23	
12	N(Me) <sub>2</sub>	-11.64	

TABLE 2

Differences with respect to unsubstituted compounds 3 and 9 of the enthalpy of protonation for derivatives 1–12

Compound	Y	$\delta\Delta H_1^0$ (kcal mol <sup>-1</sup> )
1	Br	4.78
2	Cl	4.01
3	H	0.00
4	Me	-0.01
5	OMe	-1.65
6	N(Me) <sub>2</sub>	-38.55
7	Br	3.00
8	Cl	0.23
9	H	0.00
10	Me	-1.27
11	OMe	-2.47
12	N(Me) <sub>2</sub>	-14.34

TABLE 3

Hückel–McLachlan charge density distributions for molecules 1–6

Compound	O <sub>1</sub>	N <sub>2</sub>	C <sub>5</sub>	N <sub>11</sub>
1 Y = Br	1.92146	1.65620	1.05112	0.99767
2 Y = Cl	1.92164	1.65637	1.05188	0.99740
3 Y = H	1.92080	1.65550	1.05201	0.99778
4 Y = Me	1.92338	1.65825	1.05163	0.99726
5 Y = OMe	1.92417	1.65914	1.05153	0.99748
6 Y = N(Me) <sub>2</sub>	1.93461	1.72012	1.05099	0.99541

TABLE 4

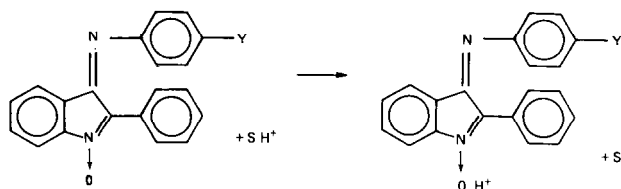
Hückel–McLachlan charge density distributions for molecules 7–11

Compound	O <sub>1</sub>	N <sub>2</sub>	N <sub>11</sub>	O <sub>18</sub>
7 Y = Br	1.88453	1.64259	1.55640	1.74552
8 Y = Cl	1.88476	1.64273	1.55604	1.74539
9 Y = H	1.88353	1.64184	1.55749	1.74563
10 Y = Me	1.88750	1.64469	1.55320	1.74530
11 Y = OMe	1.88883	1.64567	1.55201	1.74546
12 Y = N(Me) <sub>2</sub>	1.89146	1.64777	1.55083	1.74681

the highest charge density values are localized on O<sub>1</sub>, indicating that molecule–proton interaction could be determined mainly by the charge on this oxygen.

The enthalpy experimental data are compatible with the charge (electron density) distribution. Indeed the constant value of  $\Delta H^0$  for protonation, obtained by varying the  $\beta$  values from 10–100%, confirms that the oxygen atom is the most reactive site for the protonation process.

For this reaction the following scheme can be hypothesized



For the second series high electron density values were found at both O<sub>1</sub> and O<sub>18</sub> (Table 4) so that the site of the single protonation process is uncertain.

To verify these hypotheses the following correlations were examined critically, by means of a linear monoparametric analysis: (i)  $\delta \Delta H^1$  vs.  $\delta \Delta H^{\text{ref}}$ ; (ii)  $\delta \Delta H^2$  vs.  $\delta \Delta H^{\text{ref}}$ ; (iii)  $\delta \Delta H^1$  vs.  $\sigma_p$ ; (iv)  $\delta \Delta H^2$  vs.  $\sigma_p$ ; (v)  $\delta \Delta H^1$  vs.  $\delta q_{O1}^1$ ; (vi)  $\delta \Delta H^2$  vs.  $\delta q_{O1}^2$ ; (vii)  $\delta \Delta H^2$  vs.  $\delta q_{O18}^2$ ; where  $\delta \Delta H^1$  and  $\delta \Delta H^2$  are the values related to the first and second series studied, respectively, and  $\delta \Delta H^{\text{ref}}$  are the values of the reference series;  $\sigma_p$  are substituent constant values of benzoic acids carrying the same substituents;  $\delta q_{O1}^1$ ,  $\delta q_{O1}^2$  and  $\delta q_{O18}^2$  are the electron densities (charge) on the oxygens of the first and second series expressed as  $q_{OY} - q_{OH}$ .

For all these correlations the null hypotheses considered were for the intercept  $a = 0$  and for the slope  $b = 0$ . For the relations (iii) and (iv), the regressions were not forced through the origin. An intercept was obtained with the least-squares treatment, but it was normally indistinguishable from zero.

TABLE 5

Results of monoparametric regression analysis of  $\delta\Delta H^1$  vs.  $\delta\Delta H^{\text{ref}}$  for 1-6

$n$	6
Intercept	1.67
Slope	1.78
SD of intercept	0.84
SD of slope	0.09
SD of regression	1.87
$r$	0.99
n.h.: intercept = 0	C.L. < 0.95
n.h.: slope = 0	C.L. > 0.999

<sup>a</sup> n.h. = nul hypothesis.

TABLE 6

Results of monoparametric regression analysis of  $\delta\Delta H^2$  vs.  $\delta\Delta H^{\text{ref}}$  for 7-12

$n$	6
Intercept	0.99
Slope	0.66
SD of intercept	0.41
SD of slope	0.04
SD of regression	0.92
$r$	0.99
n.h.: intercept = 0	C.L. < 0.95
n.h.: slope = 0	C.L. > 0.999

The null hypotheses were tested by using the Student  $t$  test. The  $t$  values of  $a$  and  $b$  were calculated from the expressions

$$t_a = (a - A)/S_a; \quad t_b = (b - B)/S_b$$

(where  $A$  and  $B$  are variables which can be set equal to zero and  $S_a$  and  $S_b$  are the standard deviations of  $a$  and  $b$ ) and compared with values in a set of  $t$  tables.

TABLE 7

Results of monoparametric regression analysis of  $\delta\Delta H^1$  vs.  $\sigma_p$  for 1-6

$n$	6
Intercept	0.76
Slope	28.77
SD of intercept	1.87
SD of slope	3.39
SD of regression	4.23
$r$	0.97
n.h.: intercept = 0	C.L. < 0.95
n.h.: slope = 0	0.99 < C.L. < 0.999

TABLE 8

Results of monoparametric regression analysis of  $\delta\Delta H^2$  vs.  $\sigma_p$  for 7-12

$n$	6
Intercept	-0.27
Slope	10.74
SD of intercept	0.53
SD of slope	0.95
SD of regression	1.19
$r$	0.98
n.h.: intercept = 0	C.L. < 0.95
n.h.: slope = 0	C.L. > 0.999

If  $t > t_{CL, n-2}$  (where  $n - 2$  is the degree of freedom and CL the confidence level for the significance of the regression) then for  $CL < 0.95$  the null hypothesis is accepted (chemical hypothesis) while for  $CL > 0.999$  its rejection is highly significant.

The two correlations,  $\delta\Delta H^1$  vs.  $\delta\Delta H^{\text{ref}}$  and  $\delta\Delta H^2$  vs.  $\delta\Delta H^{\text{ref}}$ , both highly significant as shown in Tables 5 and 6, lead to the hypothesis that a single protonation process occurs in the two series.

The linear regressions,  $\delta\Delta H^1$  vs.  $\sigma_p$  and  $\delta\Delta H^2$  vs.  $\sigma_p$ , highlight substituent effects; the relations of the first and second series are, respectively, significant and highly significant (Tables 7 and 8). The comparison between two similar thermodynamic processes (proton dissociation of aromatic acids and protonation of polycyclic compounds) confirms that protonation occurs in a single process. To identify the actual site of protonation, a comparison of  $\delta\Delta H^1$  with the electron density charge distribution was made. The relation  $\delta\Delta H^1$  vs.  $\delta q_{O1}^1$  is highly significant (Table 9), so for the first series the most probable site of protonation is the oxygen atom. The relations  $\delta\Delta H^2$  vs.  $\delta q_{O1}^2$  and  $\delta\Delta H^2$  vs.  $\delta q_{O18}^2$  are both uncertain (Tables 10 and 11). The electron distribution in the second series is not concentrated on a single

TABLE 9

Results of monoparametric regression analysis of  $\delta\Delta H^1$  vs.  $\delta q_{O1}$  for 1-6

$n$	6
Intercept	5.82
Slope	-3122.00
SD of intercept	1.82
SD of slope	309.00
SD of regression	3.58
$r$	0.98
n.h.: intercept = 0	C.L. < 0.95
n.h.: slope = 0	C.L. > 0.999



TABLE 10

Results of monoparametric regression analysis of  $\delta\Delta H^2$  vs.  $\delta q_{O1}$  for 7-12

<i>n</i>	6
Intercept	3.22
Slope	-1822.0
SD of intercept	1.93
SD of slope	464.00
SD of regression	3.09
<i>r</i>	0.89
n.h.: intercept = 0	C.L. < 0.95
n.h.: slope = 0	0.95 < C.L. < 0.99

TABLE 11

Results of monoparametric regression analysis of  $\delta\Delta H^2$  vs.  $\delta q_{O18}$  for 7-12

<i>n</i>	6
Intercept	-1.91458
Slope	-9979.22260
SD of intercept	1.13
SD of slope	2207.55
SD of regression	2.76
<i>r</i>	0.91
n.h.: intercept = 0	C.L. < 0.95
n.h.: slope = 0	0.95 < C.L. < 0.99

oxygen atom, so that a preferred site for the protonation process cannot be hypothesized.

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