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CALORIMETRIC STUDY OF THE PROTONATION PROCESS OF SOME 3-ARYLIMINOINDOLENINE DERIVATIVES IN ACETONITRILE. CORRELATIONS WITH ELECTROREDUCTION PROCESS

F. RODANTE

Dipartimento di Ingegneria Chimica, dei Materiali, delle Materie Prime e Metallurgia, Università di Roma "La Sapienza", Via del Castro Laurenziano 7, 00161 Rome (Italy)

F. FANTAUZZI

Dipartimento di Scienze e Tecnologie Biomediche e di Biometria, Facoltà di Medicina e Chirurgia, Università dell'Aquila (Italy)

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ABSTRACT

A calorimetric study of the proton-transfer process for a series of 1-methyl-2-phenyl-3-arylimino-3*H*-indoles in acetonitrile is presented. A linear-regression analysis of the proton-transfer and electron-transfer data in acetonitrile leads to the hypothesis that substituents affect the protonation and the reduction processes in opposite ways. It was also noted that protonation occurs in a single process and molecule–proton interactions are determined by the charge localized on the endocyclic nitrogen atom.

INTRODUCTION

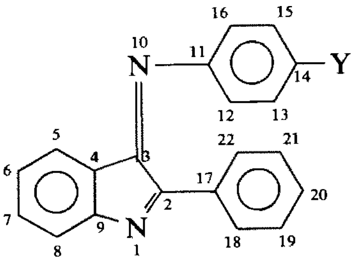
A calorimetric study of the proton-transfer process for a series of 1-methyl-2-phenyl-3-substituted-indoles in acetonitrile has been reported previously [1]. A linear-regression analysis of the proton-transfer and electron-transfer data in acetonitrile leads to the hypothesis that all substituents affect the protonation and the electro-oxidation processes in the same way, excluding the 3-nitroso derivative.

Subsequently, a study of the influence of the solvent on the electroreduction process for a series of compounds (2-phenyl-3-arylimino-3*H*-indoles) showing a structure similar to that of indoles was carried out [2]. In this work it was found that radical anions possessing localized charge strongly interact with molecules of aprotic solvents, so that for the same anion the different interactions with various solvents were related to a solvent acidic property (i.e. acceptor number).

Entropy is the thermodynamic property most often used for this purpose, since its variation $\Delta S_r^{\ominus} = S_{red} - S_{ox}$ can be related to the energy of solvation of radical anions and molecules. The use of a non-isothermal cell offers the possibility of absolute estimation of entropy difference according to the equation $\Delta S = nF\,\mathrm{d}Ef/\mathrm{d}T$. In this way the entropy quantity is found as an absolute value which must not be corrected as a function of solvent variation and depends only on the net electron density charge of the radical anion and can be related to solvent polarization.

Using acetonitrile as solvent, the behaviour of the entropy of radical anions of the above-cited compounds was divided into three pairs of compounds as a function of the inductive (I) and mesomeric (R) effects of the substituent: Cl and Br (electron-withdrawing with $I^- > R^+$); OMe and $N(Me)_2$ (electron-donating with $I^- < R^+$); and H and Me (for which I^- and R^+ are very small).

The aim of this work was to study the effects of substituents on the protonation process of the 2-phenyl-3-arylimino-3*H*-indole derivatives **1**–**6** and to compare them with the substituent effects previously found for the electroreduction process of these compounds in acetonitrile as solvent [2].



1: Y = Br
2: Y = Cl
3: Y = H
4: Y = Me
5: Y = OMe
6: Y = $N(Me)_2$

It may be expected that if the substituents at the 14 position affect both the protonation and the reduction processes of the **1**–**6** derivatives in the same way, then the thermodynamic properties of the protonation and reduction processes are related by a linear relationship. For this purpose it is convenient to use a monoparametric linear-regression analysis. Total standard deviation, standard deviations of the slope and the intercept, correlation coefficients and Student's *t*-test for the above-cited values supply the precise form of the mathematical function relating the two variables and test how well the experimental results support the theoretical relationship within the limits of experimental error of the measurements [3–8]. However, the significance level of these relations only allows the experimental results to be compared and explained in terms of probabilities.

EXPERIMENTAL

All compounds were prepared as described previously [9]. A Tronac (model 458) calorimeter was used to make the measurements. The vessel calorimeter was a rapid-response glass vacuum Dewar of maximum capacity 25 cm^3. The burette volume was 2 cm^3 and the measured titrant delivery rate was 0.493 73 cm^3 min^{-1}. 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 Fluke 88100 model digital voltmeter. The imbalance (volts) of the bridge of the calorimeter was fed into a Hitachi 561-10002/P strip chart recorder and into a digital voltmeter connected to an Olivetti M 24 computer. Data were acquired by the computer via a data-acquisition system and subsequently read and converted into enthalpy values using a BASIC program [10] run on the Olivetti M 24 computer.

Data obtained using the chart record may be slightly different from those obtained using the computer and they also give the shape of the reaction. Acetonitrile (X) (Carlo Erba RS for ultraviolet–infra-red (UV-IR) measurements) was used as a solvent and perchloric acid (Merck, 12.49 M) was used as a reactant. The acid concentration was checked by potentiometric titration of 0.25 ml of the indole derivatives **1**–**6**, the solutions measured ranging in concentration from 5.64×10^{-4} to 1.51×10^{-3} M. Acid solutions containing excess $HClO_4$ equivalents from 5% to 100% were subsequently added via a precision burette.

The protonation process of the **1**–**6** indole derivatives R–Y in acetonitrile solutions can be represented as

$$\text{R–Y}_{C_{2(X)}} + \text{H}^+_{C_{2(X)}} = \text{R–YH}^+_{C_{2(X)}} \qquad (1)$$

The partial molar enthalpy of protonation related to process (1), $\Delta\overline{H}_1$, was obtained by making the following experimental measurements.

(a) The partial molar enthalpy of reaction, $\Delta\overline{H}_2$, of the R–Y derivatives dissolved in acetonitrile at concentration C_2 with $HClO_4$ (also dissolved in acetonitrile) at concentration C_1 was measured.

$$\text{R–Y}_{C_{2(X)}} + \text{H}^+_{C_{1(X)}} + \text{ClO}^-_{4C_{1(X)}} = \text{R–YH}^+_{C_{2(X)}} + \text{ClO}^-_{4C_{2(X)}} \qquad (2)$$

(b) The partial molar enthalpy of dilution, $\Delta\overline{H}_3$, of $HClO_4$ at concentration $C_{1(X)}$ dissolved in 25 ml of acetonitrile was measured.

$$\text{H}^+_{C_{1(X)}} + \text{ClO}^-_{4C_{1(X)}} = \text{H}^+_{C_{2(X)}} + \text{ClO}^-_{4C_{2(X)}} \qquad (3)$$

The molar enthalpy of process (1) was then obtained by subtracting $\Delta\overline{H}_3$ from $\Delta\overline{H}_2$.

For each solution the $\Delta\overline{H}_1$ values refer to the reaction of 1 mol of R–Y and 1 mol of protons, both dissolved at infinite dilution in 1000 g of solvent, yielding 1 mol of $R–YH^+$ diluted in the same amount of solvent.

In processes (1) and (2), concentrations ranging from 5.6×10^{-4} to 1.5×10^{-3} M were used, therefore the $\Delta\overline{H}$ values related to these processes were assumed to be equal to $\Delta H^\ominus$ [11].

With regard to the subtraction of $\Delta \bar{H}_3$ from $\Delta \bar{H}_2$ the following considerations must be taken into account. Let us consider the equation

$$Q_o = Q_p + Q_d$$

where Q_o is the overall heat term, Q_p is the heat of protonation, and Q_d is the heat of dilution. The equation can be rewritten in the form

$$Q_o = n_1 \Delta \bar{H}_1 + n_2 \Delta \bar{H}_3$$

where n_1 and n_2 are the number of moles of the indole derivatives **1**–**6** and of perchloric acid, respectively, and $\Delta \bar{H}_1$ and $\Delta \bar{H}_3$ (as previously shown) are the partial molar enthalpies of the protonation and dilution processes, respectively. Bearing in mind that $n_2 = n_1(1+\beta)\Delta \bar{H}_3$, where β is the excess percentage of n_2 with respect to n_1, one can write

$$Q_1 = n_1 \Delta \bar{H}_1 + n_2(1+\beta)\Delta \bar{H}_3$$

and, finally, the enthalpy values of protonation, $\Delta \bar{H}_1$, can be obtained as

$$\Delta \bar{H}_1 = Q_1/n_1 - (1+\beta)\Delta \bar{H}_3$$

where Q_1/n_1 represents the partial molar enthalpy of the overall heat term with respect to the indole derivatives **1**–**6** ($\Delta \bar{H}_2$).

A constant value of $\Delta \bar{H}_1$ was obtained on varying β from 5% to 100%. This fact implies that only one proton process occurs. A useful aid to determining the size of a protonation process is given by the Hückel–McLachlan charge-density distribution, calculated by a computer program using the following values: $h^{\cdot}_{N}(N{=}C) = 0.5$; $K_{CN} = 1$; $K_{C-N} = 0.8$; $K_{CC} = 1$; $K_{C-C} = 0.8$; $K_{C-Me} = 0.7$; $h^{\cdot\cdot}_{Me} = 2.0$; $K_{C-OMe} = 0.8$; $h^{\cdot\cdot}_{OMe} = 2.0$; $K_{C-Cl} = 0.4$; $h^{\cdot\cdot}_{Cl} = 2.0$; $K_{C-Br} = 0.3$; $h^{\cdot\cdot}_{Br} = 1.5$; $K_{C-NMe} = 0.8$; $h^{\cdot\cdot}_{N}$ $(NMe_2) = 1.5$; where h is the Coulomb integral increment in β° 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

The enthalpy values for the protonation of compounds **1**–**6** and their *para* substituents, σ_p [12], are listed in Table 1. For the sake of comparison it is convenient to express the protonation enthalpy values, $\Delta H^{\ominus}$ of the above-cited derivatives, as the difference between their values and that of the reference compound **3** (Y = **3**), so that

$$\delta \Delta H^{\ominus} = \Delta H^{\ominus}_{Y} - \Delta H^{\ominus}_{H}$$

refers to the proton-transfer process

$$R{-}Y_{(X)} + R{-}H^{+}_{2(X)} = R - YH^{+}_{(X)} + R{-}H_{(X)}$$

These values show (Table 2) that the protonation processes for the deriva-

TABLE 1

Enthalpy values for the protonation process of the 2-phenyl-3-arylimino-3*H*-indoles **1**–**6** in acetonitrile and their substituent values

Compound	Y	ΔH (kJ mol^{-1})	σ_p
1	Br	−11.37	0.23
2	Cl	−13.10	0.23
3	H	−13.63	0.00
4	Me	−14.00	−0.17
5	OMe	−17.00	−0.27
6	$N(Me)_2$	−35.41	−1.27

TABLE 2

Differences in the enthalpy of protonation, with respect to the unsubstituted compound **3**, of compounds **1**–**6**

Compound	Y	$\delta\Delta H$ (kJ mol^{-1})
1	Br	2.26
2	Cl	0.53
3	H	0.0
4	Me	−0.37
5	OMe	−3.37
6	$N(Me)_2$	−22.59

tives bearing electron-withdrawing substituents are endothermic with respect to the reference compound, while for derivatives containing electron-donating substituents the processes are exothermic.

The results of the Hückel–McLachlan molecular-orbital calculations show (Table 3) that in molecules **1**–**6** the highest charge density value is found at N_1, indicating that the molecule–proton interaction is primarily determined

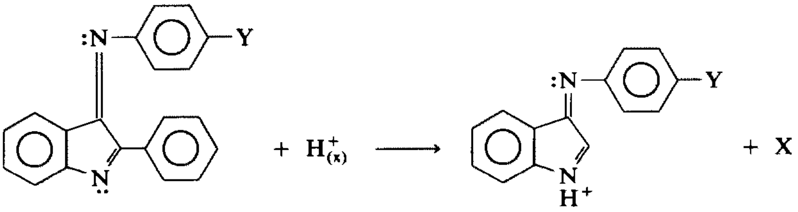
TABLE 3

Hückel–McLachlan large density distributions for molecules **1**–**6**

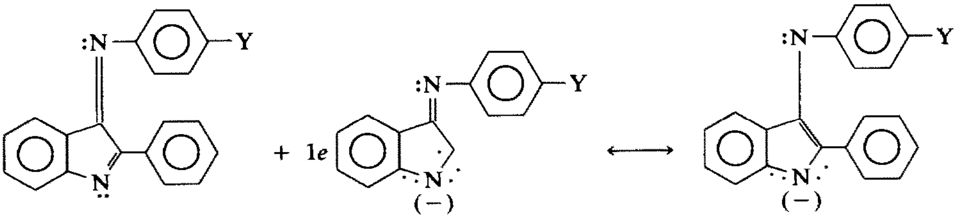
Compound	Y	Atom			
		N_1	C_2	C_3	N_{10}
1	Br	1.25264	0.91188	0.91641	1.04355
2	Cl	1.25303	0.91203	0.91720	1.04324
3	H	1.25120	0.91122	0.91375	1.04402
4	Me	1.25691	0.91383	0.92435	1.04204
5	OMe	1.25871	0.91471	0.92760	1.04169
6	$N(Me)_2$	1.26170	0.91642	0.93263	1.04239

by the charge localized on the endocyclic nitrogen atom. The experimental enthalpy data are compatible with the electron-density distribution. Indeed the constant value of the ΔH of protonation obtained by varying β from 5% to 100% confirms that the *endo* nitrogen atom is the most reactive site for the protonation process.

For this reason the following reaction scheme can be hypothesized



and the first reversible one-electron reduction process of **1–6** in the same solvent can be represented by



In order to verify whether the Y substituents affect the protonation and reduction processes in the same way, a comparison of the proton- and electron-transfer processes was considered useful. The changes in the thermodynamic properties related to the electron-reduction process, expressed as $\delta\Delta\pi = \Delta\pi_Y - \Delta\pi_H$ ($\pi = G$ or H) is given in Table 4. Enthalpy values were obtained from free-energy and entropy values [2].

From these values and those of Tables 1–3, the following correlations were examined critically by means of a linear monoparametric analysis: (i)

TABLE 4

Differences, with respect to the unsubstituted compound (**3**), in the thermodynamic properties of the reduction processes of indole derivatives **1–6** in acetonitrile

Compound	Y	$\delta\Delta G$ (kJ mol^{-1})	$\delta\Delta H$ (kJ mol^{-1})
1	Br	−5.89	3.08
2	Cl	−5.36	0.443
3	H	0.0	0.0
4	Me	1.48	2.64
5	OMe	2.12	5.99
6	$N(Me)_2$	5.40	10.69

TABLE 5

Results of the monoparametric regression analysis of $\delta\Delta H_{\mathrm{prot}}$ vs. $\delta\Delta G_{\mathrm{red}}$ for indole derivatives **1–6**

n	6
Intercept	−4.51
Slope	−1.57
SD of intercept	2.84
SD of slope	0.70
SD of regression	6.92
r	0.74
nh: intercept = 0	CL < 0.95
nh: slope = 0	CL < 0.95

$\delta\Delta H_{\mathrm{prot}}$ vs. $\delta\Delta G_{\mathrm{red}}$; (ii) $\delta\Delta H_{\mathrm{prot}}$ vs. $\delta\Delta H_{\mathrm{red}}$; (iii) $\delta\Delta H_{\mathrm{prot}}$ vs. σ_p; and (iv) $\delta\Delta H_{\mathrm{prot}}$ vs. $q_{\mathrm{N_1}}$. For all these correlations the null hypotheses considered were for the intercept $a = 0$ and for the slope $b = 0$. For relation (iii) the regression was not forced through the origin; an intercept was obtained with the least-squares treatment, but it was usually indistinguishable from zero. The null hypotheses were tested by using Student's t-test. The t values of a and b were calculated from the expressions

$$ta = (a - A)/S_a$$

and

$$tb = (b - B)/S_b$$

where A and B are variables which can be made equal to zero and S_a and S_b are the standard deviations of a and b. The calculated t values were compared with those taken from a set of t tables. If $t > t_{\mathrm{CL},n-2}$ (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.

TABLE 6

Results of the monoparametric regression analysis of $\delta\Delta H_{\mathrm{prot}}$ vs. $\delta\Delta H_{\mathrm{red}}$ for indole derivatives **1–6**

n	6
Intercept	3.98
Slope	−2.07
SD of intercept	2.81
SD of slope	0.53
SD of regression	4.76
r	0.89
nh: intercept = 0	CL < 0.95
nh: slope = 0	0.95 < CL < 0.99

TABLE 7

Results of the monoparametric regression analysis of $\delta\Delta H_{\text{prot}}$ vs. σ_p for indole derivatives **1–6**

n	6
Intercept	−0.70
Slope	18.79
SD of intercept	1.29
SD of slope	2.77
SD of regression	2.94
r	0.96
nh: intercept = 0	CL < 0.95
nh: slope = 0	0.95 < CL < 0.999

It was found that there is an insignificant relation from the statistical viewpoint between the variables $\delta\Delta H_{\text{prot}}$ and $\delta\Delta G_{\text{red}}$ (Table 5). This implies that the protonation and reduction processes are not affected in the same way by the substituents. This can be explained by the fact that the protonation process is favoured by the electron-donor substituents according to the sequence $N(Me)_2 > OMe > Me > H > Cl > Br$, while the electron-reduction process is favoured, from the free-energy point of view, by the electron-withdrawing substituents in the order $Br > Cl > H > Me > OMe > N(Me)_2$. In other words, the order of effect of the substituents in the two processes are opposite one another.

The better correlation (uncertain) between $\delta\Delta H_{\text{prot}}$ and $\delta\Delta H_{\text{red}}$ (Table 6) is due to the fact that the substituent scale which favours the reduction process from the enthalpic point of view ($H > Cl > Me > Br > OMe > N(Me)_2$) and that which favours the protonation process are not opposed to one another.

The linear regression of $\delta\Delta H_{\text{prot}}$ vs. σ_p gives prominence to substituent effects. For the derivatives **1–6**, for which the substituent constant values, σ_p, of the corresponding benzoic derivatives are reported in Table 1, a

TABLE 8

Hückel–McLachlan charge density of the radical anions of indole derivatives **1–6**

Compound	Y	Atom			
		N_1	C_2	C_3	N_{10}
1	Br	1.36484	1.03553	1.01179	1.34232
2	Cl	1.36511	1.03576	1.01215	1.34254
3	H	1.36397	1.03485	1.01054	1.34173
4	Me	1.36750	1.03765	1.01548	1.34423
5	OMe	1.36859	1.03852	1.01700	1.34501
6	$N(Me)_2$	1.37027	1.03980	1.01943	1.34618

TABLE 9

Results of the monoparametric regression analysis of $\delta\Delta H_{\mathrm{prot}}$ vs. δq_{N_1} for indole derivatives **1**–**6**

n	6
Intercept	4.42
Slope	−1.86
SD of intercept	3.89
SD of slope	0.67
SD of regression	6.08
r	0.81
nh: intercept = 0	CL < 0.95
nh: slope = 0	0.95 < CL < 0.99

significant correlation was found (Table 7). This comparison between two similar thermodynamic processes (proton dissociation of aromatic acids and protonation of polycyclic compounds) confirms that the protonation occurs in a single process.

Finally, a comparison of the protonation process with the electron density of the molecules and a comparison of the thermodynamic quantities of the reduction process with the electron density of the radical anions, also calculated using the Hückel–McLachlan method (Table 8), were made. The relations used were $\delta\Delta H_{\mathrm{red}}$ vs. $q_{\mathrm{N}_1^{\star}}$ and $\delta\Delta H_{\mathrm{prot}}$ vs. q_{N_1} where $q_{\mathrm{N}_1^{\star}}$ and q_{N_1} are the electron density on the *endo* nitrogen atom of the radical anions and the corresponding molecules, respectively, expressed as $q_{\mathrm{N}_1\mathrm{Y}} - q_{\mathrm{N}_1\mathrm{H}}$.

The relation $\delta\Delta H_{\mathrm{prot}}$ vs. δq_{N_1} is of uncertain significance (Table 9), while the relation $\delta\Delta H_{\mathrm{red}}$ vs. $\delta q_{\mathrm{N}_1^{\star}}$ is significant (Table 10). This can be explained by the fact that, according to the short-range donor–acceptor model, the interactions between the radical anions and the solvent molecules should be related to the electron density of the anions, while for neutral protonated molecules of the same compounds such a relationship does not occur [2].

TABLE 10

Results of the monoparametric regression analysis of $\delta\Delta H_{\mathrm{red}}$ vs. $q_{\mathrm{N}_1^{\star}}$ for radical anions of the indole derivatives **1**–**6**

n	6
Intercept	−0.23
Slope	1.48
SD of intercept	1.18
SD of slope	0.33
SD of regression	1.84
r	0.91
nh: intercept = 0	CL < 0.95
nh: slope = 0	0.99 < CL < 0.999

In summary, for the indole derivatives **1–6**, the electron-withdrawing substituents hinder the protonation process but favour the electroreduction process of the same compounds, while for the electron-donating groups the reverse is true. This agrees with the results of a previous study [1], where the substituents were found to affect the protonation and electro-oxidation processes of some 1-methyl-2-phenyl-3-substituted indoles in the same way. Thus it can be concluded that: (a) for the derivatives **1–6** only one proton process occurs at the endocyclic nitrogen atom; and (b) in the electro-oxidation and protonation processes of a series of compounds, the substituents show the same influence, whilst in the electroreduction and protonation processes of a series the substituents show opposite influences.

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