A Correlation between Half-wave and Ionization Potentials for Indoles and Indolizines

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Half-wave oxidation potentials ($E_{1/2}$), in acetonitrile at a platinum electrode, and gas-phase ionization potentials (P) have been measured for a number of indole and indolizine derivatives, variously substituted on the five-membered ring. Except for a few compounds, a linear correlation of P *vs.* $E_{1/2}$ was found. Deviations from linearity are discussed in terms of conformation differences between the two phases and P value uncertainties in those cases where the vibrational fine structure was resolved.

Reactions such as electrophilic substitution involving an intermediate σ-complex can occur through direct attack of the electrophile on the substrate [equation (1)],[1] or through a single-electron transfer which precedes the formation of the σ-complex [equation (2)].[2]

$$\mathrm{ArH} + \mathrm{E}^+ \longrightarrow \mathrm{Ar}^+(\mathrm{H})\mathrm{E} \longrightarrow \text{products} \qquad (1)$$

$$\mathrm{ArH} + \mathrm{E}^+ \longrightarrow [\mathrm{ArH}^{+\bullet} + \mathrm{E}^\bullet] \longrightarrow \mathrm{Ar}^+(\mathrm{H})\mathrm{E} \longrightarrow \text{products} \qquad (2)$$

In general it is difficult to ascertain which mechanism is involved. Experimental evidence from spectroscopic methods such as e.s.r. and n.m.r. (CIDNP) does not prove that electron transfer is the mechanism of the main reaction; these results could be due to side reactions.[3,4] Even the tendency of the substrate to donate its electrons, as measured by the gas-phase ionization potential (P) or the half-wave oxidation potential ($E_{1/2}$), cannot be a criterion for evaluating the feasibility of electron transfer, because the factors favouring this process are the same as those which favour the ionic mechanism. However, in cases for which it is known that the $E_{1/2}$ value refers to a reversible process, this knowledge makes it possible to calculate those thermodynamic parameters which permit one to identify the reaction mechanism.[5] The application of the Marcus theory is such an example.[6] Knowledge of the oxidation potential is more convenient also because chemists usually carry out their reactions in solution. The utility of the ionization potential derives from the fact that it can be correlated with $E_{1/2}$; thus one of the two parameters can be calculated when the other is available.

It has been known for years that there is an excellent correlation between the solution $E_{1/2}$ value for a variety of aromatic systems and the HOMO (highest occupied molecular orbital) energy, as estimated from molecular orbital calculations.[7] Accurate linear correlations between the vapour-phase ionization potentials and the solution-phase $E_{1/2}$ values were found by Miller and his co-workers[8a] and Nelsen[8b] for a wide range of compounds.

The present paper deals with the correlation between vertical ionization potential (P_v) and $E_{1/2}$ values for a large series of indole and indolizine derivatives, the re-investigated electrophilic substitution reactions of which have been interpreted in terms of an electron-transfer process.[9]

Experimental

Compounds (**1**)—(**15**)[7a,c,d] and (**16**)—(**27**)[7d] were prepared according to literature procedures.

Electrochemical Measurements.—The half-wave oxidation potentials were obtained by recording the corresponding voltamperograms with a three-electrode multipolarograph (Amel 471). The reversibility of the oxidation process was tested by recording the cyclic voltamperograms with an oscillographic plarograph (Amel 448). The working electrode was a pulsed[10] platinum disc (Amel 492) of about 1 mm diameter. The reference electrode assembly was Ag/0.1M-$AgClO_4$–MeCN//fine porosity fritted glass disk. A platinum wire served as the counter-electrode. MeCN (Erba, spectrophotometric grade), used as solvent, was purified by distillation over CaH_2, P_2O_5, and then CaH_2 again. Et_4NClO_4 (Erba, RS grade for polarography) was vacuum dried at 60 °C for 3 days. Argon (99.99%) was used to deoxygenate the test solutions. The temperature (20 °C) was kept constant within 0.1 °C. For all the examined compounds the first half-wave oxidation potential was found to be independent of concentration in the range used (0.8—1.3 × 10^{-3} M) and was measured to an accuracy of ±0.005 V.

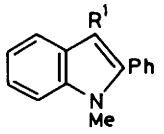
Ionization Potential Measurements.—The He^{I} photoelectron spectra were recorded by means of a Perkin-Elmer PS18 spectrometer. The spectra were calibrated with noble gas lines; reproducibility was better than ±0.05 eV. The reported values are the vertical ionization potentials (P_v) which correspond to the band maxima.

Results and Discussion

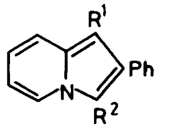
The Table lists the oxidation half-wave potentials ($E_{1/2}$) and the vertical ionization potentials (P_v) of the indoles (**1**)—(**15**) and the indolizines (**16**)—(**27**).

Indoles (**1**)—(**15**).—In dry MeCN (with Et_4NClO_4 as supporting electrolyte) all the examined compounds exhibited two or more successive oxidation steps at the pulsed platinum disc. In each case, the first oxidation step, the value for which is

Table. Half-wave oxidation potentials ($E_{1/2}$) and vertical ionization potentials (P) of the indoles (**1**)—(**15**) and the indolizines (**16**)—(**27**)



(1)-(15)



(16)-(27)

Compound	R^1	R^2	$E_{1/2}$/V	P/eV
(**1**)	MeC=CHMe		0.425	7.11
(**2**)	MeC=CH$_2$		0.515	7.31
(**3**)	SMe		0.515	7.44
(**4**)	Me		0.550	7.29
(**5**)	CH$_2$Ph		0.580	7.28
(**6**)	CH$_2$OH		0.655	7.57
(**7**)	CH(OH)Ph		0.680	7.45^a
(**8**)	SPh		0.670	7.45
(**9**)	N$_2$Ph		0.695	7.47^a
(**10**)	H		0.645	7.44
(**11**)	NO		0.725	7.50
(**12**)	Cl		0.765	7.50
(**13**)	CHO		1.085	7.94
(**14**)	COMe		0.960	7.74
(**15**)	NO$_2$		1.290	8.17
(**16**)	H	Me	0.215	7.07
(**17**)	SMe	Me	0.235	7.06
(**18**)	SPh	Me	0.310	7.00
(**19**)	N$_2$Ph	Me	0.325	6.88
(**20**)	COMe	Me	0.540	7.25
(**21**)	CHO	Me	0.610	7.38
(**22**)	H	H	0.400	7.15
(**23**)	Me	H	0.220	7.12
(**24**)	Me	SPh	0.345	7.00
(**25**)	Me	N$_2$Ph	0.360	6.85
(**26**)	Me	COMe	0.570	7.30
(**27**)	Me	CHO	0.650	7.42^a

^{a} Calculated by equation (5).

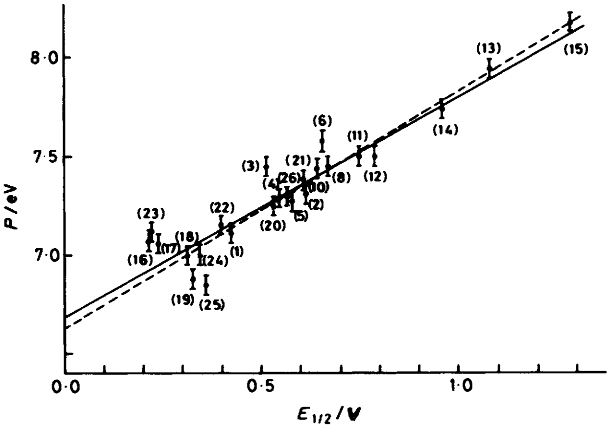


Figure. Plot of P_v against $E^3{}_{1/2}$ for the indoles (**1**)—(**15**) and the indolizines (**16**)—(**27**); the solid and dashed lines correspond to equations (5) and (6), respectively

reported in the Table, has a height corresponding to the release of about one electron per molecule of reactant. The wave slope ($E_{3/4} - E_{1/4}$) is in the 58—68 mV range, in agreement with the value (56 mV) expected for a mono-electronic reversible process. As shown in the Table, marked changes occur in the first half-wave oxidation potential of 1-methyl-2-phenylindole (**10**) when substituents are added at C-3. In fact, the $E_{1/2}$ value decreases with electron-donating groups and increases with electron-accepting groups.

To test the reversibility of the first oxidation step of the indoles studied, cyclic voltamperograms with potential-scan rates in the 0.1—10 V s^{-1} range were recorded at a stationary platinum electrode. The voltamperograms of the indole (**11**) exhibit an anodic–cathodic system (i.p.$_a$ ≈ i.p.$_c$), *i.e.* the primary one-electron oxidation product (radical cation) is stable during the time of the measurements; thus the charge transfer proves to be reversible even at a scan rate as low as 0.1 V s^{-1}. For the indoles (**3**) and (**8**) the corresponding one-electron oxidation product is quite unstable. In fact, a substantial reverse cathodic peak, corresponding to the anodic peak, also appears at 0.1 V s^{-1}, but i.p.$_a$ $\gg$ i.p.$_c$. In the voltamperograms of all other indoles the reverse cathodic peaks were not observed even at scan rates as high as 10 V s^{-1}.

The assignment of the photoelectron spectra of the 1-methyl-2-phenyl-3-R^1-indoles is based on that of *N*-methylindole. In the latter, the first two bands (7.71 and 8.36 eV) were assigned to π-MOs delocalized over all the molecules.[11] The slightly lower values (7.44 and 7.96 eV) observed for *N*-methyl-2-phenylindole (**10**) are due to the interaction of the symmetric π-MOs of the benzene ring at C-2 with those of the indole nucleus. Distortion from planarity does not allow the phenyl group to exert all its mesomeric effect. For the same reason, the HOMO energy is only slightly further reduced by electron-releasing substituents at C-3. Conversely, P_v values increase with the mainly inductive electron-withdrawing power of the substituent at C-3. In fact the CHO, COMe, and NO$_2$ substituents [see compounds (**13**)—(**15**)] can exert an inductive stabilizing effect (0.50, 0.30, and 0.73 eV, respectively) similar to that shown on the HOMO of the corresponding monosubstituted benzenes (CHO: 0.30 eV;[12] COMe: 0.31 eV;[13] NO$_2$: 0.75 eV[14]).

Indolizines (**16**)—(**27**).—In dry MeCN at a pulsed platinum anode all the indolizines studied exhibit a single step or several successive steps. The height of the first oxidation wave involves about one electron with a slope ($E_{3/4} - E_{1/4}$) in the 45—70 mV range, showing that in some cases the electron transfer may be complicated by a subsequent chemical reaction. The half-wave data in the Table show that indolizines are oxidized at potentials less positive than those of indole derivatives. This result agrees with the higher basicity of the indolizines[15] with respect to that of indoles.[16] As has been observed for indoles, the oxidation potentials of indolizines are affected by the nature of the substituents and increase with their electron-withdrawing power. The small differences found in the oxidation potentials of isomer pairs (**16**)/(**23**), (**18**)/(**24**), and (**19**)/(**25**) reflect the differences encountered in the electrophilic substitutions.[17] The cyclic voltammetric experiments show that the first one-electron primary oxidation product is quite unstable. In fact, the voltamperograms with scan rates in the 0.1—10 V s^{-1} range do not show a substantial cathodic peak.

In analogy with indoles, the first two bands in the photoelectron spectra can be ascribed to π-MOs delocalized on the condensed rings with a minor contribution from the C-2 phenyl group orbitals. In particular, the HOMO recalls the πa$_2$(HOMO) orbital of pyrrole. This is confirmed by the vibrational fine structure of the first band (*ca.* 0.17 eV), which is similar to that in the spectra of pyrrole and its derivatives.[18]

Correlation between P$_v$ *and* E$_{1/2}$ *Values.*—In the Figure the P_v values are plotted against the corresponding $E_{1/2}$ data, giving an approximately linear correlation. This correlation derives from the fact that the half-wave oxidation potentials ($E_{1/2}$) for an electrode process involving the loss of one electron [equation (3)] can be correlated with ionization potentials[19,20] by the simplified expression of equation (4).

$$\mathrm{ArH} \longrightarrow \mathrm{ArH}^{+\bullet} + \mathrm{e} \qquad (3)$$

$$E_{1/2}(\mathrm{ox}) = P + \Delta F_{\mathrm{solv}} + \mathrm{K} \qquad (4)$$

In equation (4), P is the ionization potential of ArH, ΔF_{solv} represents the difference in solvation free energies between ArH and its radical cation $\mathrm{ArH}^{+\bullet}$, and K is a constant which includes various factors, *viz.* the activity and diffusion coefficients of both species ArH and $\mathrm{ArH}^{+\bullet}$ and the types of the working and reference electrodes used in the measurement of $E_{1/2}$. Under the same experimental conditions, if ΔF_{solv} is constant within a series of compounds, or if it is an approximately linear function of P, a linear correlation between $E_{1/2}(\mathrm{ox})$ and P is to be expected. The least-squares method applied to the values reported in the Figure gives equation (5) (correlation coefficient $\rho = 0.95$), in good agreement with those previously described.[6,9]

$$P_{\mathrm{v}} = 6.69 + 1.124\, E_{1/2} \qquad (5)$$

$$P_{\mathrm{v}} = 6.63 + 1.190\, E_{1/2} \qquad (6)$$

Equation (6) (correlation coefficient $\rho = 0.99$) was calculated with exclusion of compounds (**3**), (**6**), (**16**), (**17**), (**19**), (**23**), and (**25**), which show the highest deviations. It is difficult to provide an exhaustive explanation of the deviations from linearity. However, in some cases they could be due to variations in electronic structure, derived from different experimental conditions (gas-phase and solution). In addition, the spacing and the intensity distribution of the components of the vibrational structure present in the first photoelectron spectral band of the indolizines change with the substituent. As a consequence, in some cases the P_{v} values nearly coincide with the centroid of the band, while in other cases, the vertical and adiabatic (first vibrational component) P values are equal. This could explain at least in part why the indolizine points in the Figure are more scattered from the correlation line than those of indoles. This worse correlation, however, does not seem to be connected with experimental errors in the measurements. In fact, both $E_{1/2}$ and P_{v} values are very similar for positional isomers where R^1 is exchanged for R^2.

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