Radical Cations. Part 2.[1] Oxidative Dimerization of Indolizines: A Chemical and Electrochemical Investigation

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3-Unsubstituted indolizines undergo oxidative dimerization in the presence of catalytic amounts of Fe^{III} and oxygen. Although much experimental evidence apparently indicates that Fe^{II} is reoxidised to Fe^{III} by oxygen, a chain mechanism cannot be envisaged. A chain sequence can be proposed only in the case where a stoicheiometric amount of Fe^{III} is used.

In the last decade much work has been done on the oxidation of organic compounds by metal ions.[2] In many cases Fe^{III} has been shown to act catalytically; but the suggestion that Fe^{II} is reoxidised by atmospheric oxygen is controversial.[3,4]

In the present paper we describe the oxidative dimerization of indolizines by both catalytic and stoicheiometric amounts of Fe^{III}, and discuss the importance of oxygen in the catalytic reaction.

Chemical and electrochemical investigations of the radical cation intermediates have been carried out in order to elucidate the behaviour of these radical species, which in general show multifold reactivity.

Results and Discussion

The indolizines (1a—d), oxidized in acetonitrile with 10% of the stoicheiometric quantity of Fe^{III}† at room temperature in the presence of oxygen, formed the corresponding 3,3'-dimers (2a—d), which were isolated in 75—96% yield. On the basis of our results,‡ this method is much more convenient than that previously described.[5]

To gain a better understanding of the reactions involved we carried out some experiments with the typical indolizine (1b). When this compound was treated with the stoicheiometric amount of Fe^{III}, the corresponding dimer hydrochloride (2b)·2HCl could be isolated in 60% yield irrespective of the presence of oxygen. On the other hand, (2b) was obtained in 66% yield upon stirring (1b) with only 10% of the stoicheiometric amount of Fe^{II} in the presence of oxygen, and, significantly, the yield of (2b) dropped to 10% when (1b) was treated with 10% of the stoicheiometric amount of Fe^{III} in a nitrogen atmosphere. This is a clear indication that oxygen is involved in this reaction. The oxygen pressure drop, which followed an exponential curve, was measured; the amount of oxygen consumed was *ca.* 50% of that calculated on the basis of equation (1) stoicheiometry. Thus it appears that the reaction requires oxygen when carried out with a catalytic amount of Fe^{III}; the oxidation potential of the redox system Fe^{III}/Fe^{II},§ which is more positive than those of the indolizines studied (Table), is apparently sufficient.
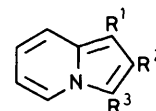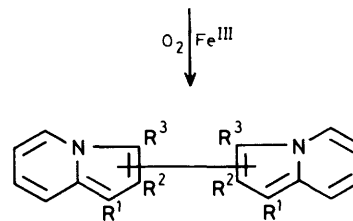
Table. Voltammetric data relative to the oxidation of the indolizines (1a—d) at a pulsed platinum electrode in MeCN containing 0.1 mol dm^{-3} Et_4NClO_4

Compd.	$E_{1/2}/V$	$i_1/\mu A$	$(i_1/c)/\mu A$ $mmol^{-1}$ dm^{-3}
(1a)	0.13	5.85	4.99
(1b)	0.22	5.60	4.87
(1c)	0.27	4.95	5.02
(1d)	0.29	5.10	4.90
(1e)	0.22	4.85	4.19

(1)

a; $R^1 = R^2 = Me$ $R^3 = H$
b; $R^1 = Me$ $R^2 = Ph$ $R^3 = H$
c; $R^1 = Me$ $R^2 = C_6H_4Me$-(p) $R^3 = H$
d; $R^1 = Me$ $R^2 = C_6H_4NO_2$-(p) $R^3 = H$
e; $R^1 = H$ $R^2 = Ph$ $R^3 = Me$

(2)

$$2HIn + \tfrac{1}{2}O_2 \longrightarrow In-In + H_2O \quad (1)$$

$$HIn \longrightarrow HIn^{+\cdot} + e \quad (2)$$

$$HIn^{+\cdot} + HIn \longrightarrow HIn-HIn^{+\cdot} \quad (3)$$

$$HIn-HIn^{+\cdot} + HIn \rightleftharpoons HIn-HIn + HIn^{+\cdot} \quad (4)$$

$$HIn + Fe^{III} \longrightarrow HIn^{+\cdot} + Fe^{II} \quad (5)$$

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† Sources of Fe^{III} and Fe^{II} were $FeCl_3$ and $FeCl_2$, respectively.
‡ The yields reported here were obtained with 0.1 mol dm^{-3} solutions of the starting indolizine (see Experimental section).
§ For $Fe^{III} + e \longrightarrow Fe^{II}$, $E_{\frac{1}{2}} = 1.1$ V *vs.* s.c.e. at a rotating platinum electrode in MeCN.[6]

$$HIn-HIn^{+\bullet} + Fe^{III} \longrightarrow HIn-HIn^{2+} + Fe^{II} \qquad (6)$$

$$2HIn^{+\bullet} \longrightarrow HIn-HIn^{2+} \qquad (7)$$

HIn = indolizine; In–In = dimer

The foregoing results seem to be in agreement with the oxidation of Fe^{II} to Fe^{III} by oxygen. Since this inference contrasts with previous reports,* an experiment was carried out on (1b) with a catalytic amount of Ce^{IV} in the presence of oxygen. In this case, reoxidation of Ce^{III} to Ce^{IV} by oxygen cannot occur, and only traces of the dimer (2b) were isolated. Although this result indirectly confirms that the reoxidation of Fe^{II} to Fe^{III} by oxygen is likely, we cannot put forward a clear chain mechanism proposal for reactions in the presence of oxygen with a catalytic quantity of Fe^{III}. Only in the case where a stoicheiometric quantity of $FeCl_3$ was used can the mechanism shown in equations (5), (3), and (6) be safely assumed. In view of the uncertainties of the chemical study, an electrochemical investigation was performed.

In the range of concentration used (10^{-4}—10^{-2} mol dm^{-3}) the indolizines (1a—e) in MeCN, with Et_4NClO_4 as supporting electrolyte, exhibited, at a pulsed platinum electrode,[8] a well defined oxidation step at potentials between 0.13 and 0.29 V (Table), followed by two successive ill-defined steps at high anodic potentials (1.7—2.1 V) near to background. A comparison of the i/c values reported in the Table with the corresponding values determined under the experimental conditions used for the reversible one-electron oxidation of 2,2-disubstituted 3-oxoindolin-1-oxyls,[9] allows us to conclude that the number of electrons involved in the first oxidative step [equation (2)] of the indolizines (1a—d) is $ca.$ 1 ($n = 1$).

The cyclic voltammetric experiments at a stationary platinum electrode show that the primary oxidation product (the radical cation $HIn^{+\bullet}$) is unstable. In fact, cyclic voltamperograms recorded with a potential span from -0.40 to 0.70 exhibit a small reverse cathodic peak, corresponding to the oxidation peak, only when the sweep rate is kept greater than 20 V s^{-1}. Below this value no reducible radical cation ($HIn^{+\bullet}$) was observed; this could be because $HIn^{+\bullet}$ undergoes a fast reaction with an HIn molecule [equation (3)] or dimerizes [equation (7)].†

Typical behaviour at very low sweep rate (0.1 V s^{-1}) of the model indolizine (1b) is shown in the Figure. In the first cyclic sweep from -0.4 to 0.7 V the irreversibility of the one-electron oxidation step was observed [Figure (a)]. If the working electrode was polarized for 5—10 s at 0.70 V and then the sweep was resumed from 0.7 to -0.4 V, a new anodic peak at less positive potential with respect to that of (1b) was observed [Figure (b)]. This new peak was attributed to the first oxidation step of the dimer (2b), since it increased when small amounts of (2b) were added and, above all, since a solution containing a small quantity of (2b) gave the same voltamperogram [Figure (c)]. In the case of the indolizine (1e) only, the cyclic voltammetric experiments do not prove the formation of the corresponding dimer (2e) at the electrode. In the sweep
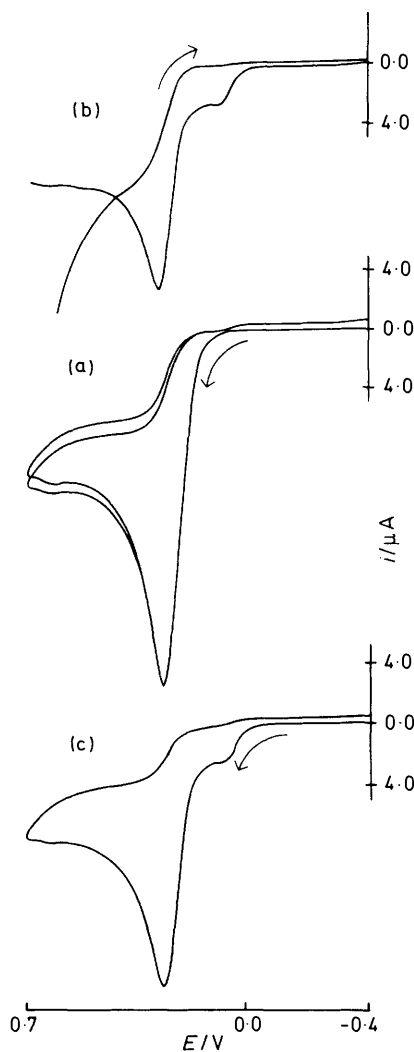
Figure. Cyclic voltamperograms of the indolizine (1b) in MeCN containing 0.1 mol dm^{-3} Et_4NClO_4 (sweep rate 0.1 V s^{-1}; arrowhead indicates direction of sweep): (a) solution containing 2.02×10^{-3} mol dm^{-3} indolizine (1b); (b) as (a) but recorded with the potential held at 0.70 V for 10 s and then the sweep resumed from 0.70 to -0.40 V; (c) solution containing 1.39×10^{-3} mol dm^{-3} indolizine (1b) plus 0.09×10^{-3} mol dm^{-3} dimer (2b)

range examined (0.1—150 V s^{-1}), the parameters of the oxidation peak of the indolizines (1a—e) meet diagnostic criteria for a reversible charge transfer followed by a very rapid and irreversible chemical reaction;[10] thus a mechanism like that shown in equation (2), (3), or (7) could be suggested for the electrode process. The rate-determining step in the formation of the dimers is the loss of protons from the dihydro dication ($HIn-InH^{2+}$). This assumption is based on the number of electrons ($1 < n < 2$) involved either in the controlled potential electrolysis or in the voltammetric curves of (1a—d) in MeCN containing a base such as picoline.

The low rate of proton loss from the dihydro dication $HIn-InH^{2+}$ could be due to the high basicity of the dimer, which in general is as basic as the monomer (pK_a $ca.$ 6.0).[11] This could also explain why the radical cations ($In-In^{+\bullet}$) are not observed when indolizines are oxidized with $I_2-AgClO_4$ in MeCN inside the e.s.r. spectrometer cavity. However the same experiment was successful for compounds with a low basicity such as indoxyls,[1] the dihydro dications of which are deprotonated by any base present in solution or by the solvent itself.

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* In acetonitrile as solvent, oxygen gives two reduction waves, both at much more negative potentials than in water (-0.75 and -1.4 V vs. s.c.e. at the dropping mercury electrode). The relatively negative reduction potential of oxygen in MeCN can be attributed to the extremely weak acidic properties of MeCN.[7]

† In this case the most probable mechanism of dimerization involves the coupling of two radical cations [equation (6)] as a result of the high concentration of the radical cation on the electrode surface; dimerization in oxidation by a catalytic amount of Fe^{III} probably occurs as shown in equation (3), as the concentration of the radical cation is lower than that of the corresponding free base.

The electrochemical results suggest that the oxygen radical anion formed during the chemical oxidative dimerization could be the chemical species responsible for deprotonation of the dihydro dication ($HIn-InH^{2+}$) and that the reoxidation of Fe^{II} to Fe^{III} is feasible on the basis of the formation of a complex between indolizines and/or dimers and the systems Fe^{III}/Fe^{II} and O_2/O_2^-, which is not detectable by chemical or electrochemical methods owing to the high reactivity of indolizines vs. Fe^{III}.

The orientation of electrophilic substitution in indolizines and substituted indolizines appears to depend on the reagent and the conditions,[12] but in general it occurs at C-3[13] or C-1.[14] On the basis of the reactivity noted here, we would have expected the indolizine (1e) [isomeric with (1b)] would form the corresponding 1,1'-dimer (2e); however the formation of (2e) was never observed by either chemical or electrochemical methods; the reasons for this remain unclear.

Experimental

I.r. spectra were recorded with a Perkin-Elmer 257 spectrometer. [1]H N.m.r. spectra were recorded with a Varian XL-100 spectrometer (Me_4Si as internal standard) and e.s.r. spectra with a Varian E4 spectrometer. Mass spectra were recorded with a Varian 112-S apparatus. H.p.l.c. determinations were performed with a Perkin-Elmer series 3 apparatus and a column of C18 SIL-X-10. The indolizines (1a),[15] (1b),[16] (1d),[12] and (1e)[17] were prepared as described in the literature.

1-*Methyl*-2-p-*tolylindolizine* (1c).—*p*-Methylphenacyl bromide[18] (11 g) and 2-ethylpyridine (5.4 g) were heated at 80 °C with stirring until 2-ethyl-1-(*p*-methylphenacyl)-pyridinium bromide was obtained, as a colourless solid (70%), m.p. 185 °C (from ethanol–diethyl ether); $\delta_H(CDCl_3)$ 1.33 (3 H, t, CH_2CH_3), 2.4 (3 H, s, CH_3), 2.63 (2 H, s, CH_2), 3.05 (2 H, q, CH_2CH_3), 6.9—8.7 (4 H, m, ArH), and 9.42 (2 H, d, ArH) (Found: C, 60.25; H, 5.45; N, 4.5. $C_{16}H_{18}BrNO$ requires C, 60.0; H, 5.7; N, 4.4%). This pyridinium salt (11 g) and $NaHCO_3$ (5 g) were refluxed in water (100 ml) for 40 min; the mixture was then cooled to room temperature and extracted with benzene (2 × 100 ml). The organic layer was separated, dried (Na_2SO_4), and evaporated to dryness. The residue was directly crystallized from light petroleum (b.p. 60—80 °C) to give the *product* (1c) (80%), m.p. 84 °C; $\delta_H(CDCl_3)$ 2.35 (6 H, d, 2 Me), 6.1—6.55 (3 H, m, ArH), and 7.03—7.8 (6 H, m, ArH) (Found: C, 86.8; H, 6.85; N, 6.15. $C_{16}H_{15}N$ requires C, 86.3; H, 6.8; N, 6.3%).

Oxidation of 1,2-*Disubstituted Indolizines* (1a—d) *with a Catalytic Amount of Iron*(III) *Chloride and Oxygen.*—The indolizine (2 mmol) and $FeCl_3$ (0.2 mmol) in MeCN (7 ml) were stirred at room temperature for 1 h in a current of oxygen. The crystalline precipitate, corresponding to nearly pure 3,3'-dimer, was filtered off. The yields reported in the Table refer to the precipitate. A small additional amount (2—10% of theoretical) could be recovered by chromatographing the filtrate on a SiO_2 column with benzene–light petroleum (7:3) as eluant. A similar reaction in a current of nitrogen gave the dimer (2b) in only 10% yield.

The *dimer* (2a) (75%) had m.p. 150 °C (from acetonitrile) $\delta_H(CDCl_3)$† 2.1 (6 H, s, 2 Me), 2.38 (6 H, s, 2 Me), 6.2—6.4 (2 H, t, ArH), 6.56—6.92 (2 H, m, ArH), and 7.1—7.57 (4 H, m, ArH); m/z 288 (M^+, 100%), 274 (18), 253 (5), and 208 (10) (Found: C,

83.35; H, 7.15; N, 9.4; M^+, 288. $C_{20}H_{20}N_2$ requires C, 83.3; H, 7.0; N, 9.7%; M, 288.38).

The *dimer* (2b) (96%) had m.p. 242 °C (lit.,[20] 242 °C; lit.,[5] 244—246 °C); [1]H n.m.r. in agreement with that reported;[5] m/z 412 (M^+, 100%), 395 (9), 332 (11), 315 (5), 303 (5), 215 (14), and 204 (25) (Found: M^+, 412. Calc. for $C_{30}H_{24}N_2$: M, 412.5).

The *dimer* (2c) (79%) had m.p. 235 °C [from benzene–light petroleum (b.p. 60—80 °C)] $\delta_H(CDCl_3)$* 2.26 (6 H, s, 2 Me), 6.16—6.4 (2 H, t, ArH), 6.5—7.0 (6 H, m, ArH), and 7.17—7.56 (8 H, m, ArH); m/z 440 (M^+, 100%), 425 (7), 362 (11), 232 (12), and 220 (25) (Found: C, 87.3; H, 6.45; N, 6.3%; M, 440. $C_{32}H_{28}N_2$ requires C, 87.2; H, 6.4; N, 6.4%; M, 440.56).

The *dimer* (2d) (20%) had m.p. 300 °C (from benzene) $\delta_H(CDCl_3)$ 2.38 (6 H, s, 2 Me), 6.4—7.0 (6 H, m, ArH), 7.2—7.56 (6 H, m, ArH), and 7.92 (4 H, d, ArH); m/z 502 (M^+, 71%), 273 (42), and 194 (100) (Found: C, 71.65; H, 4.35; N, 11.2%; M, 502. $C_{30}H_{22}N_4O_4$ requires C, 71.7; H, 4.4; N, 11.15%; M, 502.51).

Dimerization of the Indolizine (1b) *with Iron*(II) *Chloride in the Presence of Oxygen.*—Compound (1b) (2 mmol) and $FeCl_2$ (0.2 mmol) in MeCN (7 ml) were stirred at room temperature in a current of oxygen. After 1 h the dimer (2b) was filtered off (273 mg, 66%).

Oxidation of the Indolizine (1b) *with a Catalytic Amount of Iron*(III) *Chloride under Nitrogen.*—The indolizine (1b) (5 mmol) and $FeCl_3$ (0.5 mmol) in MeCN (15 ml) were stirred at room temperature for 1 h in a current of nitrogen. From the intense green solution the dimer (2b) (90 mg) was filtered off under vacuum. From the filtrate, by chromatography [SiO_2; light petroleum–ethyl acetate (95:5)] a further 10 mg of dimer (2b) (10%) was isolated, together with 850 mg of starting indolizine (1b).

Oxidation of the Indolizine (1b) *with a Stoicheiometric Amount of Iron*(III) *Chloride* $FeCl_3$ *in Air or under Nitrogen.*—The indolizine (1b) (5 mmol) and $FeCl_3$ (5 mmol) in MeCN (15 ml) were stirred at room temperature for 1 h in air. When the $FeCl_3$ was added to the solution, an intense red-violet colour appeared and a yellow precipitate was formed. After 30 min, the precipitate [dimer hydrochloride (2b)·2HCl] was filtered off, washed with MeCN (yield 610 mg; m.p. > 300 °C) and identified by comparison with an authentic sample. An identical result was obtained when the reaction was performed under nitrogen.

The Dimer (2b) *Hydrochloride.*—A solution of (2b) (100 mg) in $CHCl_3$ (5 ml) was saturated with gaseous HCl. The hydrochloride (2b)·2HCl was precipitated by adding dried Et_2O, filtered off under vacuum, and washed with MeCN; yield 98 mg, m.p. > 300 °C; $v_{max.}$ 700, 718, 735, 775, and 1 345 cm^{-1}.

Measurement of Oxygen Absorbed in the Reaction of the Indolizine (1b) *with a Catalytic Amount of Iron*(III) *Chloride.*—The reaction was performed in a round flask (100 ml) equipped with a pressure-equalized dropping funnel (10 ml) and connected to a U-tube containing $CHBr_3$ (d_4^{20} 2.84 g cm^{-3}). Solutions of (1b) (5 mmol) in MeCN (15 ml) and $FeCl_3$ (0.5 mmol) in MeCN (3 ml) were placed in the flask and the funnel, respectively. The apparatus was filled with compressed air until the barometric gradient was about 130 mmHg of $CHBr_3$, and the flask was maintained thermostatically at 25 °C. When the reaction was initiated by adding the $FeCl_3$ solution, absorption of oxygen started. Pressure was monitored against time. After 70 min the absorption of oxygen stopped and the precipitated dimer (2b) was filtered off under vacuum. In three different runs the average yield was 86% and the oxygen absorbed was 50% of the stoicheiometric quantity calculated on the basis of equation (1).

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* The dimers (2a) and (2c) in $CDCl_3$ undergo slight oxidation and the resulting traces of the corresponding radical cation give rise to the equilibrium $In-In \rightleftharpoons In-In^{+\bullet} + e$ (In = ·ndolizinyl), which compromises the resolution in the [1]H n.m.r. spectrum. A well resolved spectrum was obtained by adding traces of phenylhydrazine. This phenomenon has been described previously.[19]

Oxidation of the Indolizine (**1b**) *with a Catalytic Amount of Cerium*(IV).—Cerium ammonium nitrate (0.5 mmol) was added to a solution of (**1b**) (5 mmol) in MeCN (15 ml) and the mixture was stirred in air at room temperature for 1 h. No precipitate was formed. H.p.l.c showed that the dimer (**2b**) was present only in traces (<3%), main constituent being the starting indolizine (**1b**). [The mixture of (**1b**) and (**2b**) was separated at 45 °C (flow rate 2 mol min⁻¹, MeOH–H₂O 93:7, λ 254 nm)].

Electrochemical Measurements: Apparatus and Procedures.— A three-electrode multifunction assembly (Amel 471) was employed for the voltammetric measurements at low scan rate. The working electrode was a pulsed (or stationary, in the case of linear-sweep voltammetry) platinum disc (Amel 492) of about 1 mm diameter. Before each experiment, the disc was polished with 0.05 μm polishing alumina, washed with distilled water and acetone, and finally rubbed gently with a paper towel. The reference electrode assembly was Ag/0.1 mol dm⁻³ AgClO₄– MeCN/fine porosity glass disc/0.1 mol dm⁻³ Et₄NClO₄– MeCN/fine porosity glass disc. The counter electrode was a platinum wire. Cyclic voltammetric experiments at higher scan rate (faster than 0.2 V s⁻¹) were performed with an oscillopolarograph (Amel 448), with the same cell as the measurements at low scan rate. Coulometric determinations at controlled potential were carried out by means of a potentiostat (Amel 552), coupled with an integrator (Amel 721) and a recorder (Amel 867). The electrolysis cell contained a platinum gauze cylinder (1.5 cm diam.) as working electrode and a platinum spiral as auxiliary electrode, separated by a sintered-glass disc.

Acknowledgements

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