1,4-Diamino-and 1,4-Dibutylamino-anthraquinones: Reduction and/or Deprotonation-initiated Elimination of the Butyl Groups in Dipolar Aprotic Media

Agnès Anne
Laboratoire Chimie Analytique (UA CNRS 484), Faculté Pharmacie, Université Paris V, 4 Ave Observatoire, 75270 Paris Cedex 06, France

The standard redox potentials of the one- and two-electron reductions of the title compounds have been determined. The deprotonated form of the dibutylamino compound underwent a base-initiated elimination of the butyl groups and the basicity of the radical anion resulting from one-electron reduction was sufficient to provoke the same type of cleavage through an initial father–son reaction. A multi-step mechanism is proposed for the elimination on the basis of the identification of intermediates.

Previous papers[1,2] reported the redox and acid-base reactivity of anthraquinones with hydroxy and/or methoxy substituents at positions 1, 4, 5, and/or 8 *peri* to the quinonoid carbonyl groups, *i.e.* at positions which allow the strongest interactions between the substituents and the carbonyl groups. Those substituted anthraquinones and iminoanthraquinones are of interest in the field of synthetic dyes and can also be considered as redox models of anthracyclines, a class of effective antitumour drugs.

Anthraquinone rings with amino groups are the main fragments in a large group of anthraquinone dyes and they have been recently used in anticancer drug design,[3,4] for example in the cases of ametantrone [1,4-bis-({2-[(2-hydroxyethyl)-amino]ethyl}amino)anthraquinone] and mitoxantrone [5,8-dihydroxy-1,4-bis-({2-[(2-hydroxyethyl)amino]ethyl}amino)-anthraquinone]. As part of a systematic study of the ability of anthraquinone derivatives to generate reactive species through reductive and/or basic activation, the present work reports the electrochemical reduction of 1,4-diamino-[$AQ(NH_2)_2$] and 1,4-dibutylaminoanthraquinone [$AQ(NHBu)_2$] and the stabilities of the conjugate bases of these compounds in dipolar aprotic solvents. While $AQ(NH_2)_2$ exhibits behaviour similar to that of 1,4-dihydroxyanthraquinone, it appears that the deprotonated form of $AQ(NHBu)_2$ undergoes multi-step elimination of the butyl groups and that this elimination can also be initiated by the one-electron reduction of $AQ(NHBu)_2$.

The excitation and measurement techniques used in this work included cyclic voltammetry, controlled-potential electrolysis, u.v.–visible spectrometry and spectroelectrochemistry, h.p.l.c., t.l.c., ^{1}H n.m.r., and mass spectrometry.

Experimental

Compounds.—1,4-Diaminoanthraquinone, *N,N*-dimethylformamide (DMF), acetonitrile (ACN), and tetraethylammonium perchlorate (TEAP) were obtained from Aldrich, Merck (Uvasol purity grade), SDS (Chromatosol 230), and Fluka, respectively. A stock solution of 0.1M-tetrabutylammonium hydroxide (TBAH) in propan-2-ol was obtained from Fluka and stored under argon. Other reagent-grade chemicals were from Prolabo. All chemicals were used as received.

Apparatus and Procedures.—The apparatus and procedures for electrochemical studies were identical with those previously described.[1]

H.p.l.c. was performed with a Kontron model T-414 pump and a Waters model 481 u.v.-visible detector set at 574 nm. A Waters Nova-Pak reverse-phase steel column (C_{18}, 4 μm, 15 × 0.3 cm) preceded by a Waters Guard-Pak guard column was employed for h.p.l.c. studies. The mobile phase was 70% ACN—30% H_2O. Before analysis, samples in DMF were diluted tenfold with the mobile phase. Typically 20 portions (20 μl) were injected onto the h.p.l.c. system and eluted at a flow rate of 1.0 ml min^{-1}. Yields of products resulting from reaction of 1,4-dibutylaminoanthraquinone in basic DMF were determined from measurements of h.p.l.c. peak areas corrected for variations in the extinction coefficients at 574 nm among the components.

Preparative t.l.c. was performed on Merck silica gel 60 precoated plates (2 × 20 × 20 cm).

Electron-impact (EI; 70 eV) and chemical-ionization (CI; NH_3) mass spectrometry were performed on a Riber R10-10C spectrometer.

^{1}H N.m.r. spectra (270 MHz) were obtained with a Bruker WM-270 instrument using $CDCl_3$ as solvent and $SiMe_4$ as internal standard. Coupling constants are those observed (uncorrected for non-first-order behaviour).

1,4-*Dibutylaminoanthraquinone* [$AQ(NHBu)_2$].—$AQ(NHBu)_2$ was prepared by the procedure given in the literature,[5] *m/z* (CI) 351 (MH^+, 100%); (EI) 350 (M^+, 85) and 307 (M^+—$CH_3CH_2CH_2$, 100); δ($CDCl_3$) 1.0 (t, 6 H, *J* 7.5 Hz, 2 × CH_3), 1.55 (sextet, 4 H, *J* 7.5 Hz, 2 × CH_2CH_3), 1.78 (quintet, 4 H, *J* 7.5 Hz, 2 × $CH_2CH_2CH_3$), 3.43 (q, 4 H, *J* 6 Hz, 2 × $ArNCH_2$), 7.27 (s, 2 H, H-2 and -3), 7.69 (dd, 2 H, *J* 6, 3.5 Hz, H-6 and -7), 8.27 (dd, 2 H, *J* 6, 3 Hz, H-5 and -8), and 10.84 (br s, 2 H, 2 × $NHCH_2$, D_2O exchangeable; $\lambda_{max.}$(DMF) 560 (ε 7 700 l mol^{-1} cm^{-1}), 595 (16 000), and 644 nm (19 400); h.p.l.c. (chromatographic conditions are given above) t_R 28.8 min.

1-*Amino*-4-*butylaminoanthraquinone* [$AQ(NH_2)(NHBu)$] (**1**).—To a solution of $AQ(NHBu)_2$ (35 mg, 0.1 mmol) in DMF (100 ml), thoroughly deaerated with argon, a deaerated 0.1M-TBAH solution in propan-2-ol (3 ml) was added with stirring and argon bubbling. The colour of the solution immediately turned from deep blue to red-brown. The mixture was maintained as anaerobic for 30 s and was then stirred in the presence of air until a blue-purple colour persisted (*ca.* 2 min). The resulting solution was neutralized with a slight excess of dilute $HClO_4$ (0.35 mmol, diluted with DMF) and concentrated to a residue on a rotary evaporator. The residue was dissolved in benzene and washed several times with H_2O. The solvent was

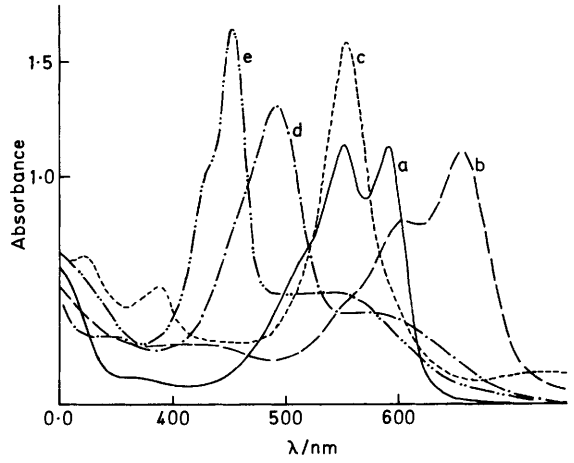


Figure 1. Spectroelectrochemistry: controlled-potential electrolysis of 0.5mM-$AQ(NH_2)_2$ in DMF (0.1M-TEAP). No TBAH added: curve a (——) $AQ(NH_2)_2$; curve c (– – – –) after exhaustive electrolysis at −1 300 mV $[AQ(NH_2)_2^{-\bullet}]$; curve e (— · · —) after electrolysis at −1 750 mV $[HAQ(NH_2)_2^{-}]$. In the presence of a five-fold excess of TBAH (2.5mM): curve b (— — —) $AQ(NH_2)(NH)^{-}$; curve d (— · —) after exhaustive electrolysis at −1 750 mV in the presence of a five-fold excess of TBAH $[AQ(NH_2)_2^{2-}]$

evaporated and the residue which contained a small amount of DMF was dried with a stream of nitrogen, leaving a solid residue that was subjected to preparative t.l.c. (silica gel) using as eluant C_6H_6–MeOH (9.7:0.3) v/v). T.l.c. showed the presence of two major bands. The first eluted band (intense blue; R_F 0.70) was removed and eluted with chloroform to give, after evaporation, $AQ(NH_2)(NHBu)$ (**1**), as a dark blue solid, *m/z* (CI) 295 (M^+, 100%), (EI) 294 (M^+, 50, and 251 (M^+ − $CH_3CH_2CH_2$, 100); δ($CDCl_3$) 1.02 (t, 3 H, *J* 7.5 Hz, CH_3), 1.53 (sextet, 2 H, *J* 7.5 Hz, CH_2CH_3), 1.72 (quintet, 2 H, *J* 7.5 Hz, $CH_2CH_2CH_3$), 3.40 (q, 2 H, *J* 6 Hz, $ArNCH_2$), 6.93 (d, 1 H, *J* 10 Hz, H-3), 7.18 (m, 3 H, H-2 and NH_2; addition of D_2O gave a doublet, *J* 10 Hz, H-2), 7.71 (m, 2 H, H-6 and -7), 8.35 (m, 2 H, H-5 and -8), and 10.71 (br s, 1 H, $NHCH_2$, D_2O exchangeable); $\lambda_{max.}$(DMF) 544 (ε7 300 l mol^{-1} cm^{-1}), 574 (13 200), and 617 nm (14 500); h.p.l.c. t_R 4.9 min, standard potential of redox couple $AQ(NH_2)(NHBu)^{-\bullet}$/$AQ(NH_2)(NHBu)$ $E°_1$ (DMF) −1115 mV.

The second major band (violet; R_F 0.33) afforded, after elution with $CHCl_3$ and subsequent evaporation, $AQ(NH_2)_2$ (**2**) (h.p.l.c. t_R 1.8 min) the proprieties of which were identical with those of commercially available 1,4-diaminoanthraquinone.

1-Amino-4-butyrylamidoanthraquinone [$AQ(NH_2)$(NHCOPr)] (**3**).—*Method A.* $AQ(NHBu)_2$ was treated with TBAH (*ca.* 6 equiv.) in DMF by using the procedure given previously for compound (**1**). The oxidized and neutralized reaction mixture was worked up as in the case of (**1**), yielding a residue which was chromatographed on silica gel using C_6H_6 – MeOH (9.7:0.3). T.l.c. showed a small, pink band (R_F 0.47) due to the very minor product (**3**) and a large band corresponding to the main product (**2**). In order to get a sufficient amount of (**3**) for its spectral characterization, the residues from identical reaction mixtures were chromatographed. The pink bands were removed, eluted with $CHCl_3$, then combined and evaporated. Purification by preparative t.l.c. using C_6H_6 – MeOH (9:1) finally afforded $AQ(NH_2)$(NHCOPr) (**3**), as a brownish powder: *m/z* (CI) 309 (MH^+, 100%), (EI) 308 (M^+, 15) and 298 [(M^+ − C_2H_4 − CH_2CO), 100]; this base peak probably corresponds to the fragmentation product $AQ(NH_2)_2^{+\bullet}$ resulting from cleavage of the C – N and C – C bonds next to the O atom with rearrangement of a terminal hydrogen; δ($CDCl_3$) 1.04 (t, 3 H, *J* 7.5 Hz, CH_3), 1.86 (app q, 2H, *J* 7.5 Hz, CH_2CH_3), 2.55 (t, 2 H, *J* 7.5 Hz, $COCH_2CH_2$), 7.04 (m, 3 H, H-2 and NH_2; addition of D_2O gave a doublet, *J* 9 Hz, H-2), 7.75 (m, 2 H, H-6 and -7), 8.29 (m, 2 H, H-5 and -8), 8.97 (d, 1 H, *J* 9 Hz, H-3), and 12.55 (br s, 1 H, NHCO, D_2O exchangeable); $\lambda_{max.}$(DMF) 537 (ε 9 400 l mol^{-1} cm^{-1}), (sh) 570 (7 400); h.p.l.c. t_R 4.2 min. standard potential of redox couple $AQ(NH_2)(NHCOPr)^{-\bullet}$/$AQ(NH_2)(NHCOPr)$ $E°_1$ (DMF) −830 mV. Compound (**3**) was identical in all aspects with an authentic sample of 1-amino-4-butyrylamidoanthraquinone prepared below.

Method B. Preparation of 1-amino-4-butyrylamido- and 1,4-bis-butyrylamidoanthraquinone by acylation of 1,4-diaminoanthraquinone. 1,4-Diaminoanthraquinone (1.19 g, 5 mmol) in nitrobenzene (5 ml) was treated dropwise with butyryl chloride (0.83 ml, 8 mmol) in nitrobenzene (3 ml) at 220 °C using an air condenser. The mixture was refluxed for 30 min. Examination of a sample of the total reaction mixture by t.l.c. showed 1-amino-4-butyrylamidoanthraquinone $AQ(NH_2)(NHCOBu)$ and a red product as the two major components. The resulting very thick mixture was diluted with $CHCl_3$ (30 ml) and then washed several times with H_2O, dilute aqueous NaOH (5%), and H_2O, successively. The organic solvents were distilled under reduced pressure to leave a residue which was taken up in ethyl acetate and then left overnight in the freezer. The red product which separated on cooling was collected and the brownish purple filtrate kept for further purification. Recrystallization of the red product from EtOAc yielded the diacylated compound, 1,4-bis-butyrylamidoanthraquinone, $AQ(NHCOPr)_2$, as red platelets with a coppery lustre: *m/z* (CI) 379 (M^+, 100%), (EI) 378 (M^+, 12), 308 [(M^+ − C_2H_4 − CH_2CO), 14], and 298 [(M^+ − 2 × C_2H_4 − 2 × CH_2CO), 100%]; δ($CDCl_3$) 1.09 (t, 6 H, *J* 7.5 Hz, 2 × CH_3), 1.86 (app q, 4 H, *J* 7.5 Hz, 2 × CH_2CH_3), 2.55 (t, 4 H, *J* 7.5 Hz, 2 × $COCH_2CH_2$), 7.82 (dd, 2 H, *J* 6, 3 Hz, H-6 and -7), 8.27 (dd, 2 H, *J* 6, 3, H-5 and -8), 9.18 (s, 2 H, H-2 and -3), and 12.53 (br s, 2 H, 2 × NHCO, D_2O exchangeable); $\lambda_{max.}$(DMF) 474 nm (ε 7 500 l mol^{-1} cm^{-1}), standard potential of redox couple $AQ(NHCOPr)_2^{-\bullet}$/$AQ(NHCOPr)_2$ $E°_1$ (DMF) −580 mV.

The filtrate previously obtained was dried on a rotary evaporator and the residue was recrystallized three times from CH_2Cl_2–n-hexane (2:1) to yield the monoacylated compound $AQ(NH_2)(NHCOPr)$ whose characteristics are given in Method A.

Results and Discussion

1,4-Diaminoanthraquinone [$AQ(NH_2)_2$].—1. *Acid–base reactions in DMF: spectrophotometric behaviour.* The absorption spectrum of $AQ(NH_2)_2$ in neutral DMF exhibits a characteristic double band at $\lambda_{max.}$ 552 (ε 11 300 l mol^{-1} cm^{-1}) and 592 nm (11 200) (Figure 1, curve a). As the spectrum remains unchanged upon addition of up to a ten-fold perchloric acid excess, it seems reasonable to consider that protonation of $AQ(NH_2)_2$ which is expected to produce visible spectral changes[6] does not occur in acidic DMF.

In contrast addition of a solution of TBAH in propan-2-ol to a rigorously deaerated solution of $AQ(NH_2)_2$ (0.5mM) in DMF results in large spectral modifications: immediately after mixing, the intensities of the two original maxima decrease and a new absorption band grows at 657 nm with increasing TBAH concentration (C_b) up to a five-fold excess (C_b 2.5mM). All spectra pass through two reasonably tight isosbestic points at 470 and 604 nm. Above C_b 2.5mM, the spectrum is little affected

* The presence of PriOH in the solution, resulting from the TBAH solution, causes a slight decrease of the absorption maxima when C_b exceeds 2.5mM.

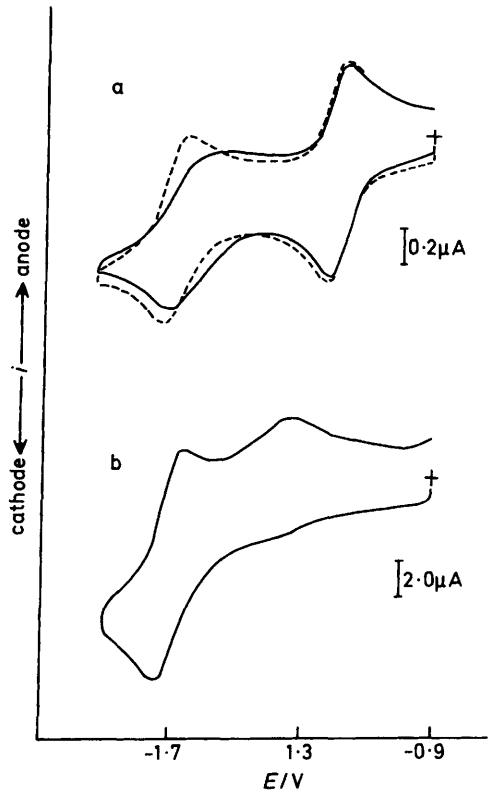
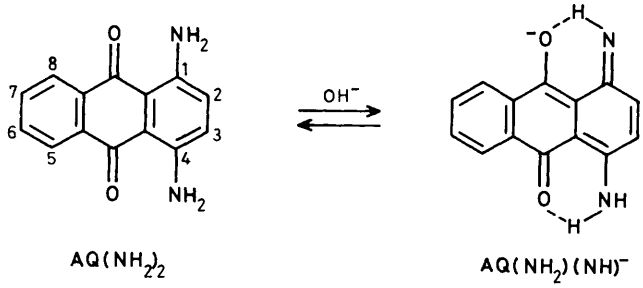


Figure 2. Cyclic voltammogram of 0.5mM-$AQ(NH_2)_2$ in DMF (0.1M TEAP): (a) v 0.1 V s^{-1}, no TBAH added (——) and in the presence of a five-fold excess of TBAH (– – – –); (b) v 10 V s^{-1}, $AQ(NH_2)_2$ solution saturated with air. Au disc electrode, area 0.02 cm^2

by variation of C_b* and can be assigned to only one species having absorption maxima at 550 (ε 4 000 l mol^{-1} cm^{-1}), 605 (7 800), and 657 nm (10 600) (Figure 1, curve b). This green species totally regenerates the purple original $AQ(NH_2)_2$ upon acidification as ascertained by means of spectrophotometry and h.p.l.c. (see Experimental section). Such results suggest that $AQ(NH_2)_2$ can behave as a weak acid in DMF through one of its amino groups to give the conjugate base under basic conditions (Scheme 1). This base can be stabilized by a strong



Scheme 1.

hydrogen bond in the enolate imine system of the resonance form $AQ(NH_2)(NH)^-$.

When exposed to air, $AQ(NH_2)(NH)^-$ tends to regenerate $AQ(NH_2)_2$. H.p.l.c. coupled with spectrophotometry shows that no other products arise from this reaction.

2. *Cyclic voltammetry.* A typical cyclic voltammogram of $AQ(NH_2)_2$ in neutral DMF (0.1M-TEAP) (Figure 2a) at a gold electrode clearly exhibits two successive one-electron reduction steps as already observed by polarography.[7] The first cathodic peak corresponds to a reversible transfer yielding the radical anion semiquinone $AQ(NH_2)_2^{-\bullet}$. Thus the value of the standard potential E°_1 of the redox couple in equilibrium can be

$$AQ(NH_2)_2 + e \overset{E^\circ_1}{\rightleftharpoons} AQ(NH_2)_2^{-\bullet} \quad (1)$$

deduced from the cyclic voltammogram and is $-1\,150 \pm 5$ mV.* The second one-electron cathodic peak cannot be assigned to a simple electron transfer as for substituted anthraquinones.[10-12] As shown in Figure 2a, departure from reversibility is observed at $v \geq 0.1$ V s^{-1} and C 0.5mM [v and C being the potential sweep rate and the $AQ(NH_2)_2$ bulk concentration, respectively], *i.e.* the anodic signal is a drawn-out S-shaped wave. Nevertheless this anodic wave regenerates the radical anion as confirmed by the presence of the oxidation peak of $AQ(NH_2)_2^{-\bullet}$ at less negative potentials. With decreasing v (or increasing C) the anodic wave tends to become a peak and form a reversible system with the second cathodic peak. This behaviour indicates that the one-electron addition to $AQ(NH_2)_2^{-\bullet}$ is accompanied by a fast and reversible chemical reaction, yielding a new species which predominates at equilibrium and which can be oxidized at the level of the anodic signal only through the back reaction; this back reaction is not very fast and thus an S-shaped anodic signal is observed at $v \geq 0.1$ V s^{-1}. As shown by controlled-potential electrolysis, the reaction can be identified as a proton abstraction from residual acid present in the medium, producing the two-electron plus one-proton reduced form of $AQ(NH_2)_2$, $HAQ(NH_2)_2^-$.

A substantial decrease in the rate of the forward reaction is easily obtained upon adding a sufficient amount of TBAH to the $AQ(NH_2)_2$ solution (Figure 2a). The corresponding voltammogram shows two one-electron and reversible cathodic peaks for all values of v (C = 0.5mM), as expected for the stepwise formation of stable one- and two-electron reduction products, $AQ(NH_2)_2^{-\bullet}$ and $AQ(NH_2)_2^{2-}$. Under these basic conditions, the value of the standard potential E°_2 of the redox reaction (2) is found to be $-1\,580 \pm 5$ mV. Spectrophotometry shows that

$$AQ(NH_2)_2^{-\bullet} + e \overset{E^\circ_2}{\rightleftharpoons} AQ(NH_2)_2^{2-} \quad (2)$$

the voltammogram above is actually that of a solution of the basic form $AQ(NH_2)(NH)^-$ and this species must be readily protonated at the electrode surface by the remaining proton sources such as Pr^iOH present in the added TBAH solution. An identical voltammogram is recorded after at least a 30 min observation period though the spectral results indicate that $AQ(NH_2)(NH)^-$ has been partially transformed into its neutral form probably as a result of air leaking into the polarographic cell.

3. *Controlled-potential electrolysis: one- and two-electron reductions.* All the controlled-potential electrolyses were carried out at a gold grid into an air-leak-proofed cell for spectro-electrochemistry.[1]

A solution of $AQ(NH_2)_2^{-\bullet}$ can be prepared by exhaustive electrolysis of an $AQ(NH_2)_2$ solution in DMF at $-1\,300$ mV. The spectrum of this quite stable species (Figure 1, curve c) exhibits an intense band in the 550 nm region typical of the semianthraquinone series.[1,2,8-10] The original $AQ(NH_2)_2$ spectrum and h.p.l.c. chromatogram can be totally recovered upon exhaustive electrolysis of the $AQ(NH_2)_2^{-\bullet}$ solution at -700 mV. Complete regeneration of $AQ(NH_2)_2$ readily occurs when oxygen is bubbled through the $AQ(NH_2)_2^{-\bullet}$ solution. The oxidation of $AQ(NH_2)_2^{-\bullet}$ by oxygen probably proceeds *via* reaction (3) which is much displaced at equilibrium

$$AQ(NH_2)_2^{-\bullet} + O_2 \rightleftharpoons AQ(NH_2)_2 + O_2^{-\bullet} \quad (3)$$

towards the right-hand side, the potential separation, $E^\circ_{1\,AQ(NH_2)_2^{-\bullet}/AQ(NH_2)_2} - E^\circ_{1\,O_2-\bullet/O_2}$,[1] being -350 mV.

* All potentials given in this work are with reference to an aqueous KCl saturated calomel electrode (s.c.e.).

In order to prepare and characterize the two-electron reduction product $AQ(NH_2)_2^{2-}$, exhaustive electrolysis was performed with a solution of $AQ(NH_2)_2$ in DMF in the presence of a five-fold excess of TBAH at −1 750 mV, as cyclic voltammetric results demonstrate that formation of this species requires that the residual acids be noticeably neutralized. Upon electrolysis, $AQ(NH_2)_2^{-\bullet}$ is produced first while the original absorption maxima decrease. In a second step, the bands due to $AQ(NH_2)_2^{-\bullet}$ also decrease and a new absorption band in the 500 nm region resulting from the formation of the two-electron reduction product develops. The spectrum recorded at the end of the electrolysis is given in Figure 1 by curve d and is similar to that of the dianionic two-electron reduction product of most common anthraquinones.[8–10] Spectrophotometric evolution shows that even in the basic medium employed, $AQ(NH_2)_2^{2-}$ slowly protonates to $HAQ(NH_2)_2^-$ [see below for the spectral characterization of $HAQ(NH_2)_2^-$], thus confirming the very high proton affinity of $AQ(NH_2)^{2-}$ in DMF. $AQ(NH_2)^{2-}$ can also be characterized electrochemically, two separated waves being observable at −1 570 and −1 150 mV. When the oxidation of $AQ(NH_2)_2^{2-}$ is carried out at −700 mV, the resulting spectrum is that of a mixture of $AQ(NH_2)_2$ and its conjugate base $AQ(NH_2)(NH)^-$ with the approximate ratio 1:1 [an increasing proportion of $AQ(NH_2)_2$ is observed upon prolonged electrolysis at this potential]. H.p.l.c. analysis of the final solution shows the complete regeneration of the starting compound.

When the electrolysis is carried out at −1 750 mV with no TBAH added to the $AQ(NH_2)_2$ solution, the quantitative production of $AQ(NH_2)_2^{-\bullet}$ is observed first. The radical anion progressively disappears to yield a new two-electron reduction product of $AQ(NH_2)_2$ in a second step, two tight isosbestic points being noted at 402 and 511 nm. The final product is stable for at least 30 min and is characterized by an intense absorption band at 455 nm and a broad and flat band at *ca.* 540 nm (Figure 1, curve e) whose overall shapes are similar to those of $AQ(NH_2)_2^{-\bullet}$ respectively (Figure 1, curve d). However the maxima for the new product occur at shorter wavelengths (*ca.* 40 nm) than in the case of $AQ(NH_2)_2^{2-}$. These main features, *i.e.* shape and relative positions of the maxima are those expected for the dianionic two-electron reduction product and its monoprotonated form in the anthraquinone series.[8–10] This provides evidence for final production of the monoanionic species $HAQ(NH_2)_2^-$ in neutral DMF. This conclusion is confirmed by the identical spectra obtained when exhaustive electrolysis of $AQ(NH_2)_2$ at −1 750 mV is performed either in neutral DMF or in DMF containing one equivalent of a weak proton donor like benzoic acid. It is worth mentioning that the absorption spectrum assigned to $HAQ(NH_2)_2^-$ does not exhibit any contribution from the totally protonated two-electron reduced form, $H_2AQ(NH_2)_2$, the spectral characteristics of which can be obtained independently with an authentic sample of leuco-1,4-diaminoanthraquinone* and are $\lambda_{max.}$ 440 (ε 10 700 l mol^{-1} cm^{-1}), 464 (15 300), and 494 nm (14 600). Upon electrolysis at −700 mV, a solution of $HAQ(NH_2)_2^-$ prepared in neutral DMF regenerates the original compound totally as expected from the cyclic voltammetric behaviour. The quantitative formation of $AQ(NH_2)_2^{-\bullet}$ observed during the reduction of $AQ(NH_2)_2$ in neutral DMF at −1 750 mV and also during the oxidation of $HAQ(NH_2)_2^-$ at −700 mV probably results from the occurrence of reaction (4).

$$HAQ(NH_2)_2^- + AQ(NH_2)_2 \rightleftharpoons 2AQ(NH_2)_2^{-\bullet} + H^+ \quad (4)$$

Visible spectral data for $AQ(NH_2)_2^{-\bullet}$, $AQ(NH_2)_2^{2-}$ and $HAQ(NH_2)_2^-$ in DMF are as follows: $AQ(NH_2)_2^{-\bullet}$ $\lambda_{max.}$ 392 (ε 5 100 l mol^{-1} cm^{-1}) and 555 nm (15 600); $AQ(NH_2)_2^{2-}$ 492 (13 000) and 580 (4 000); $HAQ(NH_2)_2^-$ 432 (10 000), 455 (16 400), and 540 (4 800).

4. *Effect of oxygen.* The progressive dissolution of oxygen in an $AQ(NH_2)_2$ solution in neutral DMF is accompanied by modification of the cyclic voltammogram when starting at −900 mV, *i.e.* at a potential where $AQ(NH_2)_2$ is not electroactive and the superoxide anion $O_2^{-\bullet}$ can be produced by electrochemical reduction of oxygen. Evolution identical with that recorded when an excess of TBAH is added to a deaerated $AQ(NH_2)_2$ solution is observed first (Figure 2a). This demonstrates that $O_2^{-\bullet}$ can noticeably deactivate the residual weak acids in the neighbourhood of the working electrode, thus rendering stable the basic species $AQ(NH_2)_2^{2-}$ formed at the level of the second cathodic peak. As the oxygen concentration is increased further, new changes occur: the height of the first cathodic peak decreases as it becomes an S-shaped wave and undergoes a negative shift of potential. With a *ca.* 1:1 mol ratio of O_2 to $AQ(NH_2)_2$ and when v is sufficiently high ($v > 5$ V s^{-1}), the cyclic voltammogram exhibits only one apparent one-electron and reversible reduction peak (Figure 2b) which appears at a potential more negative than the original second cathodic peak. This behaviour is consistent with the occurrence of a chemical reaction between the neutral form $AQ(NH_2)_2$ and electrochemically generated $O_2^{-\bullet}$ yielding a species that is much more difficult to reduce than $AQ(NH_2)_2$. This species can be prepared and characterized by means of controlled-potential electrolysis. Reduction at −900 mV of an air-saturated DMF solution containing $AQ(NH_2)_2$ carried out either at a gold grid (spectroelectrochemical cell) or a mercury pool yields a green solution after passage of a large excess of electrons. This green species is characterized by the cyclic voltammogram given in Figure 2b and thus can be considered as the species produced within the voltammetric time-scale. Its absorption spectrum is very similar to that of the basic form $AQ(NH_2)(NH)^-$ generated by reaction of $AQ(NH_2)_2$ with TBAH (Figure 1, curve b). Upon exhaustive electrolysis at −1 750 mV in the leak-proof cell, the green species solution produces the two-electron reduced form $AQ(NH_2)_2^{2-}$ via the intermediate formation of $AQ(NH_2)_2^{-\bullet}$ as ascertained by spectral changes.

These results show that $O_2^{-\bullet}$ which is known to possess various chemical properties[12] acts only as a very strong base when generated in the presence of $AQ(NH_2)_2$ in DMF. When it is not in excess relative to $AQ(NH_2)_2$, $O_2^{-\bullet}$ is predominantly decomposed by the residual acids in the medium. Such is the case in the oxidation of $AQ(NH_2)_2^{-\bullet}$ by oxygen which produces $O_2^{-\bullet}$ and $AQ(NH_2)_2$ in 1:1 stoicheiometry through reaction (3). When generated in a sufficiently high amount, $O_2^{-\bullet}$ can abstract a proton from $AQ(NH_2)_2$ yielding the basic form $AQ(NH_2)(NH)^-$. On the timescale of cyclic voltammetry the electrochemical reduction of $AQ(NH_2)(NH)^-$ prepared by reaction of $O_2^{-\bullet}$ with $AQ(NH_2)_2$ can occur without significant participation of protonation steps. The one-electron and reversible reduction peak observed in Figure 2b probably corresponds to reaction (5) yielding a dianionic radical. However this highly basic species undergoes monoprotonation as indicated by the results of controlled-potential electrolysis.

$$AQ(NH_2)(NH)^- + e \underset{}{\overset{E^\circ = -1610 \pm 10\,mV}{\rightleftharpoons}} AQ(NH_2)(NH)^{2-\bullet} \quad (5)$$

1,4-*Bisbutylaminoanthraquinone* $[AQ(NHBu)_2]$.—1. *Reaction of* $AQ(NHBu)_2$ *with hydroxide ion in DMF.* Whereas $AQ(NH_2)_2$ simply undergoes deprotonation in basic DMF, a novel reaction occurs when its dibutylamino derivative $AQ(NHBu)_2$ is treated with hydroxide ion in DMF. Upon addition of TBAH to a rigorously deaerated solution of

* Leuco-1,4-diaminoanthraquinone was generously supplied by Bayer AG, West Germany.

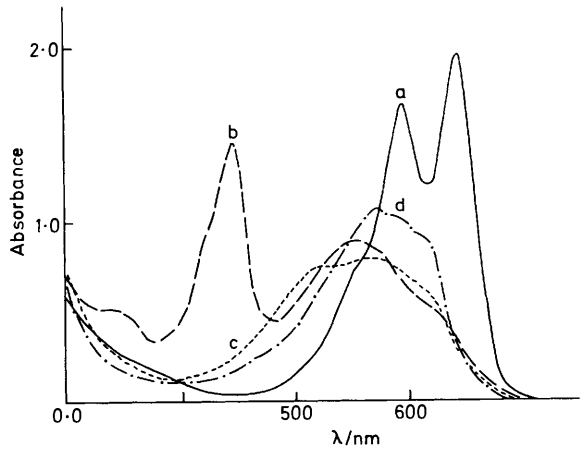


Figure 3. U.v.–visible spectrophotometry. Curve a (——) 0.5mM-$AQ(NHBu)_2$ in DMF (0.1M-TEAP) before addition of TBAH; curve b (— —) after addition of a three-fold excess of TBAH (1.5mM); curve c (- - - -) after mixing the basic solution with an excess of air; curve d (— · —) after addition of $HClO_4$ (1.8mM) to the previous solution

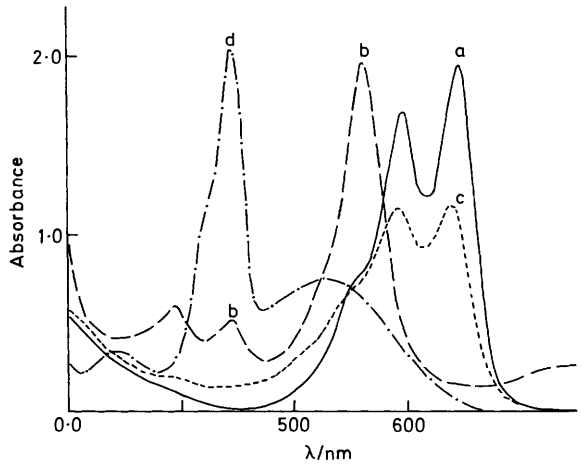
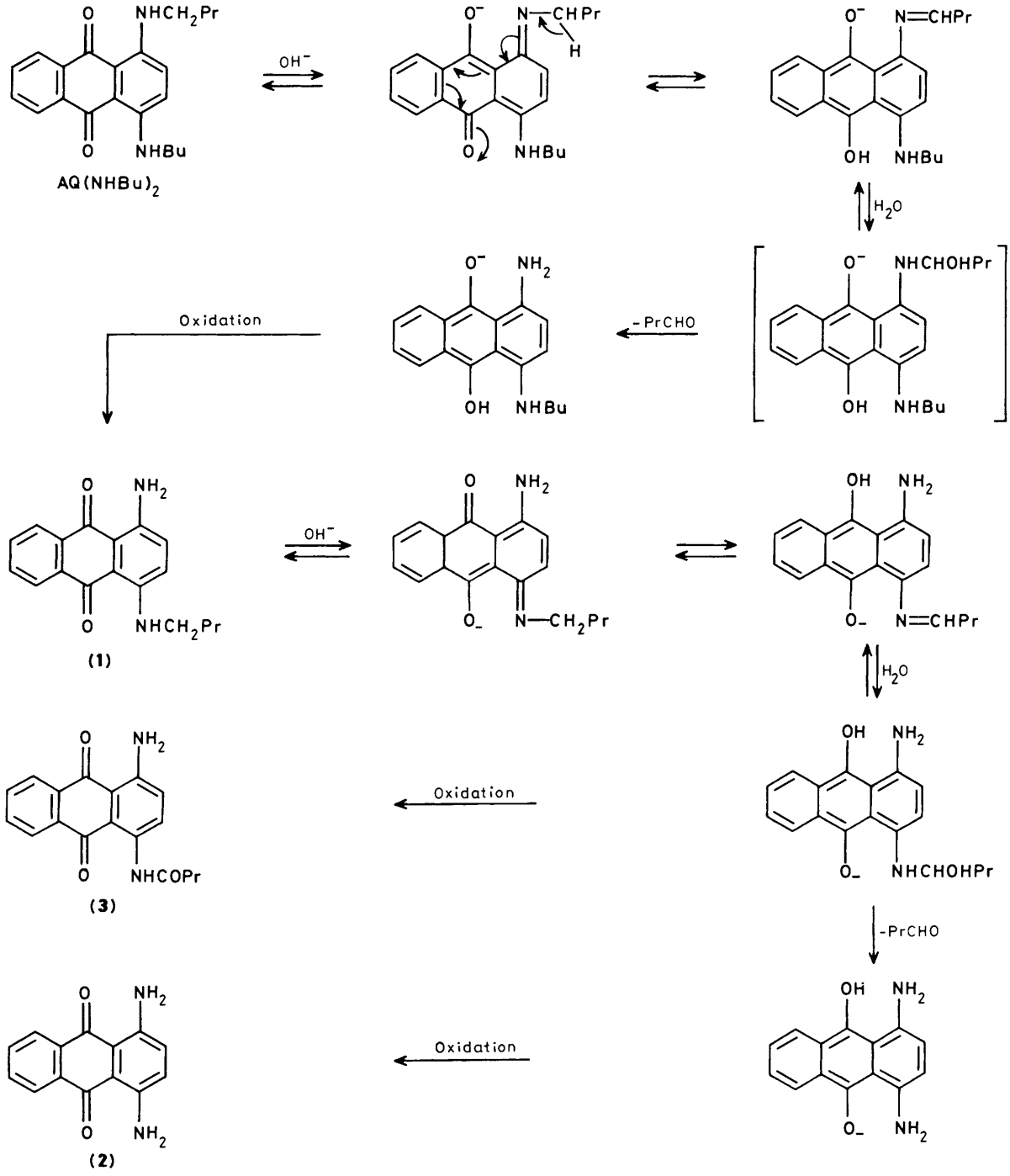


Figure 4. Spectroelectrochemistry: controlled-potential electrolysis of 0.5mM-$AQ(NHBu)_2$ in DMF (0.1mM-TEAP). Curve a (——) $AQ(NHBu)_2$; curve b (— —) after exhaustive electrolysis at −1 200 mV; curve c (- - - -) after exhaustive electrolysis of the previous solution at −600 mV; curve d (— · —) after exhaustive electrolysis of $AQ(NHBu)_2$ directly at −1 750 mV [$HAQ(NHBu)_2^-$]

$AQ(NHBu)_2$ (0.5mM) in DMF, immediate spectral changes are recorded: the absorbance of the two intense maxima due to $AQ(NHBu)_2$ ($\lambda_{max.}$ 595 and 644 nm) decreases and a new absorption band develops at shorter wavelengths, in the 445 nm region, with increasing TBAH concentration (C_b). Curve b in Figure 3 illustrates the spectrum readily obtained when a three-fold excess of TBAH is used (C_b 1.5mM). This spectrum indicates the quantitative disappearance of $AQ(NHBu)_2$ and shows the formation of new species responsible for a rather intense band at 445 nm having a shoulder at 420 nm. Such a band is characteristic of the aminoanthrahydroquinone monoanions $HAQ(NH_2)_2^-$ and $HAQ(NHBu)_2^-$ and thus can be reasonably assigned to similar types of species. In order to analyse the hydroxide-initiated reaction mixtures, a stepwise procedure was then employed which gave a typical spectral pattern represented in Figure 3 when C_b 1.5mM. Aerial oxidation following the formation of the basic reaction mixture results in the rapid disappearance of the band at 445 nm due to the hydroquinone monoanions (Figure 3, curve c). Subsequent acidification of this solution by a slight excess of $HClO_4$ neutralizes basic products (including dioxygen species such as $O_2^{-\bullet}$ resulting from the previous oxidation step) but also causes the completion of the oxidation of residual species absorbing in the 500–550 nm region which are most likely radical anions, probably through H_2O_2 formation.[13] The visible spectrum of the final solution (Figure 3, curve d) clearly shows the loss of $AQ(NHBu)_2$ with the appearance of new products. Two major products (**1**) and (**2**) can be isolated (see Experimental section). On the basis of ^1H n.m.r., mass and visible spectral data, the structure 1-amino-4-butylaminoanthraquinone, $AQ(NH_2)(NHBu)$, is assigned unambiguously to (**1**). Product (**2**) is identified with 1,4-diaminoanthraquinone [$AQ(NH_2)_2$] since its spectroscopic and electrochemical proprieties, as well as its chromatographic characteristics (t.l.c., h.p.l.c.) are identical with those of an authentic sample. The presence of the predominant products (**1**) and (**2**) [*ca.* 50% (**1**), 50% (**2**)] is well established by comparison of a linear combination of the absorption spectra of pure (**1**) and (**2**) with the absorption spectrum of the final solution (Figure 3, curve d). Confirmation of this result is found in the h.p.l.c. analysis of the solution which shows in addition to a trace amount of unchanged $AQ(NHBu)_2$ only, the presence of (**1**) and (**2**).

H.p.l.c. and spectrophotometric analysis of the ultimate product solutions resulting from the reaction of 0.5mM-$AQ(NH_2)_2$ with various TBAH concentrations (C_b) in anaerobic DMF (followed by air oxidation and acidification) indicate that the distribution of products (1) and (**2**) is altered with the change in C_b. When varying C_b from 0 to 1.5mM, (**1**) is predominantly formed along with a small amount of (**2**) [*ca.* 45% (**1**), 5% (**2**), 50% unchanged material for C_b 0.5mM]. With increasing C_b above *ca.* 1.5mM, (**2**) becomes the only predominant product; the amount of (**1**) becomes much smaller while a small amount of a new product (**3**) is formed. When C_b is *ca.* 3mM, the final solution contains *ca.* 5% (**1**), 85% (**2**), 10% (**3**). Compound (**3**) can be isolated as described in the Experimental section. Its ^1H n.m.r. and mass spectra are consistent with the 1-amino-4-butyrylamidoanthraquinone structure, $AQ(NH_2)(NHCOPr)$. The identity of the spectral, chromatographic and electrochemical characteristics of (**3**) with those of the monobutyryl derivative of 1,4-diaminoanthraquinone prepared as described in the Experimental section confirms this structural assignment.

2. *Processes initiated by the reduction of* $AQ(NHBu)_2$ *in DMF.*—The general features of the cyclic voltammogram of a solution of $AQ(NHBu)_2$ (*C* 0.5mM) in neutral DMF are similar to those previously described in the case of $AQ(NH_2)_2$. The first one-electron addition yields reversibly the radical anion $AQ(NHBu)_2^{-\bullet}$. This reduction occurs at a less negative potential ($E°_1$ −1 060 mV) than the one-electron reduction of $AQ(NH_2)_2$ ($E°_1$ −1 150 mV) as expected from the order of the electron-releasing abilities of the amino substituents (NHBu < NH_2). The one-electron reduction of $AQ(NHBu)_2^{-\bullet}$ is accompanied by a reversible protonation producing the hydroquinone monoanion $HAQ(NHBu)_2^-$. However the rate of the deprotonation is even slower than in the case of $HAQ(NH_2)_2^-$, *i.e.* the second reduction process is totally irreversible and an anodic peak due to the oxidation of $HAQ(NHBu)_2^-$ is observed at *ca.* −720 mV only when $v > 2$ V s^{-1}. Incidentally it is of interest to note that when $AQ(NHBu)_2$ (0.5mM) is combined anaerobically with a small excess of TBAH (1.5mM), the voltammogram of the reaction mixture when starting at −900 mV and going towards less negative potentials exhibits an anodic peak at *ca.* −700 mV, thus providing further support for the base-initiated formation of hydroquinone monoanions. When increasing *C* above 0.5mM, the formation of $HAQ(NHBu)_2^-$ becomes less favoured and the reversibility of the second reduction process increases. A reversible system of peaks corresponding to the redox couple $AQ(NHBu)_2^{2-}/AQ(NHBu)_2^{-\bullet}$ is observed when *C* is



Scheme 2.

2.5mM, the value of the standard potential E°_2 being −1 460 mV.

When the exhaustive reduction of a solution of 0.5mM-$AQ(NHBu)_2$ in DMF is carried out in the leak-proof cell at −1 200 mV, the original spectrum is rapidly replaced by spectrum b in Figure 4. This spectrum is apparently stable and can be assigned to a solution containing predominantly radical anions (bands at 392 and 561 nm) and small amounts of hydroquinone monoanions (band at 445 nm). Exhaustive electrochemical reoxidation of this reaction mixture can be performed rapidly at −600 mV. The final spectrum (Figure 4, curve c) indicates that the original compound is not totally regenerated. H.p.l.c. analysis shows only the recovered $AQ(NHBu)_2$ along with three minor products respectively identified as (**1**)–(**3**). The amounts in these three products can be increased when the reduced solution is maintained for a longer time at −1 200 mV before electrochemical reoxidation. These results reveal that the one-electron reduction of $AQ(NHBu)_2$ is accompanied by the same chemical processes as those arising from the reaction of $AQ(NHBu)_2$ with TBAH. These processes are probably initiated through the formation of the radical anion $AQ(NHBu)_2^{-\bullet}$ which is a stronger base than $AQ(NHBu)_2$. The quasi-stationary spectrum recorded at the end of the

reductive electrolysis is thus due predominantly to $AQ(NHBu)_2^{-\bullet}$ and to small amounts of the radical anions corresponding to (**1**)–(**3**) whose spectral characteristics are expected to be closely analogous to those of $AQ(NHBu)_2^{-\bullet}$; the small absorption band at *ca.* 445 nm most likely results from contributions of the hydroquinone monoanions of $AQ(NHBu)_2$ and (**1**)–(**3**).

When the two-electron reduction of $AQ(NHBu)_2$ is carried out at −1 750 mV, the production of $AQ(NHBu)_2^{-\bullet}$ is only observed transiently. The final spectrum is stable and exhibits absorption maxima at $\lambda_{max.}$ 346 (ε 6 000 l mol cm^{-1}), 430 (11 500), 445 (20 300), and 532 nm (7 400). These spectral characteristics are nearly identical with those of $HAQ(NH_2)_2^-$ and can be assigned to the hydroquinone monoanion $HAQ(NHBu)_2^-$. The spectrophotometric and h.p.l.c. results show that a solution of $HAQ(NHBu)_2^-$ prepared in neutral DMF regenerates quantitatively the original compound upon exhaustive electrochemical reoxidation at −600 mV, or upon aerial oxidation followed by acidification. As with $AQ(NH_2)_2$, the two-electron reduction of $AQ(NHBu)_2$ involves a quantitative monoprotonation step, the proton source being presumably H_2O (or TEA^+). Consequently, it appears that $HAQ(NHBu)_2^-$ is not subject to any transformation when generated in the presence of equal amounts of strong bases such as OH^-.

3. *Reaction mechanism.* The preceding results show that strong bases such as hydroxide ion OH^- react with $AQ(NHBu)_2$ in dipolar aprotic media to generate hydroquinone monoanions. Subsequent oxidation results in the formation of (**1**) [$AQ(NH_2)(NHBu)$] and then (**2**) [$AQ(NH_2)_2$] as the initial basicity of the medium is increased. Thus it appears that the hydroxide-initiated reaction of $AQ(NHBu)_2$ can lead to the elimination of the butyl groups from the side-chain at positions 1 and 4. A reasonable rationalization of this reaction is given in terms of the mechanism in Scheme 2. As with the quinonoid $AQ(NH_2)_2$, it is proposed that OH^- initially abstracts a proton from the N–H bond of one side-chain yielding an enolate-imine base. This base readily undergoes tautomerization between the C–H bond α to the imino group and the '*trans*' keto bond to give a fully aromatized monoanion. This *N*-phenylimine form is subject to a base-catalysed hydrolysis of the N=C bond as for Schiff's bases derived from weakly basic aromatic amines.[14] The hydrolysis reaction involves the formation of an unstable carbinolamine intermediate which decomposes to the hydroquinone monoanion $HAQ(NH_2)(NHBu)^-$ with loss of propionaldehyde. Oxidation of $HAQ(NH_2)(NHBu)^-$ yields the corresponding aminoanthraquinone (**1**). The quinonoid (**1**) can be transformed under basic conditions to the hydroquinone monoanion $HAQ(NH_2)_2^-$ corresponding to (**2**) *via* a reaction essentially similar to that outlined for $AQ(NHBu)_2$ (Figure 4).

The reaction pathway proposed for the hydroxide-initiated cleavage of the butylamino side-chains implies the formation of a carbinolamine to rupture the N–C bond. Involvement of such an intermediary is substantiated by the final production of (**3**) which simply corresponds to the oxidized form of the carbinolamine $HAQ(NH_2)(NHCOPr)^-$.

It is apparent that neither the radical anion nor the two-electron reduced forms issued from $AQ(NHBu)_2$ and $AQ(NH_2)(NHBu)$ can undergo the base-initiated elimination described previously since they do not possess the required quinonoid system. Therefore the cleavage of the second side-chain which accompanies the base-catalysed decomposition of $AQ(NHBu)_2$ must necessarily be induced from the quinonoid $AQ(NH_2)(NHBu)$. Formation of this oxidized form during the anaerobic TBAH reaction or the anaerobic electrochemically catalysed decomposition of $AQ(NHBu)_2$ requires that electron and proton transfers occur in solution. The series of steps in Scheme 3 is proposed in order to illustrate the complex situation

$$Q + e \rightleftharpoons Q^{-\bullet}$$
$$Q^{-\bullet} + Q \rightleftharpoons [Q - H]^- + QH^\bullet$$
$$QH^\bullet + Q^{-\bullet} \rightleftharpoons Q + QH^-$$
$$[Q - H]^- \longrightarrow (1)H^-$$
$$Q + (1)H^- \rightleftharpoons Q^{-\bullet} + (1)H^\bullet \rightleftharpoons QH^\bullet + (1)^{-\bullet}$$
$$(1)H^\bullet + (1)^{-\bullet} \rightleftharpoons (1) + (1)H^-$$
$$(1) + (1)^{-\bullet} \rightleftharpoons [(1) - H]^- + (1)H^\bullet$$
$$[(1) - H]^- \longrightarrow (2)H^-$$

Scheme 3.

arising from the electrochemical reduction of $AQ(NHBu)_2$ (symbolized as Q) and justify the production of (**1**), (**2**), and incidentally (**3**).

The radical anion $Q^{-\bullet}$ abstracts a proton from the starting molecule in a so-called 'father–son' reaction.[15] The conjugate base $[Q - H]^-$ then readily cleaves to give the hydroquinone monoanion of (**1**), $(1)H^-$ according to Scheme 2. A cross-redox reaction between the original molecule Q and the anion $(1)H^-$ may take place to give a mixture of the different protonated and unprotonated radical anions. The occurrence of this reaction can be envisioned for two reasons: (**1**) is almost as easily reduced as Q [see Experimental section for 1] and the formation of $Q^{-\bullet}$ is experimentally observed during the two-electron reduction of Q yielding $QH^{-\bullet}$. The radicals $Q^{-\bullet}$ and $QH^{-\bullet}$, $(1)^{-\bullet}$ and $(1)H^\bullet$ can also disproportionate yielding the expected quinonoid (**1**), and the anion $(1)H^-$ among other things. It is worth noting that the two reactions, cross-oxidation and disproportionation, are probably the predominant reactions which are involved in the regeneration of (**1**) from $(1)H^-$ during the anaerobic decomposition of $AQ(NHBu)_2$ in the presence of TBAH. A second 'father–son' step involving (**1**) and $(1)^{-\bullet}$ can lead finally to the hydroquinone anion $(2)H^-$ via the carbinolamine.

The cleavage processes for $AQ(NHBu)_2$ have been shown to be initiated by strong bases. The possibility of initiation also exists with less basic anions such as $AQ(NHBu)_2^{-\bullet}$ and can be reasonably extended to the case of $O_2^{-\bullet}$ the basic reactivity of which was well established in the previous section.

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