Hydroacridines. Part 16.[1] Steric effect in the polarographic reduction of *N*-epimeric amine oxides derived from (4aα,8aβ,9aβ,10aα)- and (4aα,8aα,9aβ,10aα)-tetradecahydro-10-methylacridine

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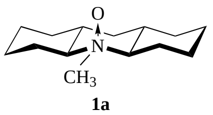
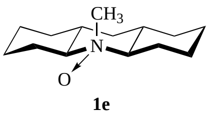
The electrochemical reduction of (4aα,8aβ,9aβ,10β,10aα)- (1a), (4aα,8aβ,9aβ,10α,10aα)- (1e), (4aα,8aα,9aβ,10β,10aα)- (2a) and (4aα,8aα,9aβ,10α,10aα)-tetradecahydro-10-methylacridine-10-oxide (2e) has been investigated by dc and ac polarography. For both of these *N*-epimeric pairs of amine oxides, the polarographic behaviour is influenced in the same way by the steric orientation of the N–O bond. So, whereas the epimers with axial oxygen (1a and 2a) give normal, single-wave polarographic curves, both epimers with equatorial oxygen (1e and 2e) give unusually shaped, double-wave curves. The steric configuration of the tricyclic framework affects only the values of the half-wave potentials and not the shape of the polarographic curves. These results suggest that polarography could be used to assign the steric configurations of the N–O bonds in saturated heterocyclic amine oxides, or to support assignments achieved by other methods.

The polarographic reduction of aliphatic amine oxides appears, so far, to be a very simple process (see refs. 2–5 and references cited therein). The electrode process is irreversible, both the half-wave potential and the steepness of the wave being pH-dependent. This proves that protonation of the reaction site takes place prior to the first electron uptake. Subsequently, the N–O bond splits and the corresponding amine forms. Some kinetic complications were reported for cycloalkyldimethylamine oxides: at pH > 7 the limiting current of such compounds shows a kinetic character due to the slow pre-protonation step.[3]

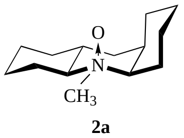
In the present paper we report the results of an investigation of the polarographic reduction of two *N*-epimeric pairs of amine oxides (**1a**, **1e** and **2a**, **2e**), derived from (4aα,8aβ,9aβ,10aα)- and (4aα,8aα,9aβ,10aα)-tetradecahydro-10-methylacridine, respectively. Due to their conformational rigidity and the different, well-defined steric orientation (axial and equatorial, respectively) of their oxygen atoms, these compounds were very well suited to the investigation of whether the steric configuration of the N–O bond and/or of the framework of saturated cyclic amine oxides has any effect on their polarographic behaviour, or not.



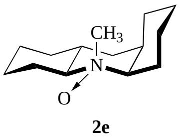
1a



1e



2a



2e

Results

Polarographic patterns in acidic medium

For the epimers with axial oxygen, **1a**, and **2a**, the direct current (dc) polarograms recorded in 1 M HCl, in the concentration range 0.05–1.0 mM show single irreversible waves ($E_{\frac{1}{2}} = -0.50$ and −0.75 V respectively), in accordance with the currently known behaviour of other aliphatic amine oxides.[2] The more negative value of the half-wave potential for **2a** seems to indicate a longer distance between the surface of the electrode and the acceptor site. This could be ascribed to the steric configuration of the heterocyclic framework of **2a**.

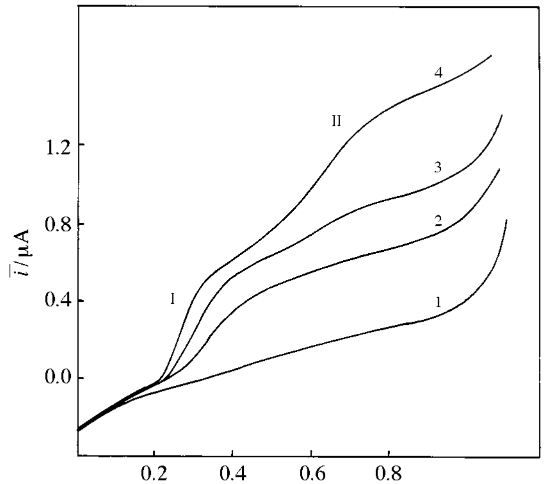


Fig. 1 Direct current polarograms of **2e** in 1 M HCl, at concentrations of (1) 0 mM; (2) 0.05 mM; (3) 0.1 mM; (4) 0.2 mM

Unexpectedly, the behaviour of the epimers with equatorial oxygen, **1e** and **2e**, is very different. For **1e** at low concentration, a single dc wave, with $E_{\frac{1}{2}} \approx -0.35$ V, appears which is termed wave I. At higher concentrations, a second wave (wave II, $E_{\frac{1}{2}} \approx -0.80$ V) also develops. Similar results were obtained for **2e** (Fig. 1), with the half-wave potentials of waves I and II of about −0.35 and −0.65 V, respectively.

The overall current (I + II) for **1e** (0.15 mM) was compared with the limiting current of the first wave of an equimolar solution of *p*-nitrobenzoic acid at pH 1. The above mentioned values were 0.76 and 1.64 μA, respectively. Since the first wave

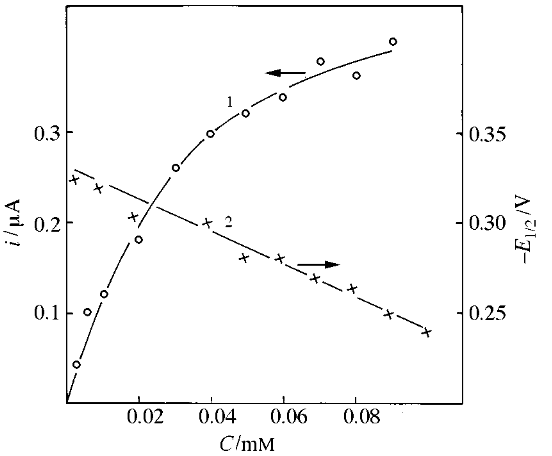


Fig. 2 Effect of amine oxide concentration on wave I of **1e** in 1 M HCl: (1) limiting current; (2) half-wave potential

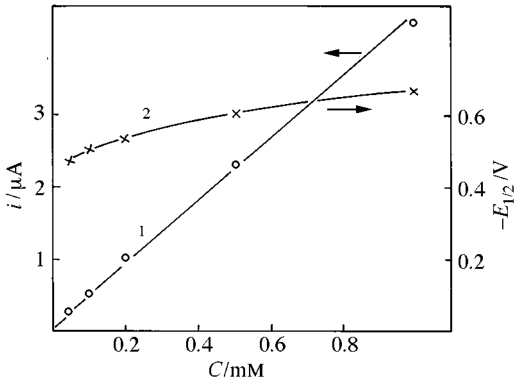


Fig. 3 Effect of amine oxide concentration on the wave of **1a** in 1 M HCl: (1) limiting current; (2) half-wave potential

of *p*-nitrobenzoic acid involves four electrons[6] the result is that the reduction of the investigated amine oxides take place *via* an overall two-electron process.

Due to the peculiar behaviour of the equatorial epimers, subsequent studies mainly focus on **1e** and **2e**.

Effect of amine oxide concentration

The effect of concentration on the polarographic curves was studied for all four amine oxides. Since the differences thus observed are quite similar for both epimeric pairs, they will be illustrated by the behaviour of the pair **1a**, **1e** only.

As shown by curve 1 in Fig. 2, in the case of amine oxide **1e**, the limiting current of wave I varies non-linearly with the reactant concentration and tends to level off above 0.05 mM. At the same time, the half-wave potential increases linearly (curve 2, Fig. 2).

Wave II of **1e** appears at concentrations higher than 0.06 mM. The overall limiting current of **1e** (wave I + wave II) is directly proportional to the concentration. For its epimer **1a**, the single dc wave behaves in the usual way. The limiting current is directly proportional to the concentration (curve 1, Fig. 3). The half-wave potential slightly shifts towards more negative values with increasing concentration (curve 2, Fig. 3).

It is important to note that, at the upper limit of the concentration range (1 mM), the half-wave potential of wave II of **1e** is very close to the half-wave potential of **1a**. This suggests that the same reduction mechanism operates in both cases.

Effect of mercury-column pressure

At low concentrations (below 0.05 mM) of the equatorial epimers (**1e** and **2e**), wave I is diffusion-controlled, the limiting current being directly proportional to the square root of the mercury-column height ($h^{\frac{1}{2}}$). Conversely, at higher concentrations (*i.e.* 0.2 mM), when both waves I and II occur, the height of wave I is independent of *h*, showing kinetic character. Under the same conditions, the overall limiting current for both epimers **1e** and **2e** is directly proportional to $h^{\frac{1}{2}}$, showing pure diffusional character.

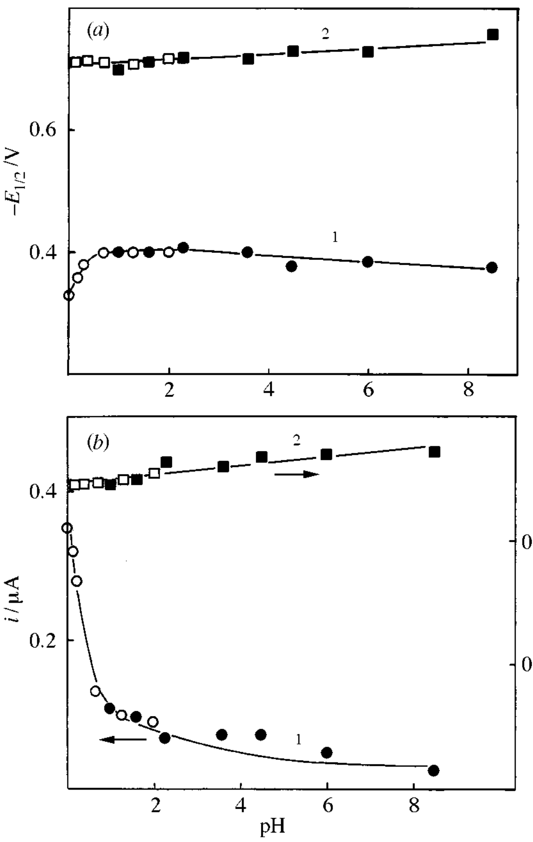


Fig. 4 (*a*) Influence of pH on the half-wave potential of **1e** (0.1 mM) in phosphate–acetate buffer: (1) wave I; (2) wave II. (*b*) Influence of pH on the limiting current of **1e** (0.1 mM) in phosphate–acetate buffer: (1) wave I; (2) overall current (waves I + II), (●, ■) phosphate–acetate buffer, pH measured by glass electrode, (○, □) HCl + KCl background electrolyte, pH computed as $-\log [H^+]$

Effect of surface-active compounds

The presence of surface-active compounds has the same effect on the polarographic curves of both equatorial epimers **1e** and **2e**. Thus, at 0.05 mM **1e** (or **2e**) wave I is shifted by gelatine towards a more negative potential whereas the steepness (slope) decreases. Even at higher concentrations of **1e** (or **2e**) (*i.e.* 0.2 mM) wave I is inhibited by gelatine, and completely suppressed at 0.005% gelatine. Conversely, wave II is not influenced by the surfactant under the same conditions. Therefore, only wave I is strongly dependent on the interface conditions.

Effect of pH

The effect of pH on the half-wave and limiting currents of the compound **1e** is shown in Fig. 4, (*a*) and (*b*), respectively. Accordingly, both the half-wave potential of wave II [Fig. 4(*a*), curve 2] and the overall current [Fig. 4(*b*), curve 2] are not dependent on pH within the limits of the experimental errors. This demonstrates that the proton uptake is subsequent to the potential-determining charge transfer step.

Conversely, the current of wave I sharply decreases with the shift in pH from 0 to 2 and almost vanishes at higher pH [Fig. 4(*b*), curve 1]. The half-wave potential shows a shift between pH 0 and 0.8 but remains almost constant at higher pH values [Fig. 4(*a*), curve 1]. Taking also into account the effect of *h* it is found that the protonation is the rate determining step in strongly acidic media. Apparently, at pH > 0.5 the protonation is extremely slow as the main proton donor is the acid component of the buffer and not H_3O^+. This is in accord with the well known kinetic behaviour of H_3O^+ as compared to other acids.[7]

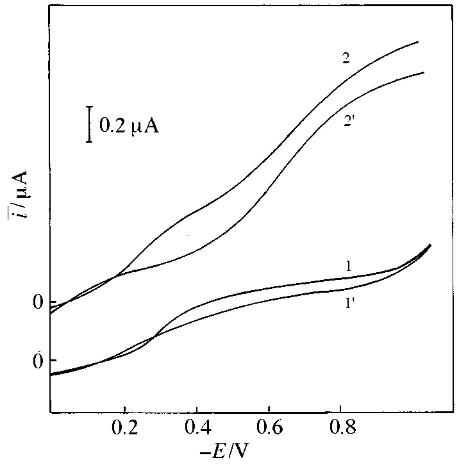


Fig. 5 Influence of the background electrolyte anion on the reduction of **1e**: (1) 0.05 mM in 1 M HCl; (1′) 0.05 mM in 0.5 M H_2SO_4; (2) 0.2 mM in 1 M HCl; (2′) 0.2 mM in 0.5 M H_2SO_4

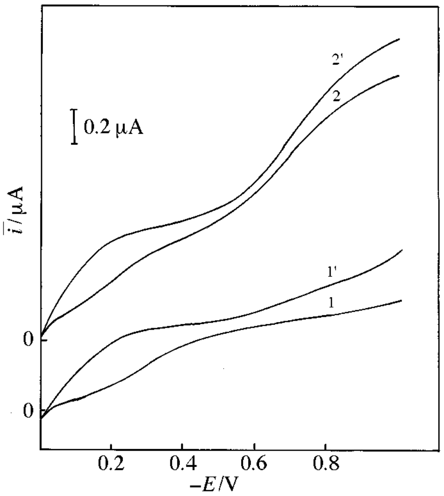


Fig. 6 Influence of solvent composition [(1,2) H_2O; (1′,2′) H_2O–EtOH 1 : 1 (v/v)] on the waves of **1e** in 1 M HCl, at (1,1′) 0.05 mM and (2,2′) 0.2 mM amine oxide concentration

Effect of the background electrolyte and solvent composition

Wave I of the equatorial epimers **1e** and **2e** is also strongly dependent on the nature of the background electrolyte anion. As may be seen from Fig. 5, especially at higher concentrations of **1e**, substitution of Cl^- by the bulky binegative anion SO_4^{2-} diminishes wave I (compare curves 2 and 2′). This effect is weaker at low concentrations of **1e** (compare curves 1 and 1′).

The effect of solvent composition on the polarographic behaviour of **1e** is shown in Fig. 6 by polarograms recorded either in water (curves 1 and 2) or in water–ethanol 1 : 1 v/v (curves 1′ and 2′). Note that wave I strongly shifts towards positive potentials when water is partly replaced by ethanol. The fact that the shift of wave I is not due to a change of the junction potential was proved by adding a small amount of Tl^+ in both media. The value of the half-wave potential of Tl^+ is not affected by the solvent composition. Consequently, the solvent effect on $E_{\frac{1}{2}}$ is certainly due to some change in the reduction mechanism. The steepness of wave I also increases under the same conditions. However, the limiting current of wave I is not influenced by the solvent composition, but the overall limiting current slightly increases (curve 2′) probably due to a change in the diffusion coefficient.

It was noticed that the effects of the background electrolyte and solvent are similar for both amine oxides **1e** and **2e**.

Studies by alternating-current polarography

Both **1a** and **1e**, in 1 M HCl, give ac-polarographic maxima at about −0.25 V (Fig. 7). Since the amine oxides are reduced at more negative potentials the maxima are ascribed to the periodical adsorption–desorption processes involving the unreduced species, and therefore have a tensammetric character.[8]

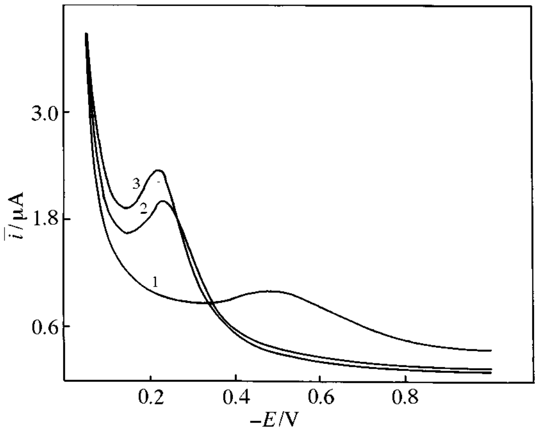


Fig. 7 Alternating current polarograms of **1e** in 1 M HCl, at concentrations of (1) 0 mM; (2) 0.5 mM; (3) 1 mM

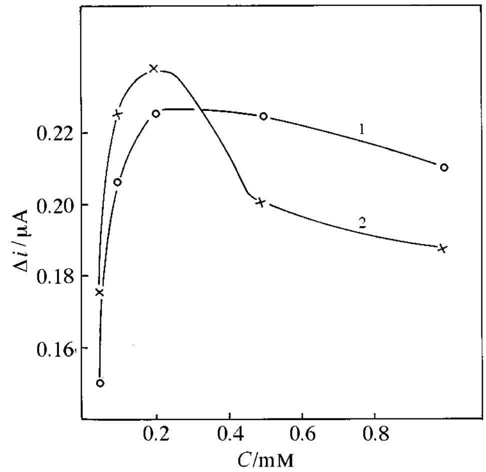


Fig. 8 Variation of the ac capacitive current (measured at −0.95 V) in 1 M HCl as a function of amine oxide concentration: (1) **1a**; (2) **1e**

The adsorption of the reduction products is proved by the decrease of the capacitive current as compared to the value measured in the pure background electrolyte. In Fig. 8, the variation in the difference between these currents (Δ*i*, measured at −0.95 V) is plotted as a function of the concentration for amine oxides **1a** and **1e** (curves 1 and 2, respectively). As usual,[8] at low concentrations Δ*i* increases with the amine oxide content, The anomalous decrease of Δ*i* at higher concentrations may be assigned to some changes in the structure of the adsorbed layer due to intermolecular interactions. This anomaly is much stronger in the case of **1e**.

Note the absence of ac maxima in the potential range of the dc waves, proving the irreversible character of amine oxide reduction. On the other hand, the reduction itself does not induce specific changes in the capacitive current. This demonstrates that the state of the nitrogen center does not influence the molecule orientation at the interface or the free enthalpy of the adsorption. Conversely, the adsorption of the reactant (either **a** or **e** form) depends only on the heterocyclic framework.

Electrocapillary curves

The electrocapillary measurements could provide useful information about the adsorption processes occurring at the interface. The electrocapillary curves obtained in the pure background electrolyte and in the presence of **1e** are shown in Fig. 9 (curves 1 and 2, respectively). Note that in the presence of **1e** the potential of the zero-charge (pzc) shifts towards more

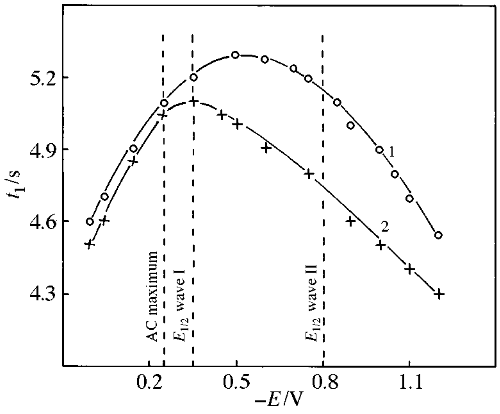


Fig. 9 Electrocapillary curves for **1e** in 1 M HCl at concentrations of (1) 0 mM and (2) 0.4 mM of the amine oxide, for a mercury reservoir height, $h = 40$ cm

positive values, probably indicating the adsorption of an organic cation at potentials more negative than $E_{\frac{1}{2}}$ of wave I. The potential of the ac-polarographic maxima (-0.25 V) is sufficiently close to the potential of the zero-charge in the presence of **1e** (about -0.3 V according to curve 2 in Fig. 9). This seems to be the positive limit of the adsorption range. The small difference at potentials more positive than -0.3 V between electrocapillary curves in the presence and in the absence of **1e** (Fig. 9) is not significant and within the experimental error. On the contrary, at more negative potentials, the decrease in the surface tension is more significant (right branch of curve 2) indicating that the adsorption involves predominantly the positively-charged reduced species. Similar results have been obtained with amine oxide **2e**.

Discussion

Among the investigated compounds, the axial epimers show the typical behaviour of aliphatic amine oxides. Their reduction in acidic medium gives irreversible waves, proving a very low rate constant for the electron transfer step. This behaviour may be related to the fact that the single acceptor orbital is of the σ-antibonding type. The adsorption of the reduction products is demonstrated by the alternating current polarography data and, for the equatorial epimers, also by the electrocapillary curves. Taking into account the strongly hydrophobic character of the aliphatic residue, the adsorbed molecules are most probably oriented parallel to the electrode surface. This orientation brings the N–O bond of the equatorial epimers very close to the surface of the electrode, which is not the case with the axial epimers.

For the equatorial epimers **1e** and **2e**, a very peculiar behaviour was observed: besides the usual wave (wave II), resembling the single wave of the axial epimers, the equatorial epimers give the additional wave I at more positive potentials. At very low reactant concentrations only this wave appears, and its height varies non-linearly with the concentration. Furthermore, the character of wave I changes from being pure diffusional at low concentrations, to kinetic at higher concentrations. This behaviour is assigned to the change of the adsorbed layer structure by the increase of the concentration, as evidenced by the ac-polarographic measurements (Fig. 8). In contrast to wave II, wave I is very sensitive to surface-active compounds, being suppressed by very low amounts of gelatine. The partial substitution of water by ethanol strongly diminishes the apparent activation energy of the reduction in the range of these waves. The parameters of wave I are also sensitive to the nature of the background electrolyte anion.

The behaviour of the equatorial epimers could therefore be explained by assuming that, owing to a shorter distance between the surface and the acceptor site, the activation energy of the reduction is lower. In this case the process gives rise to wave I. Since the reduction products thus formed are strongly adsorbed to the surface, further adsorption of the non-reduced species is hindered. The reduction of the non-adsorbed molecules through the adsorbed film gives rise to wave II with a more negative half-wave potential compared to wave I. This explains why wave II is not affected by the presence of surface-active compounds such as gelatine. Note also that wave II appears at high concentration, when the surface is covered by the reduction products formed in the range of wave I. The non-linear variation of the height of wave I as a function of the concentration (Fig. 2) is also due to the coverage of the electrode surface by the reduction products.

The orientation of the equatorial epimers at the electrode surface also explains the effect of ethanol. When present in a large excess, ethanol forms an adsorbed layer, with the hydroxy group oriented towards the solution. The adsorbed layer of ethanol has a hydrophobic character, thus favouring the adsorption of the equatorial epimers with the oxygen atoms at a minimal distance from the electrode.

At low concentrations, the single, diffusion-controlled waves (wave I) of the equatorial epimers may be assigned to Scheme 1

$$(R_3N\rightarrow O)_s \xrightleftharpoons{H^+} (R_3N^+{-}OH)_s \rightleftharpoons (R_3N^+{-}OH)_a \xrightarrow{2e^- + 2H^+} (R_3N^+H)_a + H_2O$$

Scheme 1

(where R_3 means the aliphatic substituents at the nitrogen atom and the subscripts ‘a’ and ‘s’ refer to the adsorbed and solvated states, respectively). The rate determining step is the diffusion of the protonated form. At higher concentrations, the adsorption of the positively charged $(R_3N^+{-}OH)_s$ species is hindered by the presence of the reduction product, $(R_3N^+H)_a$, and Scheme 2 predominates.

$$(R_3N\rightarrow O)_s \rightleftharpoons (R_3N\rightarrow O)_a \xrightleftharpoons{H^+} (R_3N^+{-}OH)_a \xrightarrow{2e^- + 2H^+} (R_3N^+H)_a + H_2O$$

Scheme 2

The latter reaction pathway involves protonation in the adsorbed state (*i.e.* surface reaction, according to Mairanovskii[9]). Owing to the repelling effect of the $(R_3N^+H)_a$ species the surface concentration of protons is very low, even in acidic medium. Consequently, the protonation represents the rate determining step and, although the limiting current increases with the concentration, it changes from having a diffusional to a kinetic character. A kinetic control by the protonation step was previously observed for cycloalkyldimethylamine oxides.[3]

The effects of background electrolyte composition are also accounted for by the above assumptions. Thus, chloride ion is much more strongly adsorbed than sulfate.[7] Consequently, at the same normal concentration, the repelling of H^+ ions is stronger in the presence of sulfate than in the presence of chloride, giving the effects depicted in Fig. 5.

Finally, in the case of axial epimers, a single wave appears, since the steric configuration of the heterocyclic framework does not ensure the minimum distance between the electrode and the acceptor site.

The main purpose of the present work was to study the mechanism of the reduction of equatorial epimers. Nevertheless, one can draw the conclusion that the polarographic reduction of all the investigated *N*-epimeric amine oxides is mainly governed by the interface behaviour of the reactant, in close connection with the steric orientation of the N–O bond. The peculiar polarographic behaviour of the equatorial epimers (appearance of wave I) may provide a simple method for assigning the steric configuration of the N–O bonds of six-membered saturated heterocyclic amine oxides. Further experiments are in progress in order to extend the method to other examples.

Experimental

The synthesis and separation of the amine oxide pairs **1a**, **1e**[10] and **2a**, **2e**[11] have been or will be described elsewhere. Their steric configurations were ambiguously assigned by ^{1}H, ^{13}C and 2D INADEQUATE NMR spectra.[12] Commercial pa grade reagents and redistilled water were used. Direct current polarograms were recorded by means of conventional equipment (Radelkis, Hungary). Alternating current polarograms were recorded with a non-phase sensitive instrument (Radelkis OH 105), at 60 Hz and 10 mV amplitude of the superimposed sinusoidal voltage. The electrocapillary curves have been drawn by measuring the dependence of the drop-time (t_1) on the applied potential, at a mercury reservoir height $h = 40$ cm. The cell had a saturated calomel electrode as reference. The characteristics of the capillary were: flow-rate, $m = 4.24$ mg s^{-1}, drop-time, $t_1 = 1.75$ s, at a mercury reservoir height $h = 75$ cm, measured in 1 M HCl solution, in an open circuit. The effect of pH was investigated in a buffer system consisting of Na_2HPO_4 and CH_3COONa (0.05 M each) with 0.5 M $LiClO_4$ added in order to avoid strong modification in the double layer with the change in pH and to keep constant the ionic strength. pH values were adjusted by appropriate additions of concentrated HCl or NaOH and measured by a conventional glass electrode. The effect of pH in strongly acidic range was studied by a HCl–KCl background electrolyte ([HCl] + [KCl] = 1 M).

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