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Cryoelectrochemistry: electrochemical reduction of 2(*RS*)-methyl 1-(*tert*-butoxycarbonyl)-2-iodomethyl-2,5-dihydropyrrole-2-carboxylate

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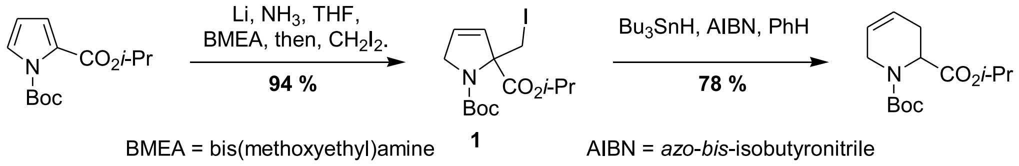
Abstract—Cryoelectrochemisty with cyclic voltammetry and chronoamperometry has been applied to give an insight into a reductive pyrroline ring opening reaction, and has allowed the number of electrons participating in the reaction to be deduced from potential step experiments.

1. Introduction

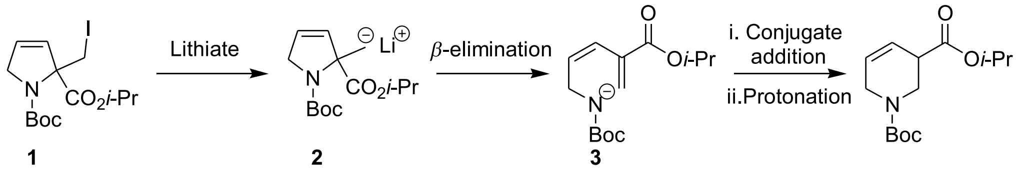
The recent discovery that the Birch-reduction of electron-deficient pyrroles[1,2] is compatible with the use of 1,1-dihaloalkanes as an electrophile, has allowed access to synthetically useful α-iodomethyl pyrrolines (such as **1**) in excellent yields (Scheme 1). It has been successfully demonstrated that these versatile pyrrolines undergo a one-carbon radical ring-expansion to yield tetrahydropyridines.[3]

With a continued interest in the stereoselective formation of tetrahydropyridines,[4–6] it was envisaged that α-iodomethyl pyrrolines (**1**) could be lithiated to produce reactive intermediate **2**. β-Elimination to form enone **3**, followed by conjugate addition and protonation could yield synthetically useful tetrahydropyridines with the ester functionality on C-3 as opposed to C-2 (Scheme 2).

However, initial attempts to transmetallate the primary iodide unit within pyrroline **1** with *n*-BuLi, *sec*-BuLi and



Scheme 1.



Scheme 2.

Keywords: Reductive elimination; Cryoelectrochemisty; Cyclic voltammetry and chronoamperometry.

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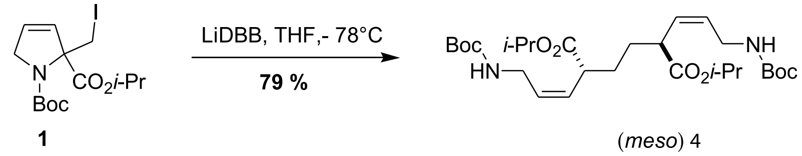


Scheme 3.

tert-BuLi were all unsuccessful and returned only starting material. The steric demands of this centre were considered too great and, therefore, formation of the anion via single electron transfer was explored. With the literature precedent of using lithium di-*tert*-butyldihphenyl (LiDBB) as a reagent for single electron transfer to form anions from halides,[7] pyrroline **1** was treated with LiDBB in THF at −78 °C for 2 h. A single crystalline product was obtained in 79% yield; however, ^{1}H NMR and ^{13}C NMR spectroscopy both ruled out the formation of a tetrahydropyridine. Instead the product was identified as the dimerised adduct **4**, formed as a single diastereoisomer[†] (Scheme 3). Dimer **4** was thought to result from the dimerisation of enone **3** through the β-position. Mechanistically, enone **3** can arise by two different routes (Scheme 4). In Route A, a ketyl radical **5** is formed and then collapses by cleaving the carbon–nitrogen bond. Route B involves reductive cleavage of the carbon–iodine bond, whereby the intermediate radical anion **6** accepts a second electron to give anion **7** and then undergoes ring opening. Enone **3** can accept an electron to form radical anion **8** which dimerises to furnish **4**. In theory both pathways consume three electrons to form **8**.

This paper describes our electrochemical studies of pyrroline **1**, in an attempt to verify the reaction pathway envisaged for the formation of enone **3**. Pyrroline **1** contains three electroactive groups; the halogen, ester and carbamate units and was thus judged too unwieldy for initial electrochemical studies. A series of simple compounds were chosen to model the different functional groups present in pyrroline **1** allowing their electrochemical response to be observed individually (Fig. 1). Pyrroline **9** was also synthesised as a molecule analogous to pyrroline **1** on which the final electrochemical experiments would be performed. In these experiments we aimed to determine the relative reactivity of the three electroactive groups (and, therefore, predict the likely route to compound **3**). We also sought to use chronoamperometry experiments to determine the number of electrons involved in the dimerisation reaction.

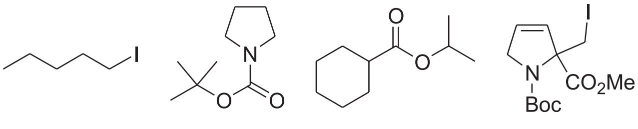
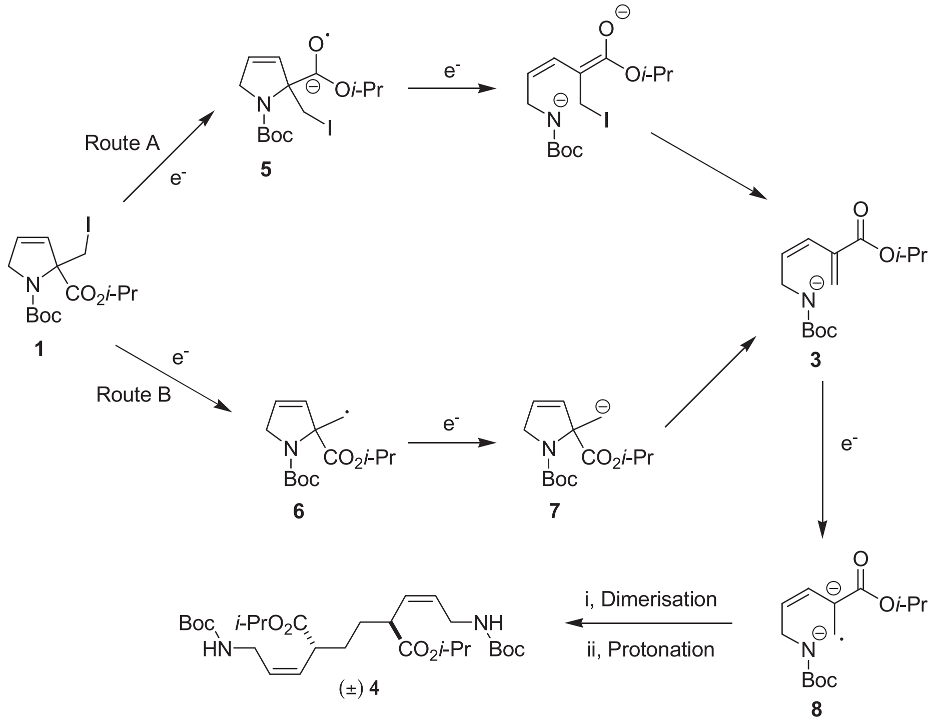


Figure 1.



Scheme 4.

[†] As determined by X-ray crystallography.

2. Theory

Chronoamperometry permits the simultaneous determination of the diffusion coefficient, D, and n, the number of electrons transferred to the electroactive species of interest. The time dependent current response, I, resulting from a diffusion-controlled reductive current after a potential step at a microdisc electrode is given in Eq. 1 below:

$$I = -4nFDCrf(\tau) \qquad (1)$$

where Eq. 2 defines $f(\tau)$:

$$f(\tau) = 0.7854 + 0.8862\tau^{-1/2} + 0.2146e^{-0.7823\tau^{-1/2}} \qquad (2)$$

and Eq. 3 defines τ:

$$\tau = 4Dt/r^2 \qquad (3)$$

F is the Faraday constant, r is the radius of the disc electrode and t the time. The above approximation (Eqs. 1–3) were derived by Shoup and Szabo,[8] and describes the current response to within an accuracy of 0.6% over all τ. Experimentally, the chronoamperometric experiment is run over a time scale incorporating a transition from transient, with a $I \propto D^{1/2}$ dependence, to steady-state with a $I \propto D$ dependence behaviour. Accordingly deconvolution of the parameters D and n is possible from a single scan. Fitting was achieved via ORGIN 6.0 (Microcal Software Inc.) where, having input accurate value for r and C, the software iterates through values of D and n until the fit of the experimental data had been optimised.

3. Results and discussion

3.1. Electrochemical reduction of 1-iodopentane

A 3.14 mM solution of 1-iodopentane in THF (0.1 M TBAP) was prepared and cooled to −72 °C. A platinum microelectrode was used to record the voltammetric response (Fig. 2). A reduction wave is observed at ca. −2.9 V (vs Ag wire) which is just before the on-set of solvent breakdown. No corresponding oxidation wave was observed in the potential window studied, suggesting a chemically irreversible process. A mass transport corrected Tafel plot (Fig. 3) of the voltammogram from Figure 2 (corresponding to the reduction of iodopentane) was constructed, the gradient of which produced an alpha value of 0.26. This relatively small value is perhaps not unexpected since Andrieux and co-workers observed low alpha values (ca. 0.3) for the reduction of butyl iodide in DMF and interpreted the low values as resulting from a dissymmetry of the potential energy curves of the reactant and products in the context of Butler-Volmer kinetics.[9]

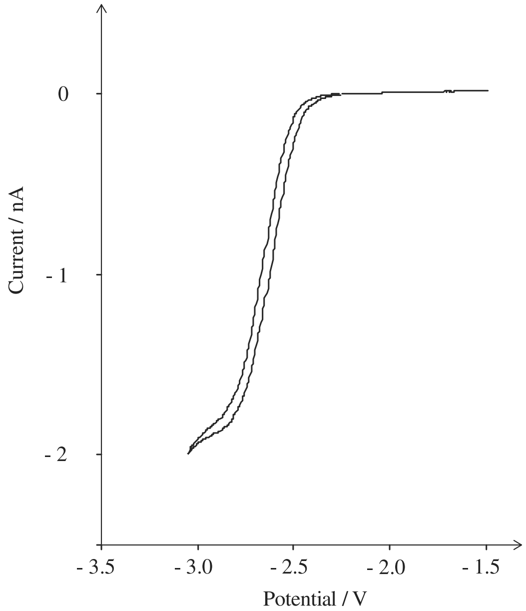


Figure 2. Voltammetric response of iodopentane (3.14 mM) in THF (0.1 M TBAP) using a 5 μm (radius) platinum microelectrode recorded at a scan rate of 20 mV s^{-1} at −72 °C (vs Ag wire).

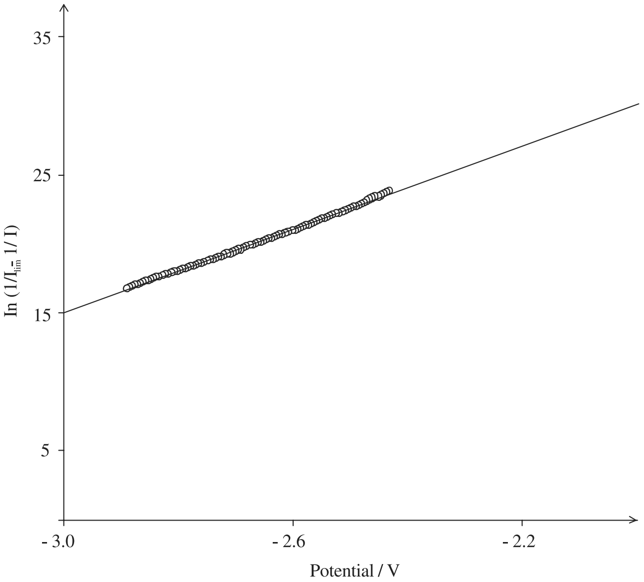


Figure 3. Mass transport corrected Tafel plot from the voltammetry presented in Figure 1.

The change in the limiting current was measured as the temperature of the solution was increased. It was found that the voltammetric wave shifted to less negative potentials as the temperature was increased, and above −40 °C moved beyond the solvent window. Accordingly, voltammetry of 1-iodopentane was impossible at or near room temperature. A 0.1 M TBAP solution in THF was prepared in which a 5 μm (radius) platinum microelectrode was used to examine the magnitude of the solvent window as a function of temperature over the range of +16 to −71 °C. The voltammetric responses are shown in Figure 4A. It can be seen that as the temperature decreased, the cathodic potential window widened to more negative potentials. This is emphasised in Figure 4B which clearly shows the onset of solvent breakdown, (taken at the point which the current rapidly drops off) is shifted from −2.8 V at +16 °C to −3.3 V at −71 °C. Clearly, there is an advantage to using cryoelectrochemistry to study the kinetics and reaction mechanism of room temperature electrochemically 'invisible' processes. We now turned to investigating the diffusion coefficient and number of electrons transferred for iodopentane using chronoamperometry.

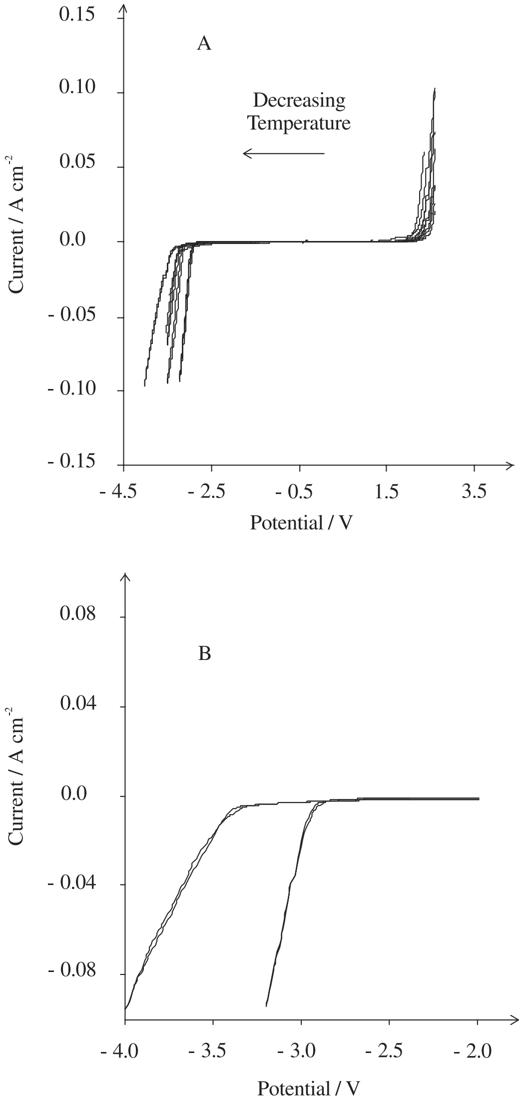


Figure 4. Solvent window of THF containing 0.1 M TBAP recorded at a range of temperatures (A) with (B) highlighting the extent of changing the temperature on the electrochemical window.

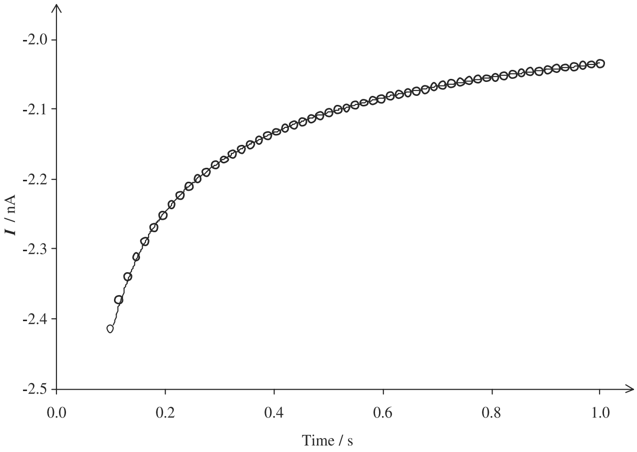


Figure 5. Experimental (solid line) and fitted theoretical (circles) chronoamperometric curve, for the reduction of 3.14 mM iodopentane in THF (0.1 M TBAP) at a 5 μm platinum electrode.

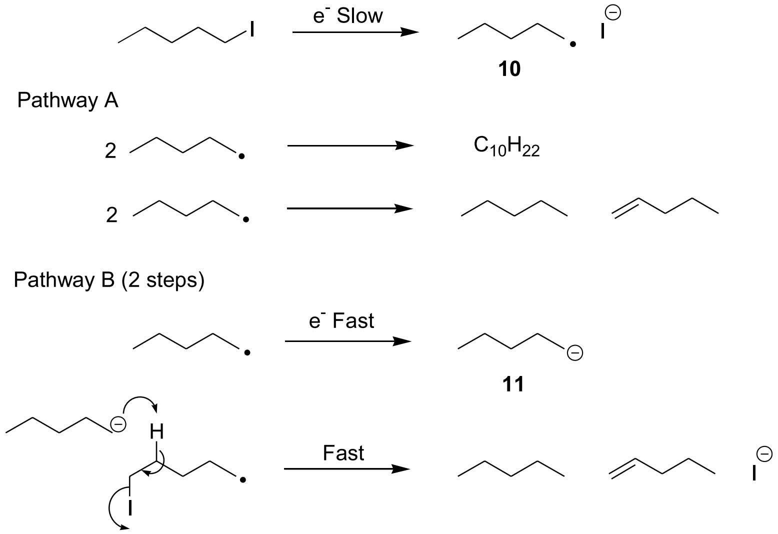
A chronoamperometric method was applied to deduce the diffusion coefficient, *D*, and number of electrons transferred, *n*, to the electroactive species. To ensure that the electrochemical system was initially at equilibrium, the potential was held at a point corresponding to the passage of no Faradaic current for a period of 20 s before being instantaneously stepped to a potential in the plateau region of the reductive wave. Analysis via the Shoup and Szabo[8] expression was then employed to yield *n* and *D* in THF at −72 °C. Figure 5 depicts a typical chronoamperometric curve with the corresponding fitting applied to deduce the required parameters. The chronoamperometric experiments were performed at both 5 and 25 μm (radii) platinum electrodes with the average *D* and *n* of the two taken. The diffusion coefficient was found to be $2.84(\pm 0.38)\times 10^{-6}$ $\mathrm{cm^2\ s^{-1}}$ with the number of electrons transferred per molecules found to correspond to 1. This is in agreement with the estimation produced from the Wilke–Chang equation[10] that predicts $3.2\times 10^{-6}\ \mathrm{cm^2\ s^{-1}}$.

The result of $n=1$ for the reduction of iodopentane is surprising given that the formation of the alkyl anion ($n=2$) has been reported using similar, shorter chain alkyl halides.[11] The result that $n=1$ implies that one electron is transferred per molecule of substrate. There are two possible explanations for this observation (Scheme 5), both have an identical first step with the heterogeneous electron transfer and concomitant C–I bond cleavage to yield the alkyl radical species (**10**) and iodide anion. Previous studies in DMF indicated no radical anion intermediate.[12]

The electrochemically produced radical is a reactive species and can either disproportionate or dimerise (Pathway A, Scheme 5), or accept a second electron to form the anion **11** which then performs an efficient elimination on 1-iodopentane (Pathway B). Pathway B results in a 1:1 production of pentane and 1-pentene with (in total) one electron transferred per molecule of iodopentane consumed. Route B implies that the second electron reduction to form the anion proceeds at a more positive potential than the C–I cleavage. The voltammogram only shows one peak (Fig. 2) indicating instantaneous reduction of the radical species. The existence of radicals, as suggested by Route A, seems unlikely as previous studies performed on 1-iodobutane have shown that no octane (dimerised product) was formed, only a ∼1:1 mixture of butane and butene.[13] The results support Pathway B given that the rate of dimerisation is much faster than disproportionation.

3.2. Electrochemical reduction of 1-(*tert*-butoxycarbonyl)-pyrrolidine and cyclohexanecarboxylic acid isopropyl ester

1-(*tert*-Butoxycarbonyl)-pyrrolidine and cyclohexanecarboxylic acid isopropyl ester were investigated since they isolate two of the potential electroactive sites on pyrroline **1**. Cyclic voltammetry was recorded at −72 °C using two different sizes of platinum electrode. The voltammetric response confirmed that the carbamate functionality was electro-inactive over the potential range studied with only a background response (scan in the absence of any electroactive species) observed; it can be assumed that this molecule has a reduction potential greater

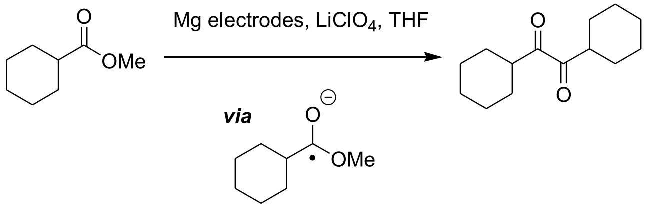


Scheme 5.

than −3.0 V (vs silver wire). This however, may not be surprising since Boc protecting groups are regularly used in Birch-type reactions without undergoing chemical reduction.

Following on, the cyclohexanecarboxylic acid isopropyl ester was analysed by cyclic voltammetry. No voltammetric responses were observed in the potential range studied (0 to −3.0 V).

The fact that no obvious reduction peak was measured for the ester in the cyclic voltammetric experiment was a surprise as electrochemical procedures for acyloin-type reactions are known at potentials approximately −2.7 V (vs SCE) as developed by Kashimura and Shono et al.[14] The reaction proceeds through the dimerisation of a ketyl radical species which is generated electrochemically (Scheme 6). This result, however, was dependent of the use of magnesium electrodes which may provide some electrophilic activation of the carbonyl group.



Scheme 6.

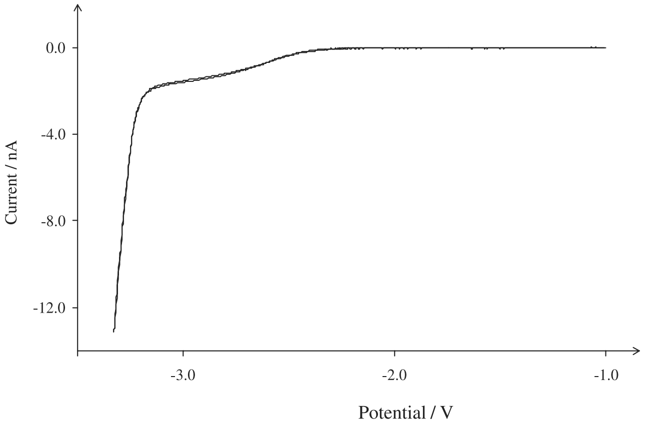


Figure 6. Voltammetric response of (2*RS*)-1-(*tert*-butoxycarbonyl)-2-iodomethyl-2,5-dihydropyrrole-2-carboxylic acid methyl ester in THF (0.1 M TBAP) recorded at −72 °C using a 5 μm platnium microelectrode (vs Ag wire) at a scan rate of 20 mV s^{-1}.

3.3. Electrochemical reduction of 2(*RS*)-methyl 1-(*tert*-butoxycarbonyl)-2-iodomethyl-2,5-dihydropyrrole-2-carboxylate

A 0.99 mM solution of pyrroline **9** was dissolved in THF also containing 0.1 M TBAP. Figure 6 shows the voltammetric response using a platinum microelectrode at −72 °C recorded at a scan rate of 20 mV s^{-1}. A limiting current is clearly observed at ca. −3.0 V which again is close to solvent breakdown as observed for the reduction of iodopentane.

Given the reduction potential of iodopentane, the electroactive site within the electrochemical cell is likely to be the carbon iodine bond, favouring Route B (Scheme 4). However, the reductive ring opening reaction is performed with the presence of lithium ions (from LiDBB) and it is not yet possible to determine the relative activation that the lithium ions provide to the three electroactive functional groups.

Chronoamperometry was applied to deduce the values of n and D. A typical experimental transient and corresponding fit is shown in Figure 7. Consequently the diffusion coefficient was found to be $2.78(\pm0.15)\times10^{-6}$ cm s^{-1} (at −71 °C) with the number of electrons transferred per molecule found to correspond to three.

Following Route B (Scheme 4) it appears that alkyl radical **6** immediately accepts a second electron to give **7**, which ring opens to furnish an enone intermediate **3** (Scheme 4). Enone **3** is either as susceptible or more susceptible to electrochemical reduction as **1** and accepts a third electron to

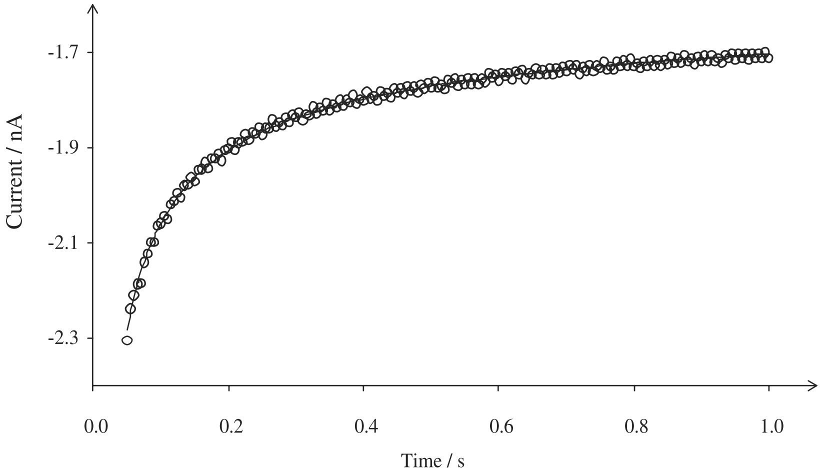


Figure 7. Experimental (circles) and fitted theoretical (solid line) chronoamperometric curves, for the reduction of (2*RS*)-1-(*tert*-butoxycarbonyl)-2-iodomethyl-2,5-dihydropyrrole-2-carboxylic acid methyl ester in THF (0.1 M TBAP) at a 5 μm platinum electrode.

produce the radical anion **8**, the species that dimerises. The rapid reduction of **6** and **3** at the potential required to reduce the C–I bond is implied by the presence of only a 'single step' in the voltammogram (Fig. 6).

The results of chronoamperometry do not allow the distinction between Routes A and B as both consume three electrons. However, as there is only a single peak in the voltagramm of **9** at a potential similar to that of 1-iodopentane (Fig. 6), the electrochemical data is most consistent with Route B for ring opening. This result further corroborates our supposition that the electrochemical reaction in the case of iodopentane is best modelled by the formation of an anion rather than a radical species.

4. Conclusions

It has been demonstrated that pyrroline **1** accepts three electrons in the ring-opening dimerisation reaction to form **4**. Within the electrochemical cell, the measured potential of **9** indicates that pyrroline **1** accepts an electron into the carbon–iodine bond first, eventually leading to dimerisation. It is worth noting that, in the synthetic reaction, the effect of lithium ions in solution is unknown and they may alter the relative reactivity of the electroactive functionalised group. More study is required to address this question.

Cryoelectrochemisty with cyclic voltammetry and chronoamperometry has been applied to give an insight into an organic mechanism at low temperature which has allowed the number of electrons participating in the reaction to be deduced from potential step experiments without recourse to bulk chrono-coulometery while the low temperature allows otherwise voltammetry invisible molecules such as iodopentane to be studied.

5. Experimental

5.1. Electrochemistry

All reagents were used as received without any further purification. Voltammetric measurements were carried out on a μ-Autolab (Eco-Chemie, Utrecht, Netherlands) potentiostat. A three-electrode arrangement was used in an airtight electrochemical cell (ca. 50 mL). The working electrodes employed were a 1 mm (diameter) platinum electrode (housed in a Teflon insulating case), 5 μm (radius) and 25 μm (radius) platinum microdisc electrodes (Cypress Systems Inc., Kansas, US) with a large area bright platinum wire (Goodfellow Cambridge Ltd, Cambridge, UK) used as the counter electrode. A silver wire was used as the quasi-reference electrode (Goodfellow Cambridge Ltd, Cambridge, UK). The working electrodes were polished using alumina of decreasing sizes on soft lapping pads. Before carrying out electrochemical experiments, the microdisc radii were electrochemically calibrated using a literature methodology.[15] Tetra-*n*-butylammonium perchlorate was added to freshly distilled THF with all experiments undertaken in an acetone/dry ice bath thermostatted at -74 ± 2 °C. Typically the solutions were degassed for 30 min using impurity-free nitrogen (BOC Gases, Guildford, Surrey, UK) to remove any trace oxygen.

5.2. General

Tetrahydrofuran was distilled before use from sodium-benzophenone ketyl radical under an argon atmosphere. All reactions were carried out under argon using oven-dried glassware. Proton and carbon NMR spectra were recorded on Fourier transform spectrometers using an internal deuterium lock. Chemical shifts are quoted in parts per million (ppm) downfield of tetramethylsilane. Coupling constants *J* are quoted in hertz. Both the proton and carbon NMR spectra of compound **1** and **9** exhibit doubling of some signals because of the presence of Boc group rotamers. Infrared spectra were recorded on an FTIR spectrophotometer. Electrospay ionization (ESI) and chemical ionization (CI) mass spectra and accurate mass data were recorded.

5.2.1. 2(*RS*)-Isopropyl 1-(*tert*-butoxycarbonyl)-2-iodomethyl-2,5-dihydropyrrole-2-carboxylate 1. Ammonia (250 mL) was freshly distilled onto cut lithium wire (111 mg, 16.0 mmol, 4.0 equiv) under an atmosphere of argon at -78 °C. The resulting dark blue solution was stirred for 1 h before the addition of bis(methoxyethyl)-amine (5.90 mL, 40.0 mmol, 10.0 equiv) and dry tetrahydrofuran (20 mL). After 5 min isopropyl 1-(*tert*-butoxycarbonyl)pyrrole-2-carboxylate[2] (1.01 g, 4.0 mmol) dissolved in dry tetrahydrofuran (30 mL) was added dropwise over 5 min and stirred for a further 55 min, the dark blue colour persisting throughout. Isoprene ($\sim$0.25 mL) was added until the dark blue colour disappeared. On addition of diiodomethane (2.26 cm^3, 28.0 mmol, 7.0 equiv) the rapidly stirring solution turned dark brown and was allowed to stir for 15 min before the addition of saturated ammonium chloride (5 mL). The reaction was allowed to warm to ambient temperature and ammonia evaporated. Aqueous citric acid (1.0 mol dm^{-3}, 125 mL) was added and the solution stirred for 5 min before being separated. The aqueous layer was extracted with ether (4×150 mL), the combined organic extracts were dried (anhydrous magnesium sulfate) and evaporated under reduced pressure. The residue was chromatographed [SiO_2, ethyl acetate-light petroleum (bp 40–60 °C), 5:95], to give the dihydropyrrole **1** (1.49 g, 94%) as an oil; R_f [ethyl acetate-light petroleum (bp 40–60 °C), 5:95] 0.11; ν_{max} (thin film)/cm^{-1} 2978 (CH), 2933 (CH), 2866, 1727 (CO), 1704 (NCO), 1550 (C=C), 1258 (COC), and 1177 (COC); δ_H (400 MHz; $CDCl_3$) 6.11, 6.05 (1H, dt, $J=6.1$, 2.0 Hz, CH=CH–C), 5.42, 5.38 (1H, dt, $J=6.1$, 2.0 Hz, CH_2CH=CH), 4.99 (1H, sep, $J=6.3$ Hz, OCH), 4.40, 4.12 (1H, d, $J=10.6$ Hz, CH_AH_BI), 4.31–4.12 (2H, m, NCH_2), 3.85, 3.83 (1H, d, $J=10.6$ Hz, CH_AH_BI), 1.47, 1.45 (9H, s, CMe_3) and 1.25–1.19 (6H, m, $CHMe_2$); δ_C (100.6 MHz; $CDCl_3$) 168.0, 167.7, 153.1, 152.7, 130.4, 130.2, 129.4, 129.1, 80.9, 80.1, 75.1, 74.4, 69.8, 69.6, 55.4, 55.2, 28.4, 21.7, 21.6, 13.7, 13.4; *m/z* (+ESI) 417 (23, MNa^+) and 396 (MH^+); (Found MNa^+, 418.0482. $C_{14}H_{22}NO_4INa$ requires MNa, 418.0491).

5.2.2. (*meso*)-Diisopropyl 2,5-bis-(3-*tert*-butoxycarbonyl-amino-propenyl)-hex-*cis*-enedioic-1-carboxylate 4.

Freshly cut lithium wire (20.8 mg, 3.00 mmol, 3.0 equiv) was hammered out into a foil, cut into several small strips, and placed in a Schlenk tube containing DBB (798 mg, 3.00 mmol, 3.0 equiv) and some glass 'antibumping' granules. The tube was evacuated and purged with argon several times. The contents of the Schlenk tube were then stirred vigorously until the lithium foil had been completely reduced to a powder (typically 0.5–2 h) under an atmosphere of argon. The Schlenk tube was cooled to -78 °C under an atmosphere of argon, and tetrahydrofuran (25 mL) added, immediately resulting in a dark turquoise solution. Pyrroline **1** (394 mg, 1.00 mmol) dissolved in dry tetrahydrofuran (30 mL) were added dropwise over a period of 2–5 min. The turquoise colour persisted throughout the course of the substrate addition. The reaction mixture was stirred at -78 °C for a further 2 h and saturated ammonium chloride (5 mL) was added. The reaction mixture was separated and the aqueous layer extracted with ethyl acetate (3×15 cm^3). The combined organic extracts were dried (anhydrous magnesium sulfate) and evaporated under reduced pressure. The residue was chromatographed [SiO_2, light petroleum (bp 40–60 °C), then ethyl acetate-light petroleum (bp 40–60 °C), 10:90], to give the carbamate **4** (198 mg, 79%) as needles, mp 87–90 °C [(from dichloromethane-light petroleum (bp 40–60 °C)]; R_f [ethyl acetate-light petroleum (bp 40–60 °C) 20:80] 0.50; ν_{max} (solution cell)/cm^{-1} 3370 (NH), 2978 (CH), 2936 (CCH_3), 1713 (CO), 1457 (CH_2), 1441 (CH_3), 1420 (CH_2), 1250 (COC), 1043 (COC) and 1021 (COC); δ_H (400 MHz; $CDCl_3$) 5.63–5.60 (2H, m, NCH_2CH=CH), 4.46–5.40 (2H, m, NCH_2CH=CH), 4.97 (2H, sep, $J=6.3$ Hz, OCH), 4.73–4.69 (2H, br m, NH), 3.86–3.69 (4H, dm, NCH_2), 3.27–3.52 (2H, m, $CHCO_2$), 1.78–1.66 (2H, m, $CHCH_AH_B$), 1.43 (20H, apparent s, CMe_3 and $CHCH_AH_B$) and 1.22–1.19 (12H, m, $CHMe_2$); δ_C (100.6 MHz; $CDCl_3$) 172.7, 155.7, 130.1, 129.2, 79.3, 68.2, 44.0, 37.7, 29.6, 28.4, 21.7 and 21.6; δ_H (400 MHz; C_6D_6) 5.46–5.36 (4H, m, CH=CH), 4.97, 4.96 (2H, sep, $J=6.3$ Hz, OCH), 4.55, 4.45 (2H, s, NH), 3.90–3.79 (2H, NCH_AH_B), 3.66–3.60 (2H, m, NCH_ACH_B), 3.33 (2H, s, $CHCO_2$), 1.84–1.80 (2H, m, $CHCH_AH_B$), 1.58–1.49 (2H, m, $CHCH_AH_B$), 1.44, 1.43 (18H, s, CMe_3) and 1.02, 1.00 (12H, d, $J=6.3$ Hz, $CHMe_2$); δ_C (100.6 MHz; C_6D_6) 172.8, 155.9, 130.5, 130.4, 78.9, 68.1, 44.4, 38.3, 30.2, 28.7, 22.0 and 21.9; *m/z* (+ESI) 563 (100%, MNa^+), 542 (1, MH^+) and 442 (100, MH^+–CO_2CMe_3); (Found MH^+, 541.3488. $C_{28}H_{49}N_2O_8$ requires MH, 541.3489).

5.2.3. 1-(*tert*-Butoxycarbonyl)-pyrrolidine.

Pyrrolidine (372 mg, 5.23 mmol) was dissolved in dichloromethane (50 mL) and stirred at ambient temperature. Di-*tert*-butyl dicarbonate (1.24 g, 5.69 mmol, 1.1 equiv) dissolved in dichloromethane (10 mL) was added dropwise and the reaction stirred under an atmosphere of argon for 2 h. The mixture was evaportated under reduced pressure. The residue was chromatographed [SiO_2, ether-light petroleum (bp 40–60 °C), 10:90], to give the carbamate (604 mg, 68%) as an oil; δ_H (400 MHz; $CDCl_3$) 3.30 (4H, d, $J=9.6$ Hz, NCH_2), 1.83 (4H, m, CH_2) and 1.46 (9H, s, CMe_3). δ_C (100.6 MHz; $CDCl_3$) 154.7, 78.8, 45.9, 28.5 and 25.0. All data agreed with that previously published.[16]

5.2.4. Isopropyl cyclohexanecarboxylate.

Isopropyl alcohol (0.38 mL, 4.97 mmol) was dissolved in dichloromethane (30 mL) and triethylamine (2.20 mL, 15.8 mmol, 3.2 equiv) added. The reaction was cooled to 0 °C under an atmosphere of argon and cyclohexane carbonyl chloride (0.91 mL, 6.80 mmol, 1.4 equiv) was added dropwise and allowed to warm to room temperature. After 4 h of stirring the mixture was poured into saturated ammonium chloride (50 mL) and the layers separated. The aqueous layer was extracted with ether (3×50 cm^3), the combined organic extracts were dried (anhydrous magnesium sulphate) and evaporated under reduced pressure. The residue was chromatographed [SiO_2, ethyl acetate-light petroleum (bp 40–60 °C), 2:98], to give the ester (651 mg, 77%) as a liquid; δ_H (400 MHz; $CDCl_3$) 4.99 (1H, hp, $J=6.3$ Hz, OCH), 2.24 (1H, tt, $J=11.2$, 3.6 Hz, CHCO), 1.94–1.84 (2H, m, $C_2H_AH_B$, $C_6H_AH_B$), 1.82–1.69 (2H, m, $C_3H_AH_B$, $C_5H_AH_B$), 1.49–1.35 (2H, m, $C_2H_AH_B$, $C_6H_AH_B$), 1.34–1.12 (4H, m, $C_3H_AH_B$, $C_5H_AH_B$, and CH_2), 1.66 (6H, d, $J=6.3$ Hz, $OCHMe_2$). δ_C (100.6 MHz; $CDCl_3$) 175.6, 67.0, 43.4, 29.0, 25.8, 25.4 and 21.8. All data agreed with that previously published.[17]

5.2.5. 2(*RS*)-Methyl 1-(*tert*-butoxycarbonyl)-2-iodo-methyl-2,5-dihydropyrrole-2-carboxylate 9.

Ammonia

(150 mL) was freshly distilled onto cut lithium wire (55.2 mg, 8.00 mmol, 4.0 equiv) under an atmosphere of argon at −78 °C. The resulting dark blue solution was stirred for 1 h before the addition of bis(methoxyethyl)-amine (1.48 mL, 10.0 mmol, 5.0 equiv) and dry tetrahydrofuran (20 mL). After 5 min methyl 1-(*tert*-butoxycarbonyl)-pyrrole-2-carboxylate (452 mg, 2.0 mmol) dissolved in dry tetrahydrofuran (30 mL) was added dropwise over 5 min and stirred for a further 55 min, the dark blue colour persisting throughout. Isoprene (∼0.25 mL) was added until the dark blue colour disappeared. On addition of diiodomethane (0.83 mL, 8.00 mmol, 4.0 equiv) the rapidly stirring solution turned dark brown and was allowed to stir for 15 min before the addition of saturated ammonium chloride (5 mL). The reaction was allowed to warm to ambient temperature and ammonia evaporated. Aqueous citric acid (1.0 mol dm^{-3}, 125 mL) was added and the solution stirred for 5 min before being separated. The aqueous layer was extracted with ether (4×150 mL), the combined organic extracts were dried (anhydrous magnesium sulfate) and evaporated under reduced pressure. The residue was chromatographed [SiO_2, ethyl acetate-light petroleum (bp 40–60 °C), 5:95], to give the dihydropyrrole **6** (134 mg, 18%) as an oil; R_f [ethyl acetate-light petroleum (bp 40–60 °C), 4:96] 0.11; ν_{max} (thin film)/cm^{-1} 2980, 1730, 1703, 1393, 1258, 1176, 1106 and 973; δ_H (400 MHz; $CDCl_3$) 6.19–6.07 (1H, m, CH=CH–C), 5.49–5.39 (1H, m, CH_2CH=CH), 4.43, 4.12 (1H, d, J=10.9 Hz, CH_AH_BI), 4.37–4.12 (2H, m, NCH_2), 3.82, 3.79 (1H, d, J=10.9 Hz, CH_AH_BI), 3.74 (3H, s, OMe) and 1.40, 1.45 (9H, s, CMe_3); δ_C (100.6 MHz; $CDCl_3$) 169.3, 168.8, 153.2, 152.6, 130.7, 130.4, 129.2, 128.9, 80.9, 80.4, 75.0, 74.3, 55.2, 55.1, 53.0, 52.9, 28.4, 28.3, 13.5 and 13.1; *m/z* (+CI) 368 (1, MH^+); (Found MNa^+, 368.0364. $C_{12}H_{19}NO_4INa$ requires MH, 368.0359).

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