Electroreductive coupling of vinylpyridines and vinylquinolines: radical anion–substrate cycloaddition?

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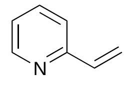
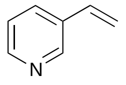
Cathodic reduction of 2- and 4-vinylpyridine and of 2-vinylquinoline gives *trans*-1,12-di(heteroaryl)cyclobutanes as major products; they arise *via* radical anion–substrate cycloaddition.

Much recent evidence[1,2] is in favour of electrohydrodimerisation (EHD) proceeding through the coupling of the initially-formed radical anions (the radical anion–radical anion route). An alternative, less well supported, is attack on the starting material by conjugate addition (the radical anion–substrate route) or, much less discussed, by cycloaddition between radical anion–substrate. Oxidative analogues of this possibility are well-known,[3] and there is one report[4] of the formation of cyclobutanes from aryl vinyl sulfones in a cathodically initiated reaction.

In examining templating effects on the stereoselectivity of EHD reactions[2] we explored the controlled potential cathodic reduction of 2-vinylpyridine **1** at a mercury cathode in DMF (see Table 1). Compound **1** has a potentially ligating nitrogen atom which is close to the reaction centre for EHD. Previously the EHD reactions of both **1** and 4-vinylpyridine (**3**) were reported[5] to give, respectively, only the linear hydrodimers **6a** and **6b**. However, we discovered that substantial amounts of pyridine-substituted cyclobutanes were formed, together with the expected linear hydrodimers **6a** and **6b**. We now find that cyclobutane formation is quite general for vinylpyridines **1** and **3** and the vinylquinoline **4**. We present here compelling evidence for the proposed cycloaddition between radical anion–substrate.



1



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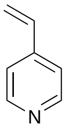

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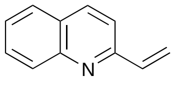

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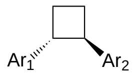
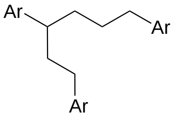
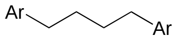


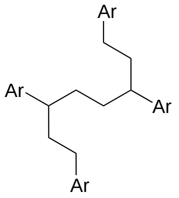
5a Ar^{1} = 2-pyridyl, Ar^{2} = 2-pyridyl
b Ar^{1} = 4-pyridyl, Ar^{2} = 4-pyridyl
c Ar^{1} = 2-quinolyl, Ar^{2} = 2-quinolyl
d Ar^{1} = 4-pyridyl, Ar$_{2}$ = 2-pyridyl
e Ar^{1} = 2-pyridyl, Ar$_{2}$ = 2-quinolyl



7a



6a Ar = 2-pyridyl
b Ar = 4-pyridyl
c Ar = 2-quinolyl



7b

7a,**b** Ar = 4-pyridyl

Controlled potential electrolysis (CPE) of alkenyl-substituted pyridines and quinolines gave the *trans*-1,2-di(heteroaryl)cyclobutanes **5a-e**. For two examples **5b** and **5c** this conclusion was established by X-ray crystallography,[6] which in turn allowed unambiguous interpretation of high-field NMR spectroscopic data used to characterise all of the cyclobutane products.[7] The other major products of the electrolyses were the linear hydrodimers **6a–c**.

From **3** and **4** substantial amounts (*ca.* 30%) of oligomers were formed and found, for **3**, to be the trimer **7a** and the tetramer **7b**. The position of vinyl-substitution is important; electrolysis of 3-vinylpyridine **2** gave predominantly cathodic hydrogenation of the double bond with only a 22% yield of an inseparable mixture of the corresponding cyclobutane and linear hydrodimer (3 : 7 ratio). The results of controlled potential electrolyses and the conditions used are summarised in Table 1.

The cyclobutanes **5a–c** have also been made[8] by a photochemical method which gave in our hands inseparable mixtures of the *cis*- and *trans*-isomers in case of cyclobutanes **5a** and **5b** with overall yields substantially lower than those reported. In addition to its mechanistic significance the electrochemical method is superior with regard to yield and product selectivity.

The cyclobutanes are electroactive at potentials close to the reduction potentials of the starting materials. Similar reduction, with ring opening, of cyclobutanes occurs in pulse radiolysis[9] of the methyl esters of truxillic acids. Cyclic voltammetry typically indicates an irreversible reduction followed by reversible reduction of the corresponding linear hydrodimer. Controlled potential electrolysis of cyclobutane **5c** gave linear hydrodimer **6c** quantitatively in a 2 F process. Electrolysis was therefore carried out at the foot of the relevant cyclic voltammetric wave, usually at low current density (1–3 mA

Table 1 Preparative scale controlled potential electrolyses[a]

Cyclobutane	Yield (%)[b]	E_{work}/V[c]	Charge/F mol^{-1}
5a	49	−2.0	0.80
	63	−1.75	0.43[d]
5b	trace	−2.0	0.81
	15	−1.6	0.16
5c	trace	−1.6	0.75
	53	−1.4	0.30
5d	8	−1.6	
5e	14	−1.4	

[a] Hg pool cathode, DMF–Et$_4$NBr (0.1 M), divided cell. [b] Isolated yields. [c] Ag wire reference electrode; $E°$ (Ag/AgBr) = −0.170 V *vs.* SCE. [d] Electrolysis followed by GC analysis of reactant and products.

Table 2 Reduction potentials[a] of vinylheteroaromatics and cyclobutanes

Vinylhetero-aromatic	$E°$/V	Cyclo-butane	$E_{\text{pc}}(1)$/V	$E°(2)$/V
1	−2.313	**5a**	−2.585[b]	
2	−2.322	**5b**	−2.441[b]	
3	−2.147	**5c**	−2.118[c]	−2.182
4	−1.915	**5d**	−2.495[b]	
		5e		−2.154[d]

[a] Hg–Pt microelectrode, DMF–Et$_4$NBr, V *vs.* SCE; concentration for $E°$ values = 4 mM, for E_p values = 2 mM. [b] v = 10 V s^{-1}. [c] v = 1 V s^{-1}; shoulder on second reduction wave. [d] First irreversible reduction wave was cathodically shifted under reversible second reduction wave.

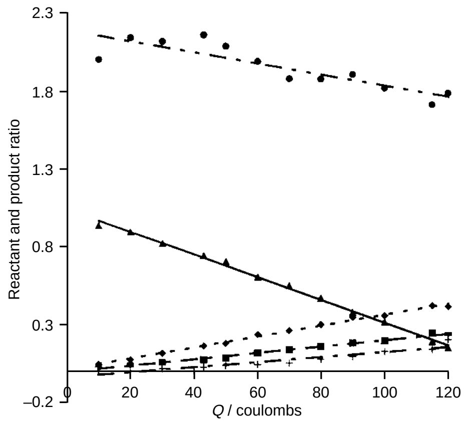


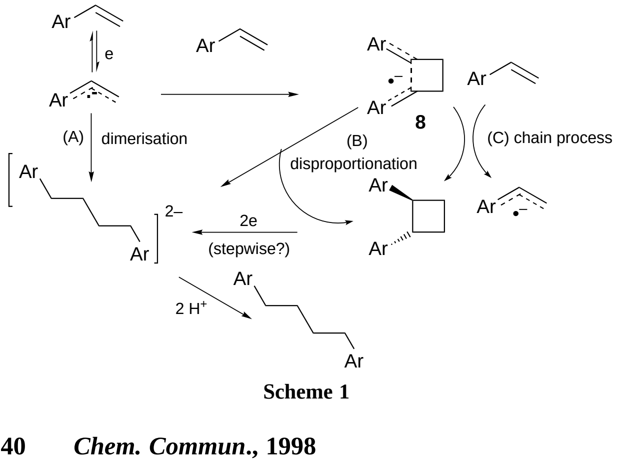
Fig. 1 Reaction profile for controlled potential electrolysis of **1** (see Table 1); (●) (CB)/(EHD), (▲) (VP)/[Total], (◆) (CB)/[Total], (■) (EHD)/[Total], (+) (VPH_2)/[Total]. [Total] = (VD) + (CB) (EHD) + (VPH_2).

cm^{-2}) for concentrations in the range 60 mM–0.3 M. Relevant reduction potentials[10] are given in Table 2.

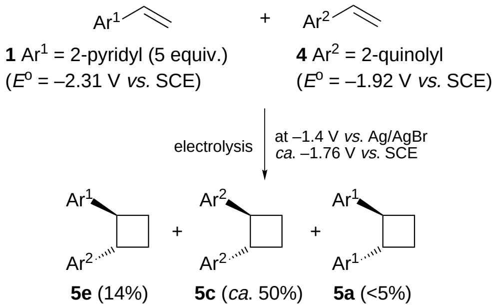
Vinylpyridines **1** and **3** give chemically irreversible reduction on cyclic voltammetry at low scan rates but reversibility is apparent for the reductions of **2** and **4** at modest scan rates (< 10 V s^{-1}). Thus, apart from direct further reduction of the cyclobutanes it is possible that electron transfer from the persistent first-formed radical anions will take place to give redox-catalyzed cleavage of the cyclobutanes.

A reaction profile was constructed (Fig. 1) for cathodic constant potential reduction of **1** by using GLC analysis to follow relative concentrations of reactant and products as a function of charge passed. The results show clearly that **1** (VP) was consumed using 0.70 F. Furthermore cyclobutane **5a** (CB) and linear hydrodimer **6a** (EHD) were formed in almost constant proportion (2 : 1) throughout the electrolysis. A third product was that of 2 F cathodic hydrogenation (2-ethylpyridine). The profile and coulometry are consistent with consumption of the first-formed radical anion in parallel reactions; dimerisation leading to linear EHD, cycloaddition leading in a catalytic chain process to the cyclobutane, and cathodic hydrogenation leading to 2-ethylpyridine. The final molar proportions of products were **6a** (0.29), **5a** (0.51) and 2-ethylpyridine (0.20). Consequently the proportion of charge consumed, given that EHD is a 1 F process and hydrogenation a 2 F process, must be linear hydrodimer (0.29 F) and 2-ethylpyridine (0.4 F), totalling 0.69 F. 2-Vinylpyridine **1** was consumed in 0.70 F, which indicates that the cyclobutane is formed without overall charge consumption. This experiment is reproducible and repeated experiments gave similar results.

The possibilities are detailed in Scheme 1, which illustrates formation of the linear hydrodimer by the usual radical anion–radical anion route (A), by disproportionation of the first product of cycloaddition, the radical anion route (B), and by subsequent 2e reduction of the cyclobutanes. The 1,2-di(heteroaryl)cyclobutanes are formed by oxidation of the intermediate radical anion (tentatively represented as **8**); in principle this could be the result of disproportionation (route B) or of a chain process as in the vinyl-sulfone case[3] (route C). The results from the reaction profile (Fig. 1) indicate cyclobutane formation *via* the chain process with no overall consumption of charge.



Scheme 1



Scheme 2

Co-electrolysis gives further insight (Scheme 2 and Table 1). Co-electrolysis of **3** in the presence of a five-fold excess of **1**, at the potential of the more easily reduced substrate **3**, gave the cross-coupled cyclobutane **5d** and the homo-coupled cyclobutane and linear dimer **6b**, respectively. Cyclobutane **5a** was found in only trace amounts. Similar behaviour was observed for the co-electrolysis of **4** and **1**. Cross-coupled cyclobutanes are therefore formed by reaction between the radical-anion formed at the lower potential and the other, unreduced, component. Formation of both radical anions, *e.g.* by homogeneous electron transfer, would give all three possible cyclobutanes in comparable amounts.

Thus there is compelling evidence for the formation of the cyclobutanes by allowed cycloaddition between vinylpyridines or vinylquinolines and the radical anions derived from them. A detailed mechanistic and kinetic examination is underway, aimed at distinguishing conclusively between the possibilities for the follow-up reactions as outlined in Scheme 1.

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Notes and References

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6 *Crystal data* for **5b**: colourless crystal, monoclinic, $P2_1n$, a = 26.095(10), b = 7.138(2), c = 6.134(3) Å, β = 92.59(3)°, V = 1141.4(8) Å^3, Z = 4, R = 0.0706, GOF = 0.677. CCDC 182/719.
7 All cyclobutanes were characterised by high resolution mass spectrometry, ^1H NMR (250 and 600 MHz) and ^{13}C NMR (62.5 MHz) spectroscopy; signal assignments were made using 600 MHz TOCSY, NOESY and HMQC spectroscopy. Satisfactory elemental analyses were obtained from all crystalline compounds, while the purity of oils was checked by GC analysis.
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10 Formal reduction potentials (*E*°) were measured in collaboration with O. Hammerich and M. F. Nielsen (University of Copenhagen).

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