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Electro-organic reactions. Part 52: Diels–Alder reactions in aqueous solution via electrogenerated quinodimethanes

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Abstract

ortho-Quinodimethanes (*o*-QDMs) are conveniently generated cathodically in aqueous electrolyte in the presence of *N*-methylmaleimide, which acts as both redox mediator and dienophile. *endo*-Diels–Alder adducts are formed efficiently and rapidly and competition from electrohydrodimerisation of *N*-methylmaleimide is completely suppressed. Kinetic and coulometric evidence suggests that initial electron transfer is to a complex between the *o*-QDM precursor and *N*-methylmaleimide (hydrophobic packing). © 2000 Elsevier Science Ltd. All rights reserved.

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Water is the ideal solvent for clean organic electrosynthesis. It has high conductivity, is cheap, benign and a poor hydrogen atom donor. The problem of usually poor solubility of reactants has to be overcome and where initial formation of radical-anions or radical-cations is involved protonation and deprotonation, respectively, can compete with more desirable coupling reactions. Detergent electrolytes with an hydrophobic cation may be used, as in the Monsanto process for the conversion in aqueous media^{1–4} of acrylonitrile into adiponitrile (electrohydrodimerisation, EHD). We have shown⁵ that the high stereoselectivity associated with cyclic EHD in DMF is retained in an aqueous solution with tetraethylammonium tosylate electrolyte. Functionalisation of reactants with hydrophilic groups is an alternative and neutral reactive intermediates such as quinodimethanes (QDMs) are unlikely to undergo acid–base reactions in water.

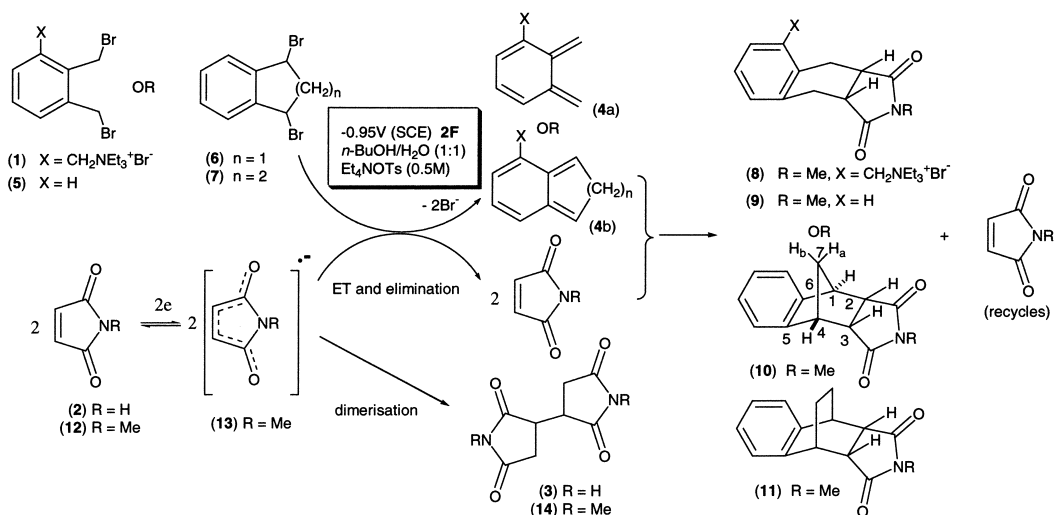
We have demonstrated^{6,7} the versatility in Diels–Alder reactions of *ortho*-quinodimethanes generated cathodically from α,α' -dibromo-*o*-xylenes in the presence of dienophiles that also act as redox catalysts. We report here on the successful redox catalysed electro-generation in aqueous electrolyte of *o*-QDMs from α,α' -dibromo-*o*-xylene derivatives with an effective in situ Diels–Alder

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reaction. Diels–Alder reactions in water have received much attention^{8–13} because of reported rate enhancement and differences in stereochemistry vis-à-vis reaction in aprotic solvents.

Mediated cathodic reduction in water: voltammetry and coulometry. Scheme 1 outlines the experiments performed and the likely reaction pathways based on the precedent^{6,7} for similar reactions in DMF. Preliminary experiments involved **1**, a water-soluble precursor for the QDM (**4**), and maleimide (**2**), a water-soluble dienophile/redox catalyst. The coulometric evidence for reactions proceeding according to the predictions in Scheme 1 was confirmed by controlled potential electrolyses on a voltammetric scale (1 mM) with monitoring of the peak current decay as a function of charge (Fig. 1). It is evident that in the presence of **1** the electrolysis of **2** changes smoothly from 1 F reaction to 2 F reaction. Preparative scale electrolysis in H₂O–NaBr (0.2 M) proceeded smoothly with a consumption of 2 F for the co-electrolysis of **1** and **2** and with 1 F for electrolysis of maleimide (**2**) alone. However, the separation of products was problematical. Maleimide is, however, known¹⁴ to undergo quantitative one-electron electrohydrodimerisation (EHD) in water, to **3**, which is consistent with our observation. In contrast, consumption of 2 F, at the reduction potential of the mediator **2**, as also observed, is what is expected for redox-catalysed formation of the quinodimethane (**4**).



Scheme 1. Mediated cathodic formation of *o*-quinodimethanes with concurrent cycloaddition

Preparative-scale co-electrolysis of *N*-methylmaleimide (12**) and *o*-QDM precursors (**1**, **5–7**).** The proposal that the radical-anion of *N*-methylmaleimide (**12**) acts as a redox mediator, as indicated in Scheme 1, is firmly based on the precedent⁶ of analogous reactions in DMF. Successful preparative electrolysis of **1** was accomplished using *N*-methylmaleimide as dienophile/mediator, in water–NH₄OAc (0.1 M). Equivalent amounts (0.06 M) of the two substrates were reduced at a mercury pool cathode in the range –0.6 to –0.9 V versus SCE and gave **8** in ca. 50% yield. Isolation of the hygroscopic product was difficult (removal of the solvent at 50°C, azeotropic distillation with benzene, and trituration with dry ether). For more convenient isolation of products and the use of less water-soluble QDM precursors, and *N*-methylmaleimide (**12**) as the dienophile, a detergent electrolyte (Et₄NOTs) and a protic co-solvent (*n*-BuOH) were used. Derivatives **5–7** were sufficiently soluble in this electrolyte and smooth co-electrolysis, analogous

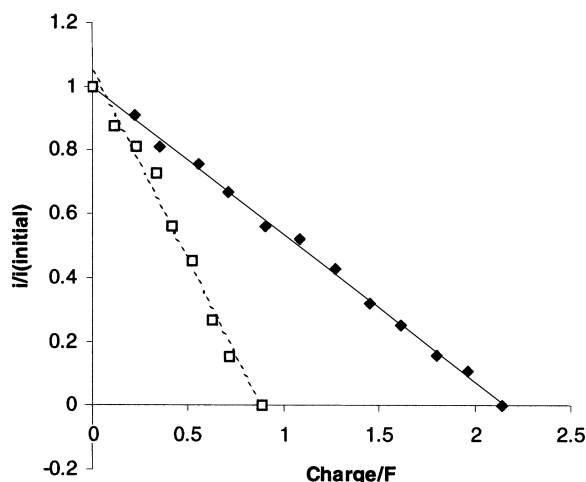


Figure 1. Controlled potential coulometry in H₂O–NaBr (0.2 M): (---) maleimide (2); (—) maleimide (2)+(1), both 1 mM

to that found for DMF solution, was observed yielding the expected Diels–Alder adducts **9–11** (see Table 1). Where relevant, only *endo* adducts were obtained and EHD of (**12**) was not detected. The yields of **9** and **10** are good; the lower yield of **11** is a consequence of competing elimination from **7** with loss of HBr and formation of naphthalene.

Stereochemistry of the adducts. The adduct **10** was formed exclusively as the *endo*-isomer; the assignment was made by observation of the 2D NOESY correlations in the ¹H NMR spectrum. In particular, using the structure and numbering for **10** in Scheme 1, a crucial correlation was observed between H²=H³, and H^{7a}. Complete assignment of the NMR spectrum is given at the end. Furthermore, the adduct was crystalline and an X-ray crystallographic structure was determined (Fig. 2).

The influence of solvent on the stereochemistry of the Diels–Alder reaction has been examined^{9,10} and it is commonly held that aqueous conditions favour *endo* product formation. We observe this but in DMF solution *endo* adducts also predominated in the electrochemical route.^{6,7}

Further mechanistic discussion. Cyclic voltammetric experiments give clear evidence⁶ of redox catalysis in the cathodic reaction in DMF between dienophiles (maleic anhydride derivatives) and 1,2-bis(bromomethyl)arenes. Characteristic catalytic currents are seen as a consequence of homogeneous electron transfer from the persistent radical-anions of the dienophiles. Similarly, it is not possible to verify this mechanism for aqueous solution because reduction of maleimide and *N*-methylmaleimide is irreversible at least up to 100 V s⁻¹, indicating rapid dimerisation of the radical-anions. However, the dimerisation of *N*-methylmaleimide radical-anion is relatively slow in DMF and quasi-reversible reduction is easily observed. Consequently, the rate coefficient for dimerisation in DMF of *N*-methylmaleimide radical-anion was measured by cyclic voltammetry at 50 V s⁻¹, combined with digital simulation (DigiSim), and found to be $k_2 = (9.02 \pm 0.02) \times 10^4 \text{ M}^{-1} \text{ s}^{-1}$. The value¹⁵ for methyl cinnamate radical-anions in DMF–H₂O (0.28 M) is $k_2 = (7.8 \pm 0.72) \times 10^2 \text{ M}^{-1} \text{ s}^{-1}$, i.e. in DMF the *N*-methylmaleimide electrohydrodimerisation is relatively fast.

Table 1
Reduction potentials^a and products of co-electrolyses

Substrate	-E _p /V vs. SCE	Electrolysis components	-E _{red}	Charge/F	Product (yield)
2	1.3 (aqueous) 1.2 (DMF)	2	ca. 1.0	1	Dimer (3, not isolated)
12	1.2 (aqu.) 1.22 (DMF)	12	0.95	1	Dimer (14, 40%) ^b
1	1.4 (aqu.) 1.42 (DMF)	12 + 1	-0.6 to -0.9	2	Adduct (8, 52%) ^c
5	1.7 (aqu.) 1.22 (DMF)	12 + 5	0.95	2	Adduct (9, 84%) ^b
6	1.44 (aqu.)	12 + 6	0.5 to 0.9	2	Adduct (10, 60%) ^b
7	1.44 (aqu.)	12 + 7	0.4 to 0.9	1.4	Adduct (11, 33%) ^b

a. By cyclic voltammetry at 0.3 V s⁻¹, Hg/Pt cathode in DMF-Et₄NBr (0.1M) or in H₂O-BuOH (1:1)-Et₄NOTs (0.5 M); b. exhaustive electrolysis in H₂O-BuOH (1:1)-Et₄NOTs (0.5 M), controlled potential, Hg pool cathode, divided cell; c. in H₂O-NH₄OAc (0.1 M).

Linear sweep voltammetry¹⁶ shows that a change from DMF to a protic solvent (methanol) causes an increase in the rate for cinnamate esters of 2–3 orders of magnitude [for phenyl cinnamate^{15,16} in DMF–H₂O (0.28 M) $k_2 = (8.1 \pm 0.4) \times 10^3 \text{ M}^{-1} \text{ s}^{-1}$ cf. 7.3×10^5 in methanol]. This is explained¹⁶ in terms of hydrogen bonding to the carbonyl group so that the developing radical-anion is protonated in concert with electron transfer; it is the protonated radical-anions (neutral radicals) that dimerise. *N*-Methylmaleimide would be at least as strongly hydrogen bonded in water as cinnamate is in methanol and a similar increase in rate would give $k_2 = \text{ca. } 10^7 \text{ to } 10^8 \text{ M}^{-1} \text{ s}^{-1}$. To outrun dimerisation the homogeneous electron transfer reaction between ‘free’ *N*-methylmaleimide radical-anion (if formed) and the 1,2-bis(bromomethyl)arenes must be even faster. Rate constants for homogeneous electron transfer in DMF between organic radical-anions and, e.g. *vic*-dibromocyclohexanes¹⁷ are in the range 10^2 – $10^6 \text{ M}^{-1} \text{ s}^{-1}$.

In line with explanations given^{8,11,13} for the substantial rate enhancements for Diels–Alder reactions in water vis-à-vis non-polar organic solvents we propose (Scheme 2) that in water the dienophile and 1,2-bis(bromomethyl)arene form a complex driven by ‘hydrophobic packing’ associated with binding interactions between substances with non-polar regions dissolved in water. *N*-Ethylmaleimide is one of the dienophiles for which this effect is observed.⁸ In our case the association will promote rapid intramolecular electron transfer, possibly concerted with halide elimination and rapid second electron transfer. Thus, the *ortho*-quinodimethane will be formed whilst proximate to the dienophile, ensuring rapid Diels–Alder reaction at the expense of hydrodimerisation.

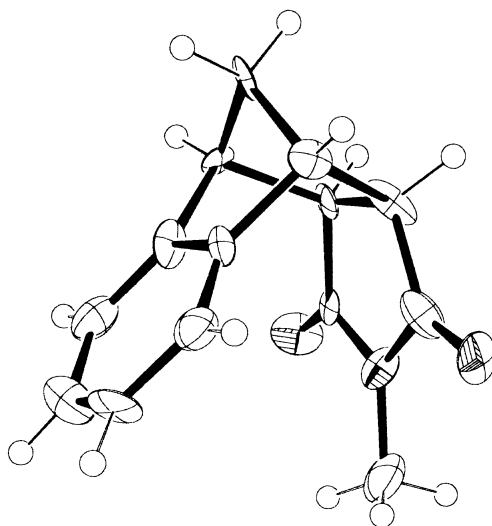
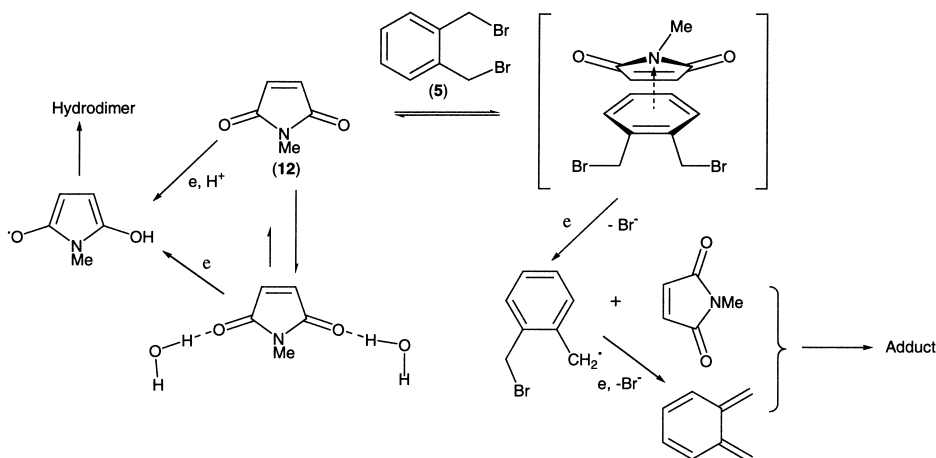


Figure 2.



Scheme 2. Mechanistic hypothesis re. competition between fast EHD and homogeneous electron transfer

Electrochemical experiments. Equipment and procedures were as described in earlier papers^{6,7,15} in this series.

Starting materials and products. Known starting materials were prepared by minor modification of literature methods. Exceptions were: [2,3-bis(bromomethyl)benzyl]triethylammonium bromide (**1**) that was obtained in 70% yield from the known¹⁸ 1,2,3-tris(bromomethyl)benzene by treatment with triethylamine in chloroform (48 hours/rt). Recrystallisation (EtOH–H₂O) gave white crystals, m.p. 155–156°C; ¹H NMR (250 MHz, D₂O): 1.48 (t, 9H, *J* = 8 Hz, N(CH₂CH₃)₃), 3.53 (q, 6H, *J* = 8 Hz, N(CH₂CH₃)₃), 4.72 (s, 2H, CH₂N), 4.95 (s, 2H, 3-CH₂Br), 5.05 (s, 2H, 2-CH₂Br), 7.65 (m, 4,5-H), 7.79 (m, 1H, 6-H); *cis*-1,2,3,4-tetrahydronaphthalene-2,3-dicarboxy-*N*-methyl imide (**9**), white crystals, m.p. 143–145°C; IR (KBr, ν , cm⁻¹): 3004 (Ar-H), 2954, 2848 (CH₂), 1697, 1684 (CONR), 771 (Ar-H); ¹H NMR (600 MHz, CDCl₃): 2.70 (3H, s, N-CH₃), 2.85 (2H, dm, *J* = 14.6,

2.0 Hz, Ar-CH₂), 3.04 (2H, dd, $J = 14.6, 2.5$ Hz, Ar-CH₂), 3.17–3.21 (2H, m, CH-CO), 7.03–7.11 (4H, m, Ar-H), m/z (FAB, M+1) 216.1016, C₁₃H₁₃NO₂+1 requires: 216.1025; *endo-N*-methyl-2,3-dicarboxyimido-5,6-benzobicyclo[2.2.1]heptane (**10**), white crystals, m.p. 158–159°C (lit.¹⁹ 158°C); ¹H NMR (600 MHz, CDCl₃): 1.92 (1H, dm, $J = 9.3$ Hz, H-7_a), 2.11 (1H, dm, $J = 9.3$ Hz, H-7_b), 2.27 (3H, s, N-Me), 3.45–3.48 (2H, m, CH-CO), 3.79–3.83 (2H, m, CH-Ar), 7.11 (2H, dd, $J = 5.2, 2.1$ Hz, Ar-H), 7.18 (2H, dd, $J = 5.2, 2.1$ Hz, Ar-H), m/z (FAB, M+1) 228.1018, C₁₄H₁₅NO₂+1 requires: 228.1025; *endo-N*-methyl-2,3-dicarboxyimido-5,6-benzobicyclo[2.2.2]octane (**11**), m.p. 173–176°C, ¹H NMR (250 MHz, CDCl₃): 1.50–1.65 (2H, m, 2×CH), 1.83–1.94 (2H, m, 2×CH), 2.45 (3H, s, N-Me), 3.09 (2H, m, 2×CH), 7.05–7.14 (2H, m, ArH), 7.20–7.30 (2H, m, Ar-H).

Crystal data. Structure of **10**, determined by M. Motevalli (QMW Crystallographic Service): C₁₄H₁₃NO₂, $M = 227.25$, orthorhombic, $a = 6.617(1)$, $b = 7.718(2)$, $c = 21.854(4)$ Å, $U = 1116.1(4)$ Å³, $T = 180$ K, space group $P2_12_12_1$, $Z = 4$, $\mu = 0.091$ mm⁻¹. The final R indices (all data) were $R_1 = 0.0698$, $wR_2 = 0.1565$. Full crystallographic data and lists of refined co-ordinates will be deposited at the Cambridge Crystallographic Data Centre, Cambridge, UK.

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