Controlled Oxidation of Enolates to α-Carbonyl Radicals and α-Carbonyl Cations[1]

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Depending on the oxidation strength of the one-electron oxidants either persistent α-carbonyl radicals or α-carbonyl cation derived benzofurans are formed from enolates **A1–A6**, a result which can readily be rationalized by the measured oxidation potentials of enolates **A1–A6** and α-carbonyl radicals **R1–R6**.

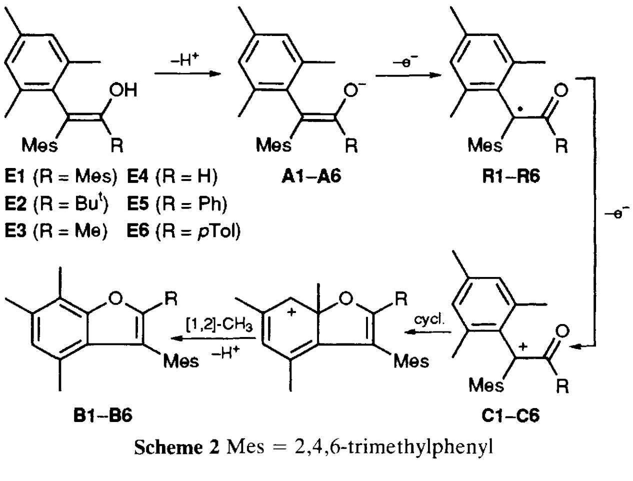
The transformation of stable carbanions to carbocations by two subsequent one-electron oxidation steps (or vice versa) represents an intriguing preparative umpolung reaction (Scheme 1).[2] As a consequence, this protocol has been used in the oxidation of phenolates to phenoxenium intermediates[3] and cyclopentadienyl anions to the antiaromatic cations[4] or reduction of iminium ions,[2] cyclopropenyl,[5] tropylium[5b] and triphenylmethyl[5b,6] cations to the corresponding anions. However, in spite of the facile generation of enolates, the above approach has never been investigated to generate α-carbonyl cation intermediates.[7] Herein, we report on the controlled one-electron oxidation of enolates to either α-carbonyl radicals or α-carbonyl cation intermediates and the relevant oxidation potentials.

The enolates **A1–A6** were formed quantitatively from enols **E1–E6**[8] (25×10^{-3} mol dm^{-3} in acetonitrile) by adding tetramethylammonium hydroxide (1 equiv.) as a base. Upon addition of the well-defined one-electron oxidant, tris(1,10-phenanthroline)iron(III) hexafluorophosphate $\mathrm{Fe^{III}(Phen)_3(PF_6)_3}$ (2 equiv.) ($E_{1/2}^{\mathrm{red}} = +0.70$ V *vs.* $\mathrm{Cp_2Fe}$), the reaction proceeded within several seconds affording the benzofurans **B1–B6** (55–88%), that could be identified by comparison with authentic material.[9] In accordance with our recent investigations on enol cation radical reactions[9a,b] the following mechanistic scheme seems to be operative. Thus, after two subsequent one-electron oxidation steps the enolates **A1–A6** form the α-carbonyl cations **C1–C6** which cyclize rapidly, and after a [1,2]-methyl shift followed by proton loss the benzofurans **B1–B6** are obtained (Scheme 2).

$$\mathrm{R^-} \underset{+\,e^-}{\overset{-\,e^-}{\rightleftharpoons}} \mathrm{R^\cdot} \underset{+\,e^-}{\overset{-\,e^-}{\rightleftharpoons}} \mathrm{R^+}$$

Scheme 1

One-electron oxidation of the enolates **A1–A6** in $\mathrm{CH_2Cl_2}$ using a weaker oxidant, tris-(*p*-methoxyphenyl)aminium hexafluoroantimonate (1 equiv.) ($E_{1/2}^{\mathrm{red}} = +0.13$ V *vs.* $\mathrm{Cp_2Fe}$), immediately afforded the red-coloured α-carbonyl radicals **R1–R6** in basically quantitative yield (measured by magnetic susceptibility). Although their EPR spectra were only poorly



Scheme 2 Mes = 2,4,6-trimethylphenyl

resolved, the *g*-values (2.0030–2.0040) are indicative of α-carbonyl radicals.[10] Even at room temperature they proved to be remarkably persistent (**R1**: observable for hours). Eberson has recently obtained the same EPR spectra[11] by the oxidation of our enols **E2–E4** using his 'T-complex'.[12] Also in this system the α-carbonyl radicals were stable for long periods. Similarly, the electrooxidation of **A1–A6** at a controlled potential ($E = 0.5\ V_{Ag}$) furnished the same radicals, as judged by their EPR spectra.

Direct evidence for some intermediates in the enolate oxidation was provided by cyclic voltammetry (CV) experiments (see Fig. 1),† confirming the proposed mechanistic scheme. In the case of R = Bu^t, which is representative for the other systems, we assign the first reversible wave (*A*) to the oxidation **A2** $\rightleftarrows$ **R2**‡ and the second irreversible one (*B*) to **R2** → **C2**. It is important to note that the i_p^{ox}(**A2** → **R2**) is approximately equal to i_p^{ox}(**R2** → **C2**). The third wave (*C*) is ascribed to the reversible oxidation of the benzofuran **B2**, the oxidation potential of which has been determined previously.[9a]

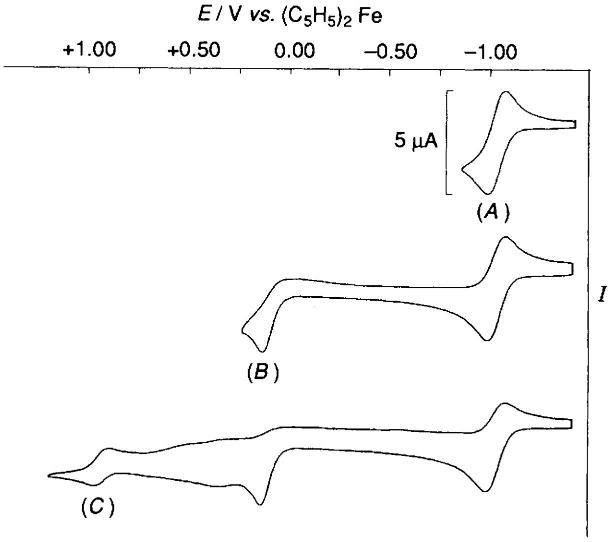


Fig. 1

To the best of our knowledge the transformation **A** $\rightleftarrows$ **R** constitutes the first example of a fully reversible redox system enolate $\rightleftarrows$ α-carbonyl radical.‡ The oxidation potentials $E_{1/2}^{ox}$ (Table 1) are comparable to those of related systems which have been reported by Fox[13] (triphenylethenolate, $E_{ox} = -0.82$ V *vs.* Cp_2Fe) and by Federlin[14] (*e.g.* PhHC=C(O$^-$)Me, $E_p^{ox} = -0.74$ V *vs.* Cp_2Fe). Since our $E_{1/2}^{ox}$ (**A1–A6**) are thermodynamically valid, a thermochemical cycle calculation[5,6,14,15] can be used to determine the pK_a values of enols **E1–E6** in acetonitrile (Table 2).§ In retrospect, these values readily explain why the enols can be quantitatively deprotonated in acetonitrile by $^-$OH [pK_a(H_2O) > 40].[16]

Despite extensive recent work on the redox data of organic radicals,[15a,17] the oxidation potentials E_p^{ox} of **R1–R6** are the first that have been directly determined for α-carbonyl radicals. The only other data known stem from the work of Okamoto, who determined the irreversible reduction potentials of three stable α-carbonyl cations,[18] however these values might be severely distorted by ion pairing and adsorbtion processes. Unfortunately, no reversible waves could be obtained for **R1–R6** even at scan rates of 2000 V s^{-1} or low temperatures. Although the peak potentials E_p^{ox} are irreversible data, they all exhibit the narrowness ($E_p - E_{p/2} = 50 \pm 5$ mV)¶ which is characteristic of a rapid follow-up reaction. The data‖ can be used for a first estimate of solution hydride affinities of α-carbonyl cations $\Delta G_{hydride}(\mathbf{C})_s$ and the corresponding pK_{R^+} data using Parker's approach (Table 2).[20] When compared to the pK_{R^+} (Mes_2CHOH) = −6.6[21] the above values suggest a significant destabilization exerted by the α-carbonyl group.

The irreversible waves (*B*), even at scan rates of 2000 V s^{-1}, point to a fast follow-up reaction of the α-carbonyl cations. Thus, the intramolecular cyclization of **C2** to finally afford the benzofuran **B2** exhibits a rate constant of at least 2.5×10^4 s^{-1}. This high reactivity of **C** may be explained by the severe out-of-plane twisting of the *syn* mesityl ring allowing for optimum orbital overlap in the cyclization reaction. In contrast, the corresponding benzofuran formation from An_2C^+COAn, a stable α-carbonyl cation described by Okamoto,[22] is very slow (50 °C, 8 h).

In summary we conclude that enolate oxidation is a feasible way not only to α-carbonyl radicals but, in the presence of stronger oxidants, also to α-carbonyl cation chemistry. The oxidation potential data are especially interesting in light of the recently discussed electron transfer pathway that may be

Table 1 Oxidation potentials† of the various enolates, α-carbonyl radicals, enols and benzofurans (*vs.* Cp_2Fe) (add 0.39 V to obtain potentials *vs.* SCE)

Compound R	$E_{1/2}^{ox}$/V **A**	E_p^{ox}/V **R**[a]	**E**[a]	$E_{1/2}^{ox}$/V **B**
1 Mes	−0.75	0.26	0.76	0.94
2 Bu^t	−1.01	0.15	0.64	0.93
3 Me	−0.90	0.21	0.68	0.99
4 H	−0.73	0.36	0.67	1.02[b]
5 Ph	−0.83	0.24	0.61	0.87
6 *p*Tol	−0.86	0.22	0.57	0.81

[a] E_p^{ox}: anodic peak potential. [b] Determined at $v = 1000$ V s^{-1} at a 25 μm Au ultramicroelectrode.

Table 2 pK_as of enols **E1–E6**, solution hydride affinities $\Delta G_{hydride}(\mathbf{C})_s$ and pK_{R^+} data for the corresponding α-hydroxy carbonyl compounds, derived from the redox potentials using thermochemical cycle calculations[20] (in acetonitrile)

Compound R	pK_a(**E**)	$\Delta G_{hydride}(\mathbf{C})_s$/ kJ mol^{-1}	pK_{R^+}
1 Mes	29	−454	−16
2 Bu^t	33	−443	−14
3 Me	31	−436	−13
4 H	28	−463	−18
5 Ph	30	−451	−16
6 *p*Tol	31	−449	−15

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† Cyclic voltammetry experiments: Potentiostat Model 362 (Princeton Applied Research) Pt 1 mm disc working electrode, substrate (1 mmol dm^{-3} in acetonitrile), 0.1 mol dm^{-3} Bu_4NPF_6 as electrolyte, scan rate: 0.1 V s^{-1}, all potentials are referenced against ferrocene/ferrocenium (Cp_2Fe), which has $E_{1/2} = +0.39$ V *vs.* SCE. All potential data were cross-checked by using tri-*p*-chlorophenylamine ($E_{1/2}^{ox} = 0.69$ V *vs.* Cp_2Fe) as internal standard.

‡ All criteria for a fully reversible system are fulfilled at $v = 0.5$ V s^{-1}: $\Delta E_p = 60$ mV and $i_{pa}/i_{pc} = 1$.

§ A homolytic bond dissociation energy BDE (RO–H) of 343 kJ mol^{-1} was used in the thermochemical cycle calculations for all enols.

¶ Peak potential minus potential at half-height.

‖ The thermodynamic potential E^0 can be approximated according to Nicholson and Shain assuming that heterogeneous electron transfer is fast. Using a rate constant of $2.5 \times 10^4 \le k \le 10^{10}$ s^{-1} for the intramolecular cyclization, the formal standard oxidation potential is $E_p^{ox} + 0.09\ V \le E^\circ \approx E_{1/2}^{ox} \le E_p^{ox} + 0.26$ V, see ref. 19.

operative in the general acyl-CoA dehydrogenase catalysed oxidations.[23]

Financial support by the Stiftung Volkswagenwerk, the BASF (scholarship for M. R.) and the Fonds der Chemischen Industrie is gratefully acknowledged. In particular, we thank Prof. C. Rüchardt for his generous support of our research.

Received, 21st June 1993; Com. 3/03570K

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