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Linear free energy relationships of half-wave reduction potentials of (*E*)-4-aryl-4-oxo-2-butenoic acids

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ABSTRACT

Half-wave reduction potentials of a set of twelve (*E*)-4-aryl-4-oxo-2-butenoic acids obtained by direct current polarography in methanol are reported. $E_{1/2}$ is correlated with Hammett sigma values as well as with values of frontier molecular orbitals calculated at a semiempirical molecular orbital level. Constant potential electrolysis of a representative compound shows that the first polarographic wave corresponds to one-electron reduction. The isolation of the product proves reduction of the activated double bond.

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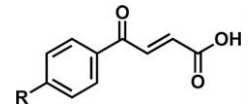
Many compounds with activated double bonds exert biological activities. The antiproliferative potency of naturally occurring flavonoids and related chalcones is well documented.[1] A long-standing interest of our group has been (*E*)-4-aryl-4-oxo-2-butenoic acids (aroylacrylic acids) and their derivatives. It has been shown that the substitution pattern on the aroyl moiety influences both the antiproliferative activity[2] of the compounds and the reactivity of the distal position of the molecules. So far, acidity constants[3] and reactivities of the –COOH group[4] have been reported.

Alkyl-substituted aroylacrylic acids are significantly more potent towards human dedifferentiated cell lines than halogen or methoxy derivatives, whereas MeO– and HO–phenyl-substituted chalcones exert more potent antiproliferative action.[5] Recently, an extensive study on the correlation between reduction potentials and electron affinities of a set of chalcones was reported.[6] The electrochemical reduction of the activated double bonds in many molecular classes is well documented;[7] to the best of our knowledge, the electrochemical reduction of 4-aryl-4-oxo-2-butenoic acids has not been described in the literature.

To establish a set for linear free energy relationships (LFERs), it is common to choose compounds having well-balanced electron-donating and electron-accepting groups, which span a broad range of Hammett sigma values. The introduction of compounds bearing substituents for which Hammett sigma values span a narrow range, for example, a group of alkyl substituted compounds, often results in deviation from a straight line. To explore different reactivities amongst more potent compounds, our chosen set includes several alkyl-substituted derivatives.

Twelve compounds (**1**–**12**, Table 1) were prepared as described previously,[8] and were characterized by ^{1}H and ^{13}C NMR spectroscopy, and by HR-MS (ESI). All the compounds had >98% purity. Half-wave reduction potentials of **1**–**12** were measured[9] by direct

Table 1
Half-wave reduction potentials for substrates **1**–**12** and the Hammett σ_p values used in Equation 1



Substrate	R	$-E_{1/2}$ (V)	σ_p
1	H	0.527	0
2	4-Me	0.543	−0.17
3	4-Et	0.536	−0.15
4	4-*i*-Pr	0.539	−0.16
5	4-*n*-Bu	0.532	−0.12
6	4-*sec*-Bu	0.543	−0.12
7	4-*t*-Bu	0.548	−0.20
8	4-*n*-Dodecyl	0.528	−0.16
9	4-F	0.532	−0.07
10	4-Cl	0.498	0.11
11	4-Br	0.474	0.23
12	4-MeO	0.569	−0.27

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current (DC) polarography in 0.1 M NaCl in MeOH, at 25 ± 0.2 °C versus a 3.0 M Ag/AgCl reference electrode. On all the polarograms (of **1**–**12**) two waves occurred (Fig. 1a). Waves appeared at about −0.5 V and −1.1 V versus the 3.0 M Ag/AgCl reference electrode. We focused our attention on the electrochemical reaction that corresponded to the first wave. In order to determine whether this reaction was due to the reduction of the double bond or the aroyl keto group, constant potential electrolysis of **2** was performed (see experimental), with the addition of CF_3COOH in an attempt to suppress di- or polymerization.

Substrate **2** was chosen because the AA′BB′ aryl pattern of the signals in its ^{1}H NMR spectrum allowed the unambiguous detection of the doublets due to the ketovinyl double bond. Moreover, one Me resonance in the aliphatic region of both the ^{1}H and ^{13}C NMR spectra could easily be distinguished from the signals of the products of polymerization.

To find the optimal potential for electrolysis, linear sweep polarograms were recorded. Figure 1b shows linear sweep polarograms of deaerated 0.1 M LiCl in methanol (i), after the addition of 2.0×10^{-3} mol of trifluoroacetic acid (ii), and the same solution with 1.0×10^{-4} mol of **2** (iii). At −0.7 V, reduction of **2** occurred, while the reduction of hydrogen was still negligible, so this potential was chosen as optimal. On the basis of net charge during constant potential electrolysis, we found that the electrochemical reaction that corresponded to the first wave was a single-electron reaction; more exactly, the electrolysis required 1.06–1.16 equiv of electricity per mole of substrate **2**. After a few attempts, using different molar equivalents of CF_3COOH, we were unable to obtain a quantitative yield of nonpolymerized product. All the $E_{1/2}$ values reported are the mean of three subsequent DC polarograms giving half-wave potentials within 0.006 V.

Along with two triplets positioned between δ 2.8 and δ 3.4 in the ^{1}H NMR spectra of the products, which belong to the reduced bond (–CH=CH– → –CH_2–CH_2–), an ABX pattern at δ 2.5 to δ 4.5, characteristic of a –CH_2–CHR– moiety was also found (Fig. 2a). At the same time, the ^{1}H NMR spectra clearly showed that the double bond had been reduced, due to the absence of doublets originating from –CH=CH– at ~δ 8 and δ 6.9. The aroyl keto group was not reduced, as was evident from the signal at δ 198 in the ^{13}C NMR spectrum (Fig. 2b).

Half-wave reduction potentials were correlated with Hammett sigma values (σ_p for alkyl substituents, MeO and Br, and σ_p^+ for F and Cl). Hammett sigma values were obtained from the literature.[10] Equation 1 and derived statistical values were obtained using the BILIN program.[11]

A linear correlation having reasonable statistics was obtained, Equation 1:

$$-E_{1/2} = -0.165\ (\pm 0.035)\ \sigma_p + 0.516\ (\pm 0.006)$$

$n = 12$, $r = 0.958$, sd = 0.007, $F = 110.263$, $Q^2 = 0.882$, $S_{PRESS} = 0.009$

For the *n*-dodecyl-derivative **8**, a Hammett σ_p value could not be found in the literature, and so the value for an *n*-octyl-group was used. The exclusion of compound **8** gave a better correlation ($r = 0.976$, $F = 179.483$, $Q^2 = 0.929$).

A graphical presentation of $-E_{1/2}$ versus σ_p is given in Figure 3.

As can be seen from Equation 1 and the corresponding graph in Figure 3, reasonable linear dependences exist between $E_{1/2}$ and Hammett sigma values. This indicates that substituents influence

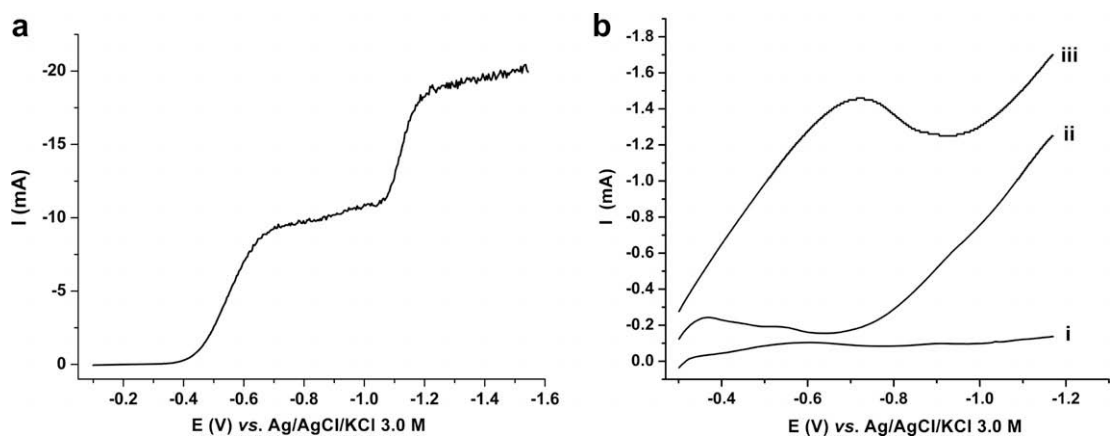

Figure 1. (a) Polarogram of 5.0×10^{-3} M **2** in 0.10 M NaCl in MeOH in the presence of 0.002% Triton X-100; (b) determination of the optimal potential for the constant potential electrolysis: linear sweep polarograms of deaerated 0.1 M LiCl in MeOH (i), after addition of 2.0×10^{-3} mol of trifluoroacetic acid (ii), and the same solution with 1.0×10^{-4} mol of **2** (iii).

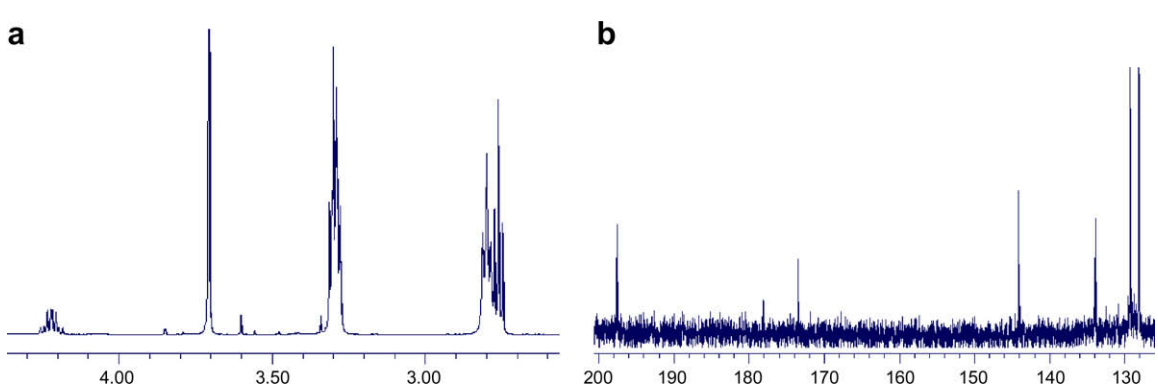

Figure 2. (a) Aliphatic ^{1}H NMR signals and (b) aromatic ^{13}C NMR signals of the product of electrolysis of substrate **2**.

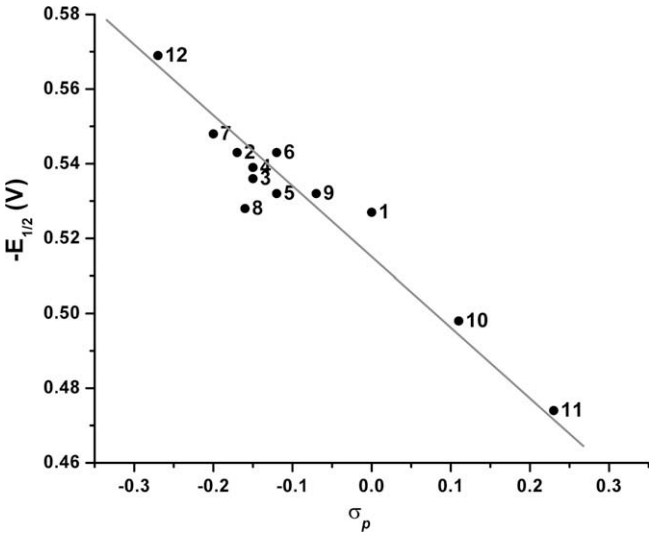

Figure 3. Graphical presentation of $-E_{1/2}$ versus σ_p.

the electronic properties of the activated double bond of the substrates in a regular manner. Similar correlations for chalcones and other ketovinyl-containing compounds are known in the literature. To the best of our knowledge, for (*E*)-4-aryl-4-oxo-2-butenoic acids, this is the first report. From Figure 3, it can be seen that the linearity holds for the alkyl-substituted compounds (**2**–**8**), a situation rarely found in the literature.

Having in hand a fair correlation between $E_{1/2}$ and Hammett sigma values, we tried to obtain statistically good correlations with descriptors derived from semiempirical calculations. The initial structures of **1**–**12** were constructed by OMEGA[12] using MMFF94s.[13] In this way, the structure obtained was in good agreement with the crystal structure of unsubstituted derivative **1**.[14] The structures, in their neutral and radical anion forms, were further optimized by RM1[15] and PM6[16] semiempirical molecular orbital methods. Neutral and ionized forms were treated both in vacuum and in the implicit solvent MeOH, in which half-wave potentials were determined. Optimization constraints were imposed on the atoms of the –C(O)–CH= fragment in all molecules in their neutral forms. Full optimization of structures **1**–**12** by MOPAC2009[17] unrealistically distorted the –C(O)–CH= bond. We did not observe a similar problem for radical anions. Improved geometries could not be assessed at higher levels of calculation; at the DFT level (B3LYP/6-311G**) after full optimization, the molecules were in unrealistic perfectly flat conformations. Similar situations can be found in the literature for chalcones and related compounds. As the geometries of the radical anions optimized by both RM1 and PM6 semiempirical MO methods were reasonable, we considered the reported results to be confined with respect to the calculation protocols used.[18]

It should be also mentioned that the optimization algorithms used decide the final geometries, rather than the level of calculation. Applying semiempirical MO AM1[21] or PM3[22] methods in GAUSSIAN03,[23] gave results with perfectly planar output geometries, the same as B3LYP/6-311G**. This situation is independent of the choice of starting optimization geometries. For MOPAC2009 and GAUSSIAN03 calculations, eigenvector and eigenvalue following optimizers, respectively, were used.

Also, both PM6 and RM1 semiempirical MO methods, as applied in MOPAC2009, distinguished well moieties where radical anions should form, as is illustrated by the radical anion α SOMO (−3.348 eV) of substrate **2**, optimized in MeOH, as an implicit solvent (Fig. 4).

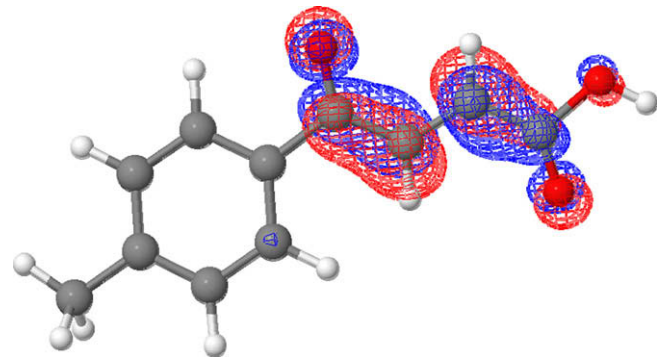

Figure 4. α SOMO of compound **2** in the radical anion form, obtained using the semiempirical MO PM6 method.

All the relevant data were collected from MOPAC outputs for substrates **1**–**12**, including the charges of atoms on which reduction occurred and the superdelocalizabilities of these atoms, the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) energies for the neutral forms, and the alpha singly occupied molecular orbital (SOMO) and the corresponding LUMO for radical ions. As a consequence of the selection of substituents on the compounds included in the set, perfect statistics cannot be obtained, as alkyl-substituted compounds always deviate from a straight line. However, the intercorrelation matrix of frontier orbital energy values derived from semiempirical calculations versus $E_{1/2}$ should be indicative. In Table 2 an intercorrelation matrix of PM6 and RM1 calculated HOMO and LUMO values for neutral forms, as well as alpha SOMO and the corresponding LUMO energies for radical anions, and differences between HOMO–LUMO and SOMO–LUMO versus $E_{1/2}$ are given.

The results summarized in Table 2 suggest that the RM1 calculated LUMOs of molecules in their neutral form is better correlated with $E_{1/2}$, than those calculated using PM6. In contrast the RM1 calculated (alpha) LUMOs give fair correlation for the radical ion forms of molecules in an implicit solvent or in a vacuum. Only PM6 calculated α SOMO energies of molecules obtained both in implicit solvent and in vacuum exert good correlations with the experimentally obtained $E_{1/2}$ values. SOMO–LUMO differences for radical anions calculated by both PM6 and RM1 semiempirical molecular orbital methods in vacuum or in an implicit solvent gave reasonable correlations with experimentally obtained $E_{1/2}$ values, while RM1 was superior when an implicit solvent is used. It should be emphasized that the aroylacrylic acids studied contain a –COOH group close to the reduction center. This group is prone to hydrogen bonding. It is well known that the use of an implicit solvent does not influence output geometries of optimized structures to a significant extent, but influences atom charges, and consequently MO energies. Stabilization of radical anions in a solvent can be seen from HOMO (neutral forms) and SOMO (radical anions) energies in the solvent and in vacuum (Table 3).

Half-wave reduction potentials ($E_{1/2}$) experimentally obtained in MeOH for the set of 12 *para*-phenyl-substituted (*E*)-4-phenyl-4-oxo-2-butenoic acids have been reported. The $E_{1/2}$ values obtained display good correlations with Hammett sigma values. Attempts to obtain good correlations using frontier orbitals of the molecules optimized at the semiempirical MO level in their molecular and radical anion forms was not successful, contrary to the literature reports for similar types of compounds. Trials with optimizations of molecules on different levels of theory (i.e., semiempirical and DFT) using different software showed that attention must be paid to the resulting geometries, prior to the use of descriptors derived from such calculations. It is a good compromise to use semiempirical optimized radical anions for single point DFT

Table 2
Intercorrelation (r values) of $E_{1/2}$ for substrates **1**–**12** versus frontier molecular orbital energies calculated for the neutral and radical anion forms of the studied compounds

Method		PM6 versus $E_{1/2}$[a]	RM1 versus $E_{1/2}$[a]
Neutral (in vacuum)	HOMO	0.555	0.607
	LUMO	*0.819*	*0.792*
Neutral (in MeOH)	HOMO	0.531	0.636
	LUMO	*0.785*	*0.846*
Radical anion in vacuum	α SOMO	*0.835*	0.499
	α LUMO	*0.824*	*0.827*
Radical anion in MeOH	α SOMO	*0.792*	0.356
	α LUMO	0.664	*0.851*
Neutral (in vacuum)	HOMO–LUMO	0.084	0.106
Neutral (in MeOH)	HOMO–LUMO	−0.329	−0.418
Radical anion in MeOH	SOMO–LUMO	0.770	*0.861*
Radical anion in vacuum	SOMO–LUMO	0.784	0.787

The numerical values of HOMO, LUMO, and SOMO are in eV.
[a] Relevant intercorrelation coefficients are given in italic.

Table 3
HOMO (neutral form of molecules) and SOMO (radical anions) energies of substrates **1**–**12**, obtained using the semiempirical MO PM6 method

Substrate	Solvent (MeOH)		Vacuum	
	HOMO	SOMO[a]	HOMO	SOMO[a]
1	−10.143	−7.609	−10.227	−3.404
2	−9.918	−7.561	−9.920	−3.348
3	−9.959	−7.566	−9.942	−3.359
4	−9.977	−7.567	−9.942	−3.364
5	−9.946	−7.613	−9.922	−3.369
6	−9.970	−7.567	−9.934	−3.372
7	−9.948	−7.567	−9.900	−3.361
8	−9.948	−7.569	−9.926	−3.379
9	−10.342	−7.612	−10.419	−3.533
10	−10.028	−7.616	−10.078	−3.595
11	−10.096	−7.625	−10.119	−3.627
12	−9.605	−7.547	−9.532	−3.368

[a] α SOMO reported.

calculations. This method will be used for a larger set of congeners in the future.

Acknowledgments

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9. *Apparatus*: DC polarograms were recorded on a VA 797 Computrace, Metrohm, Switzerland. A three-electrode cell consisting of Metrohm MME in dropping mercury electrode mode as the working electrode, a platinum rod as the auxiliary, and aqueous 3.0 M Ag/AgCl as the reference electrode was used. The desired temperature of the solution was held constant using an Ultra-Thermostat, type U 10, Medingen, Dresden. Constant potential electrolysis experiments (and the corresponding linear sweep polarography, used for the determination of the optimal potential of electrolysis) were performed using a CHI 760B Electrochemical Workstation, CH Instruments, USA. A two-compartment cell with a 12 mm diameter mercury pool electrode and a 3.5 M aqueous Ag/AgCl reference electrode in the first and a platinum auxiliary electrode in the second compartment was used. The compartments were separated with sintered glass. *Measurement of half-wave reduction potentials*: DC polarography: The concentrations of the substrates, whose half-wave potentials were determined in 0.10 M NaCl in methanol, were 5.0×10^{-3} M. Triton X-100 was used as a maximum suppressor at a concentration of 0.002%. All reported $E_{1/2}$ values are the mean of three subsequent measurements giving values within 0.006 V. Before the first run, the solution was thermostated over 10 min, and during the last 5 min, deaerated with nitrogen. Between successive runs, the solutions were deaerated with nitrogen for 30 s. The scan rate was 10 mV s^{-1}. The temperature of solutions was 25 ± 0.2 °C. Half-wave potentials were determined by smoothing using the wave evaluation function of Metrodata 797 PC-Software 1.0 (smoothing factor 6). *Constant potential electrolysis*: The compartments of the electrolytic cell were filled with 0.1 M LiCl in methanol to equal levels. The volume of the solution in the main compartment was approximately 16 cm^3. The solution was deaerated with nitrogen over 5 min and the linear sweep polarogram was recorded. In the main compartment between 5×10^{-4} and 2.0×10^{-3} mol of trifluoroacetic acid was added, the solution deaerated again, and the second linear sweep polarogram was recorded. After the addition of 1.0×10^{-4} mol of **2** in the main compartment and deaeration, a third linear sweep polarogram was recorded. From the recorded linear sweep polarograms, depending on the number of moles of trifluoroacetic acid added, potentials from −0.7 to −0.8 V versus the 3.5 M aqueous Ag/AgCl reference electrode were found to be optimal for electrolysis. During electrolysis, the solution in the main compartment was stirred and purged with nitrogen. The product of electrolysis was extracted with $CHCl_3$. The organic layer was washed with H_2O, dried over anhydrous Na_2SO_4, and evaporated to dryness. ^1H and ^{13}C NMR spectra were recorded on Bruker Avance instruments at 500/125 MHz in $CDCl_3$. Chemical shifts (δ) are referred to in *ppm*, downfield from TMS as the internal standard.
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18. *Computational protocols*: Initial 3D structures of substrates **1**–**12** were generated by OMEGA from SMILES notation. MMFF94s force field was used. All structures were optimized by semiempirical MO PM6 and RM1 methods, using MOPAC2009. Constraint was imposed on atoms of the –C(O)–CH= fragment in molecular forms of compounds, as described in the main text. Eigenvector following optimizer was used and the structures were optimized to the root mean square gradient below 0.1 kcal/mol. An implicit solvent was treated by the COSMO[19] formalism, as applied in MOPAC2009. Molecules in their ground state were treated by configuration interactions (C.I. = 4,4). A more realistic description of the frontier orbitals should be obtained in this way. Radical anions were defined by using the MOPAC keyword CHARGE = −1; implying the odd-electron systems. Several compounds in their neutral forms (**1**, **4**, **9** and **12**) were optimized by semiempirical MO AM1 and PM3 methods and on the DFT level (B3LYP/6-311G**), as applied in GAUSSIAN03, by specification that the force constants are computed at every point. Cut-offs on forces and step size to determine convergence were tightened using the 'Tight' option. Two-electron integrals and derivatives were used (Gaussian keyword Int = UltraFine). The alpha SOMO of **2** was visualized by Jmol,[20] from the MOPAC output. All computations were performed using a dual core 5 GHz AMD processor in the Linux or Windows environment.
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