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sulting rate constants follow the linear freeenergy relationship $\lg k_2 = s_N(N + E)$, which allowed us to derive their reactivity parameters N and s_N .

FULL PAPER

Carbanions

F. Corral-Bautista, H. Mayr* 1-8

Quantification of the Nucleophilic Reactivities of Ethyl Arylacetate Anions

Keywords: Carbanions / Kinetics / Linear free-energy relationships / Michael addition / Substituent effects



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Quantification of the Nucleophilic Reactivities of Ethyl Arylacetate Anions

Francisco Corral-Bautista^[a] and Herbert Mavr*^[a]

Dedicated to Professor Manfred Braun on the occasion of his 65th birthday

Keywords: Carbanions / Kinetics / Linear free-energy relationships / Michael addition / Substituent effects

The kinetics of the reactions of substituted ethyl arylacetates with quinone methides and structurally related diethyl benzylidenemalonates have been studied in DMSO. The second-order rate constants $(\lg k_2)$ correlated linearly with the electrophilicities *E* according to the linear free-energy rela-

tionship $\lg k_2 = s_N(N + E)$, allowing us to determine the nucleophilicity parameters N and s_N for these anions. The nucleophilic reactivities of the carbanions vary from N = 27.5 for the parent compound to N = 20.0 for the 4-nitro-substituted derivative.

Introduction

The anions of ethyl arylacetates are frequently used as nucleophiles in Michael additions^[1] and Claisen condensations.^[2] Furthermore, they can easily be alkylated or added to carbonyl groups, imines, or acetylenes, leading to a wide variety of products of biological and medicinal interest.[1d,3-5]

During the last decades, we have constructed a comprehensive nucleophilicity scale, which is based on reactions of π -, n-, and σ -nucleophiles with benzhydrylium ions, structurally related quinone methides, and diethyl benzylidenemalonates.^[6-11] The second-order rate constants of these reactions have been described by Equation (1), where E is an electrophile-specific parameter, and N and s_N are nucleophile-specific parameters.^[12]

$$\lg k_2 (20 \ ^{\circ}\text{C}) = s_{\text{N}}(N + E)$$
 (1)

We now report on the kinetics of the reactions of the anions of ethyl arylacetates 1 (Scheme 1) with the reference electrophiles 2 and 3 (Table 1) in DMSO solution, and use these data to include the anions **1a-f** in our nucleophilicity scale.^[6f] Subsequently, we determine the rate constants for the reactions of the ethyl 4-nitrophenylacetate anion (1e) with different types of electrophiles and compare the results with the rate constants calculated by Equation (1).

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Scheme 1. Anions of the ethyl arylacetates 1, the ¹H NMR chemical shifts of the signals of the corresponding benzylic protons and λ_{max} (in nm) of the anions in DMSO solution. [a] ¹H NMR in [D₆] DMSO solution at 200 MHz. [b] Due to H/D exchange with the solvent, $\delta(1a)$ was not observable.

Table 1. Quinone methides 2 and diethyl benzylidenemalonates 3 as reference electrophiles employed in this work.



[a] Electrophilicity parameters from refs.^[6b,6e,13] [b] Used only for product studies.

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Results and Discussion

Product Studies

Solutions of the anions 1 were generated by treatment of the esters 1-H with potassium *tert*-butoxide (KOtBu, ca. 1.05 equiv.) in DMSO and then combined with solutions of 2 in DMSO (with 5–10% dichloromethane as cosolvent). After aqueous, acidic workup, the crude reaction products 4 were purified by chromatography and characterized by NMR spectroscopy and mass spectrometry. In all cases, the products 4 were obtained in good to excellent yields as mixtures of two diastereoisomers (Scheme 2).

Ar__CO₂Et



Scheme 2. Products of the reactions of the anions of ethyl arylacetates (1) with quinone methides 2 in DMSO at 20 °C. [a] Determined by ¹H NMR spectroscopy after purification by chromatography.

Only 14% of 5a was obtained when 1a was combined with the benzylidenemalonate 3a in DMSO, even when 10 equiv. of 1a were employed. Combinations of 1a with less reactive electrophiles, such as 3d, gave complex product mixtures, from which the addition products 5 could not be separated. The adducts 5 could be isolated as the only products after acidic workup, however, when the reactions where carried out in THF (Scheme 3). While the reactions of the unsubstituted anion 1a and the *m*-chloro-substituted anion 1b with 3a gave around 45% of 5a and 5b, respectively, almost quantitative yields of 5d and 5f were obtained from the reactions of the less reactive anions 1d and 1f with 3a. Methylation of the initially formed anionic Michael adducts (5' and 5'') yielded different types of products: **6a** for Ar = Ph, and 6d for Ar = 4-CN-C₆H₄. The HMBC spectra of both diastereoisomers of 6a show ${}^{3}J_{CH}$ couplings of the methyl group to the two carbonyl carbon atoms of the malonate group. On the other hand, the HMBC spectra of both diastereoisomers of **6d** show ${}^{3}J_{CH}$ couplings from the methyl group to only one carboxyl carbon atom, and ${}^{2}J_{CH}$ couplings of the CH group to the two carboxyl carbon atoms of the malonate group (Scheme 3). Though it is quite likely that the formation of 6a and 6d indicates that 1a and **3a** yield an adduct with a malonate anion structure (5'), while 1d and 3a yield an ester-stabilized p-cyano-substituted benzyl anion (5''), this conclusion is not unequivocal, because we do not know the relative rates of methylation and proton transfer.

The reaction of ethyl (4-nitrophenyl)acetate (1e-H) with the (E)- β -nitrostyrene 7a catalyzed by 10 mol-% of 1,5-di-



Scheme 3. Products of the reactions of the anions of ethyl arylacetates 1 with diethyl benzylidenemalonates 3 in THF at ambient temperature, and HMBC correlations (double-headed arrows in formula of 6). [a] Determined by 1 H NMR spectroscopy after purification by chromatography.

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Scheme 4. Reaction of 1e-H with the (*E*)- β -nitrostyrene 7a with catalytic amounts of DBN in dichloromethane at 20 °C. [a] Determined by ¹H NMR spectroscopy.



Scheme 5. Reaction of the anion 1e with the 1,2-diaza-1,3-diene 9a in DMSO at ambient temperature. [a] Determined by 1 H NMR spectroscopy.



Scheme 6. Reaction of the anion 1e with 11 in $[D_6]DMSO$.

azabicyclo[4.3.0]non-5-ene (DBN) in dichloromethane gave 52% of **8** as a 1:1.1 mixture of two diastereoisomers (Scheme 4).

From the reaction of **1e** (generated from **1e**-H and KOtBu) with the 1,2-diaza-1,3-diene **9a** in DMSO, **10** was obtained in 87% yield as a 1:1 mixture of diastereoisomers (Scheme 5).

As the reactions of the anions 1 with the benzylidenemalononitrile 11 in DMSO were highly reversible, the addition products could not be isolated. However, when the CH acid 1e-H was mixed with 1 equiv. of KOtBu and 1 equiv. of 11 in $[D_6]DMSO$, the formation of the adduct 12 (as a mixture of two diastereisomers) was observed by NMR spectroscopy (Scheme 6).

Though not all ¹H NMR signals could be assigned to the reaction product **12**, the signals of the benzylic protons and carbon atoms could unequivocally be assigned. With ³J = 12 Hz, the vicinal coupling constant between the benzylic doublets is of similar magnitude as in the structurally analogous products **4** and **5**.

Kinetic Investigations

The reactions of the ethyl arylacetate anions **1a–f** with the electrophiles **2**, **3**, **7**, **9**, and **11** were performed in DMSO solution at 20 °C and monitored by UV/Vis spectroscopy at or close to the absorption maximum of one of the reagents (see Supporting Information). Due to their low stability, the potassium salts of the ethyl arylacetates (1a-f)-K were not isolated, but were generated by deprotonation of the corresponding CH acids (1a-f)-H with KOtBu (typically 1.05 equiv.) in DMSO prior to the measurements. The complete deprotonation of the CH acids was demonstrated by combining solutions of (1a-f)-H with 1.05 equiv. of KOtBu in DMSO. After completion of the deprotonation, the concentrations of the carbanions (determined by UV/ Vis spectroscopy) remained constant and did not increase even when additional 2–5 equiv. of KOtBu were subsequently added.

To simplify the evaluation of the kinetic experiments, one of the reactants, either the nucleophile or the electrophile, depending on the corresponding absorption spectra, was used in large excess (> 10 equiv.). Thus, the concentrations of the major components remained almost constant throughout the reactions, and pseudo-first-order kinetics were obtained in all runs. The first-order rate constants k_{obs} were derived by least-squares fitting of the time-dependent absorbances A_t of the minor component to the exponential function $A_t = A_0 \exp(-k_{obs}t) + C$. Second-order rate constants were obtained as the slopes of plots of k_{obs} vs. the concentrations of the compound used in excess (Figure 1).

For all reactions described in Tables 2 and 3, second-order rate constants were derived as the slopes of the linear plots of k_{obs} vs. the concentrations of the compounds used in excess. Quantification of the Reactivities of Ethyl Arylacetate Anions





Figure 1. Plot of the absorbance A_t (521 nm) vs. time for the reaction of **1a** ($1.77 \times 10^{-5} \text{ mol } \text{L}^{-1}$) with **2h** ($1.95 \times 10^{-4} \text{ mol } \text{L}^{-1}$) in DMSO at 20 °C. Inset: Plot of the first-order rate constants k_{obs} vs. the concentration of **1a**.

Table 2.	Second	-order ra	te consta	ants k ₂	for the	reactions	of the
carbanic	ons 1a–f	with the	reference	e electro	philes 2	2 and 3 in	DMSO
at 20 °C.							

Nucleophile	$N s_{ m N}$	Electrophile	k_2 [Lmol ⁻¹ s ⁻¹]	λ [nm] ^[a]	Excess of
		2f	2.21×10^{6}	407	1a
		2g	5.51×10^5	486	1a
	27.54 0.57	2h	$2.86 imes 10^5$	521	1a
		3b	$7.43 imes 10^4$	340	3b
Id		3c	$1.00 imes 10^4$	340	3c
		3d	3.91×10^3	345	3d
	27.57 0.53	2f	9.06×10^5	407	1b
ÇI		2g	$2.33 imes 10^5$	486	1b
		2h	1.24×10^5	521	1b
OEt		3b	$2.29 imes 10^4$	350	3b
1b		3c	$6.09 imes 10^3$	350	3c
		3d	2.49×10^3	350	3d
Br		2f	9.89×10^5	407	1c
OEt	27.62	2g	3.21×10^5	486	1c
1c	0.55	2h	$1.53 imes 10^5$	521	1c
NC 0	23.64 0.65	2g	1.14×10^4	486	1d
OEt		2h	5.90×10^3	521	1d
1d		3b	9.65×10^2	405	3b
	t 20.00 0.71	2a	2.63×10^5	422	1e
O ₂ N		2b	1.35×10^4	374	1e
		2c	3.68×10^3	354	1e
		2d	8.80×10^2	371	1e
ie		2e	4.90×10^2	393	1e
		2g	$7.21 imes 10^1$	450	1e
	23.27 0.70	2d	1.54×10^{5}	371	1f
N Q		2e	9.46×10^4	393	1f
OEt		2g	1.51×10^4	486	1f
1f		2h	6.77×10^3	521	1f
		3b	8.74×10^{2}	351	3b

[a] Monitored wavelength.

Table 3. Experimental and calculated [by Equation (1)] second-order rate constants for the reactions of ethyl (4-nitrophenyl)acetate anion (1e) with electrophiles 7, 9 and 11 in DMSO at 20 °C.

Electrophile		$E^{[a]}$	k_2^{exp} [Lmol ⁻¹ s ⁻¹]	k_2^{calc} [Lmol ⁻¹ s ⁻¹] ^[b]	$k_2^{\text{exp}}/k_2^{\text{calc[b]}}$
NO ₂	R = OMe	7a -14.70	3.15×10^3	5.79×10^3	0.54
R	R = Br	7b −13.37	1.66×10^4	$5.10 imes 10^4$	0.33
	$R = NMe_2$	9a -15.38	5.43×10^3	1.91×10^3	2.8
R' N' T' Ph O	R = OEt	9b -13.28	1.34×10^{5}	$5.90 imes 10^4$	2.3
Me ₂ N CN		11 –13.30	1.85×10^{4}	$5.71 imes 10^4$	0.32

[a] Electrophilicity parameters from refs.^[14–16] [b] Calculated with Equation (1) from *E* in this table and *N* and s_N from Table 2.

For all investigations in DMSO solution, the CH acids (**1a**–**f**)-H were deprotonated with KOtBu leading to anions with potassium as counterion, (**1a**–**f**)-K. It was found that the first-order rate constants k_{obs} obtained in the presence and in the absence of 18-crown-6 ether were on the same k_{obs} vs. concentration plots (see Supporting Information), indicating that the nature of the counterion does not play a role, i.e., that the determined rate constants reflect the reactivities of the free anions.

Correlation Analysis

Plots of $\lg k_2$ for the reactions of the carbanions **1** with the reference electrophiles **2** and **3** against the electrophilicity parameters *E* were linear, as shown for some representative examples in Figure 2. As depicted in the Supporting Information, all reactions studied in this work followed analogous linear correlations, indicating that Equation (1) is applicable to these reactions. From the slopes of these correlations, the nucleophile-specific parameters s_N were derived, and the negative intercepts on the abscissa ($\lg k_2 =$ 0) corresponded to the nucleophilicity parameters *N* (Table 2).



Figure 2. Correlation of the rate constants $\lg k_2$ for the reactions of the nucleophiles 1 with the electrophiles 2 and 3 in DMSO with their electrophilicity parameters *E*.

In order to examine the applicability of the *N* and s_N parameters thus derived to predict rate constants for reactions with other classes of electrophiles, we investigated the rate constants for the reactions of the ethyl (4-nitrophenyl) acetate anion (1e) with the (*E*)- β -nitrostyrenes **7a**,**b**, the 1,2-diaza-1,3-dienes **9a**,**b**, and the benzylidenemalononitrile **11** in DMSO at 20 °C by the photometric method used above. Table 3 shows that in all cases the experimental rate constants agreed within a factor of 3 with those calculated by Equation (1), confirming the applicability of the reactivity parameters *N* and s_N reported in Table 2 for predicting rate constants with other types of electrophiles.

Structure–Reactivity Relationships

The narrow range of s_N for all nucleophiles listed in Table 2 (0.53 $< s_{\rm N} < 0.71$), which is illustrated by the almost parallel correlation lines in Figure 2, implies that the relative reactivities of these anions depend only slightly on the electrophilicities of the reaction partners. The reactivities towards the quinone methide 2g, for which rate constants with all carbanions 1a-f were determined, therefore reflect general structure-reactivity trends. The m-chloro-(1b) and *p*-bromo-substituted (1c) ethyl phenylacetate anions react approximately two times more slowly with the electrophile 2g than the unsubstituted ethyl phenylacetate anion (1a), which indicates only a little stabilization of the negative charge by the halogen substituents. The anion of the p-cyano-substituted ethyl arylacetate (1d), which is as reactive as the ethyl 2-(pyridin-4-yl)acetate anion (1f), is more than one order of magnitude less reactive than the unsubstituted anion 1a. The influence of the *p*-nitro group is tremendous: le is 7600 times less reactive than the unsubstituted anion 1a.

As previously reported for the reactivities of other α -acceptor-substituted benzyl anions,^[11d] only a poor corre-

lation between nucleophilic reactivities of 1a-e and Hammett's σ_{p}^{-} substituent constants^[17] was observed (Figure 3). The downward curvature of the graph indicates that the conjugative interaction between the nitro group and the carbanionic reaction center is much stronger than in the phenoxides that were employed for calibrating the σ_p^- values. Accordingly, Kiyooka et al.^[18] reported that the ¹H and ¹³C NMR chemical shifts of the anionic center of ethyl arylacetates and the corresponding infrared absorption maxima are affected more strongly by acceptor substituents in the *p*-position than expected from the correlations with σ and $\sigma_{\rm p}^{-}$ parameters. Obviously, the nonlinearities of the Hammett correlations depicted in Figure 3 and reported by Kiyooka have the same origin, as Figure 4 shows a good linear correlation between the nucleophilic reactivities of the carbanions 1b-e and their ¹H NMR chemical shifts in DMSO solution.



Figure 3. Correlation of the $\lg k_2$ values for the reactions of **1a–e** with the quinone methide **2g** in DMSO at 20 °C with Hammett's substituent constants $\sigma_{\rm p}^{-}$.



Figure 4. Correlation of the $\lg k_2$ values for the reactions of **1b**–e with the quinone methide **2g** in DMSO at 20 °C vs. the ¹H NMR chemical shifts (from Scheme 1) of the benzylic proton of the anions.

Scheme 7 shows how the reactivities of benzyl anions are affected by α -acceptor substituents (reference quinone methide **2g**): the anion of ethyl phenylacetate has a similar nucleophilicity as the anion of phenylacetonitrile. While the phenylsulfonyl group reduces the nucleophilic reactivity by

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one order of magnitude relative to ethoxycarbonyl, a benzoyl group reduces the reactivity by more than two orders of magnitude. Benzyl anions with an α -nitro group or an α trifluoromethylsulfonyl group are five orders of magnitude less reactive.



Scheme 7. Comparison of the relative second-order rate constants for the reactions of different benzyl anions with the quinone methide **2g** in DMSO at 20 °C (refs.^[11b,11d-11f,19]). The rate constants for the reactions of the ethyl arylacetates with **2g** were set to unity. [a] Rate constant was calculated by Equation (1).

The Brønsted correlation in Figure 5 depicts that the nucleophilic reactivities of α -acceptor-substituted carbanions correlate only poorly with their Brønsted basicities in



Figure 5. Correlation of $\lg k_2$ for the reactions of the anions of the ethyl arylacetates **1a** and **1e** and other benzyl anions^[11b,11d–11f,19] with the quinone methide **2g** in DMSO at 20 °C vs. the p K_a values^[21] of their conjugated acids.

DMSO, indicating the important role of the intrinsic barriers.^[20] It is obvious, however, that the α -ethoxycarbonylsubstituted benzyl anions are among the most nucleophilic as well as most basic carbanions of the series depicted in Figure 5.

Conclusions

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The rate constants for the reactions of the anions of ethyl arylacetates with guinone methides and diethyl benzylidenemalonates in DMSO followed the linear free-energy relationship [Equation (1)], allowing us to include these compounds in our comprehensive nucleophilicity scale and to compare their nucleophilicities with those of other nucleophiles (Figure 2). Variation of the substituents on the arene ring from X = H to X = 4-NO₂ decreased the reactivities by four orders of magnitude. Their nucleophilic reactivities were comparable to those of analogously substituted α -cyano-substituted benzyl anions, and 10⁵ times higher than those of the corresponding α -nitro- and α -trifluoro methyl-substituted benzyl anions with the same substituents at the arene ring. The agreement of the experimental and calculated [by Equation (1)] rate constants for the reactions of 1e with the electrophiles 7a.b. 9a.b. and 11 within a factor of three demonstrated the applicability of the N and s_N parameters in Table 2 for predicting the rates of their reactions with various electrophiles. The ethyl arylacetate anions 1a-c belong to the most reactive nucleophiles studied so far, and therefore, they should be applicable for deriving reactivity parameters of very weak electrophiles.

Experimental Section

Reaction of the Anions 1 with the Quinone Methides 2: The anions 1 were generated by addition of the ethyl arylacetates 1-H (50–70 mg, 1 equiv.) to a solution of KOtBu (30–40 mg, 1.05 equiv.) in dry DMSO (5 mL). A solution of the quinone methide 2 in DMSO (approx. 5 mL with 5–10% dichloromethane as cosolvent) was then added. The mixture was stirred for 5 min, before 0.5% aqueous acetic acid (ca. 50 mL) was added. The mixture was extracted with ethyl acetate (3×20 mL), and the combined organic phases were washed with brine (2×20 mL), dried with sodium sulfate, and the solvent was evaporated under reduced pressure. The crude reaction products were purified by column chromatography on silica (pentane/ethyl acetate) and subsequently characterized by NMR spectroscopy and mass spectrometry.

Reaction of the Anions 1 with the Diethyl Benzylidenemalonates 3: The anion 1 was generated in situ by addition of the ethyl arylacetates 1-H (50–80 mg, 1 equiv.) to a solution of KO*t*Bu (40–60 mg, 1.05 equiv.) in dry THF (10 mL). After 2 min, the diethyl benzylidenemalonate **3** was added. After stirring at room temperature for 5 min, the mixture was poured into 0.5% aqueous acetic acid (ca. 50 mL). The mixture was extracted with diethyl ether (3×30 mL), and the combined organic layers were washed with brine (2×20 mL), dried with sodium sulfate, and the solvent was evaporated under reduced pressure. The crude reaction products were purified by column chromatography on silica (dichloromethane/methanol) and subsequently characterized by NMR spectroscopy and mass spectrometry.

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Kinetics: Because the reactions of colored quinone methides 2 with colorless nucleophiles 1 or of colored anions 1 with colorless diethyl benzylidenemalonates 3 result in colorless products (or products with a different absorption range than the reactants), the reactions could be monitored by UV/Vis spectroscopy. Because all reactions were fast ($\tau_{1/2} < 10$ s), the kinetics were monitored by using stopped-flow techniques. The temperature of all solutions was kept constant at 20.0 ± 0.1 °C by using a circulating bath thermostat. In all runs, the concentration of the colorless compound was at least 10 times higher than the concentration of the colored compound, resulting in pseudo-first-order kinetics with an exponential decay of the concentration of the minor compound. First-order rate constants k_{obs} were obtained by least-squares fitting of the absorbances to a single-exponential $A_t = A_0 \exp(-k_{obs}t) + C$. The second-order rate constants k_2 were obtained as the slopes of the linear plots of $k_{\rm obs}$ against the concentration of the excess components.

Supporting Information (see footnote on the first page of this article): UV spectra of compounds **1a–f**; k_{obs} vs. concentration plots, $\lg k_2$ vs. *E* plots.

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