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Determination of the Electrophilicity Parameters of Diethyl Benzylidenemalonates in Dimethyl Sulfoxide: Reference Electrophiles for Characterizing Strong Nucleophiles

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Abstract: The second-order rate constants of the reactions of nine substituted diethyl benzylidenemalonates **1a–i** with the carbanions **2a–e** have been determined spectrophotometrically in dimethyl sulfoxide (DMSO). Product studies show that the nucleophiles attack regioselectively at the electrophilic C=C double bond of the Michael acceptors to form the carbanionic adducts **4**. The correlation $\log k(20\,^{\circ}\mathrm{C}) = s(N+E)$ allows the determination of the electrophilicity parameters E for the electrophiles **1a–i** from the rate constants determined in this work and the previously published N and s parameters for the nucleophiles **2a–e**. The electrophilicities E for compounds **1a–i** cover a range of six units ($-17.7 > E > -23.8$) and correlate excellently with Hammett's substituent constants σ_p. The title compounds are roughly ten orders of magnitude less reactive than analogously substituted benzylidene Meldrum's acids, their cyclic analogues. Due to their low reactivities, compounds **1a–i** are suitable reference electrophiles for determining the reactivities of highly reactive nucleophiles, such as carbanions with $16 < N < 30$.

Keywords: carbanions · electrophilicity · kinetics · linear free-energy relationships · Michael addition

Introduction

In recent years, large efforts have been made to develop nucleophilicity scales for comparing the reactivities of structurally different compounds, such as alkenes and arenes,[1–3] alcohols and amines,[4–6] carbanions,[7,8] and organometallics[1,9] or hydride donors.[1,10] To characterize the nucleophilicities of these compounds, the kinetics of their reactions with benzhydrylium ions (Ar_2CH^+) and structurally related quinone methides have been investigated and evaluated by using the linear free energy relationship given in Equation (1), in which N and s are nucleophile-dependent parameters and E is an electrophile-dependent parameter.

$$\log k_{20\,^{\circ}\mathrm{C}} = s(N + E) \qquad (1)$$

With the set of colored reference electrophiles defined in references [1,2,8] it has become possible to determine the reactivity parameters N for nucleophiles up to $N \approx 22$.

The characterization of more reactive nucleophiles has been problematic until now, because the least reactive electrophile parameterized had an electrophilicity parameter of $E = -17.9$, that is, its reactions with nucleophiles of $N > 22$ are very fast and cannot easily be determined.

Recently we demonstrated that Equation (1) also holds for the reactions of carbanions with ordinary Michael acceptors, such as benzylidene malononitriles,[11] benzylidene indandiones,[12] benzylidene barbituric acids,[13] and benzylidene Meldrum's acids.[14] We now report on the reactivities of diethyl benzylidenemalonates, which are less electrophilic than benzylidene Meldrum's acids, their cyclic analogues, and therefore may be suitable for extending the scale of reference electrophiles on the low-reactivity end.

Oh and Lee showed that the reactions of substituted benzyl amines with 2-benzylidene-1,3-diketones[15] and diethyl benzylidenemalonates[16] are much slower than the analogous reactions with benzylidene malononitriles,[17] benzylidene Meldrum's acids,[18] and benzylidene indandiones.[19] The considerably higher CH acidity of Meldrum's acid relative to those of acyclic esters, such as dimethyl malonate, has been ascribed to the fixed E conformation of the ester linkage in the bislactone structure of Meldrum's acid.[20]

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This rationalization has been supported by quantum chemical calculations by Houk and Wiberg, who showed that the deprotonation of the *E* conformer of methyl acetate requires approximately 20 kJ mol^{-1} less energy than deprotonation of the *Z* conformer.[21]

Benzylidene malonates **1** have found synthetic applications as Michael acceptors in reactions with propargyl alkoxides to create a variety of heterocycles, such as highly substituted tetrahydrofurans under mild reaction conditions,[22] and in diastereoselective oxy-Michael additions of 6-methyl δ-lactol to yield protected β-hydroxy ester derivatives.[23] Organocatalytic enantioselective additions of ketones to benzylidene malonates,[24] and copper-catalyzed nucleophilic additions of indoles with formation of enantiomerically enriched 3-substituted indoles have been reported.[25]

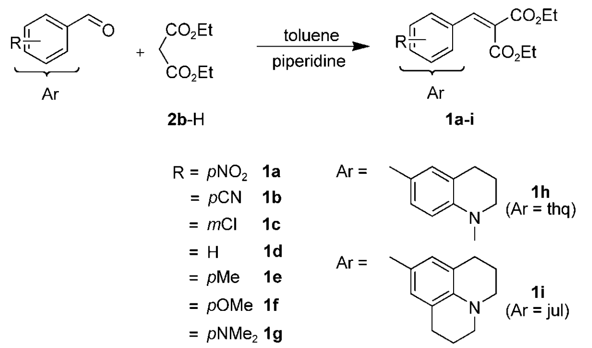
Benzylidene dimalonates, which have been claimed to serve as bone affinity agents, have previously been synthesized by tandem Michael additions of aryl sulfonimines with diethyl malonate.[26]

We now report on the kinetics of the additions of carbanions towards electrophiles **1a**–**i** in dimethyl sulfoxide (DMSO) and show that the second-order rate constants of these reactions can be described by Equation (1).

Results and Discussion

The previously reported compounds **1a**–**g** and the novel substrates **1h**,**i** (Scheme 1) were prepared by Knoevenagel condensation from diethyl malonate (**2b**-H) and the corresponding aldehyde in boiling toluene following a modified protocol of Zabicky.[27]

Abstract in German: *Geschwindigkeitskonstanten 2. Ordnung für die Reaktionen von neun substituierten Benzylidenmalonsäurediethylestern* ***1a*****–*****i*** *mit den Carbanionen* ***2a*****–*****e*** *in DMSO wurden photometrisch bestimmt. Die Produktstudien zeigen, dass die Nucleophile regioselektiv die elektrophile Kohlenstoff–Kohlenstoff Doppelbindung der Michael-Akzeptoren angreifen, wobei die carbanionischen Addukte* ***4*** *gebildet werden. Mit den in dieser Arbeit bestimmten Geschwindigkeitskonstanten und den bereits veröffentlichten N- und s-Parametern der Nucleophile* ***2a*****–*****e*** *ermöglicht die Korrelation* $\log k(20\,°C) = s(N+E)$ *die Bestimmung der Elektrophilie-Parameter E für die Elektrophile* ***1a*****–*****i****. Die Elektrophilie E der Verbindungen* ***1a*****–*****i*** *deckt einen Bereich von sechs Größenordnungen ab* ($-17.7 > E > -23.8$) *und korreliert ausgezeichnet mit Hammett's Substituentenkonstanten* σ_p. *Die Titelverbindungen sind ca. zehn Größenordnungen weniger reaktiv als analog substituierte Benzyliden-Meldrum-Säuren, ihre cyclischen Analoga. Wegen ihrer geringen Reaktivität sind die Verbindungen* ***1a*****–*****i*** *passende Referenzelektrophile zur Bestimmung der Reaktivitäten hoch reaktiver Nucleophile, z. B. von Carbanionen mit* $16 < N < 30$.



Scheme 1. Synthesis of diethyl benzylidenemalonates **1a**–**i** by Knoevenagel condensation.

The electrophiles **1a**–**f** are colorless compounds with absorption maxima between 277 and 316 nm, while their amino-substituted analogues **1g**–**i** are yellow with absorption maxima between 383 and 407 nm (Figure 1). The molar decadic absorption coefficients ε in DMSO were found to be similar to those previously reported for some of these compounds in dioxane.[28]

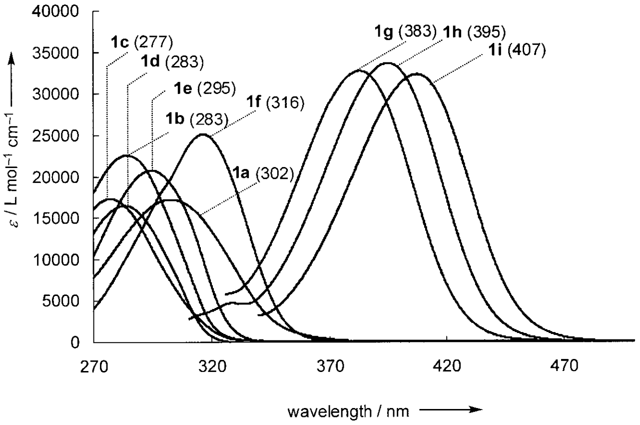


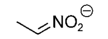
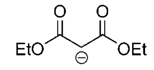
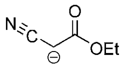
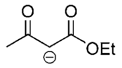
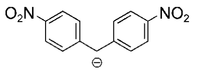
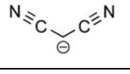
Figure 1. UV/Vis spectra of the electrophiles **1a**–**i** in DMSO, λ_{max} in parentheses. Molar decadic absorption coefficient ε for **1a**: 17200, **1b**: 22500, **1c**: 17300, **1d**: 16500, **1e**: 20700, **1f**: 25100, **1g**: 32800, **1h**: 33700, and **1i**: 32400 L mol^{-1}cm^{-1} (for ε values for **1a**, **1d**, **1f**, and **1g** in dioxane see ref. [28]).

To characterize the electrophilic reactivities of compounds **1a**–**i**, the kinetics of their reactions with the carbanions **2a**–**e** (Table 1) were investigated.

Product studies: To confirm the course of the investigated Michael additions (Scheme 2), the products of representative combinations of the arylidene malonates **1a**–**i** with the carbanions **2a**–**f** were studied by NMR spectroscopy (Table 2).

As depicted in Scheme 2, the nucleophilic additions of the carbanions **2a**–**f** to the diethyl benzylidenemalonates **1a**–**i** initially yield the anionic adducts **3**, which may undergo a

Table 1. Nucleophilicity parameters of carbanions **2a–f** in DMSO.

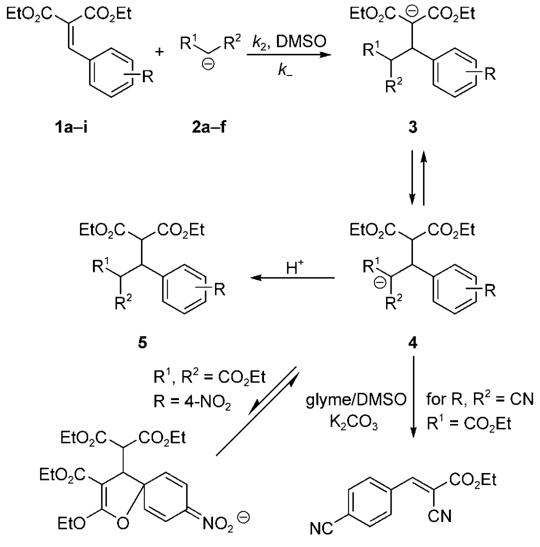
	Nucleophile	N[a]	s[a]
2a		21.54	0.62
2b		20.22	0.65
2c		19.62	0.67
2d		18.82	0.69
2e		19.92	0.67
2f		19.36	0.67

[a] For N and s-parameters of **2a** see reference [11], for **2b–d**,**f** see reference [8], for **2e** see reference [29]

Table 2. Characterized Michael adducts **4** and **5**.

Entry	Electrophile	Nucleophile	Product	Yield/%
1	**1c**	**2b**	**5cb**	47
2	**1d**	**2b**	**5db**	83
3	**1e**	**2b**	**5eb**	47
4	**1f**	**2b**	**5fb**	78
5	**1a**	**2c**	**4ac**	[a]
6	**1b**	**2c**	**4bc**	[a]
7	**1b**	**2c**	[b]	25
8	**1c**	**2c**	**4cc**	[a]
9	**1d**	**2c**	**4dc**	[a]
10	**1e**	**2c**	**4ec**	[a]
11	**1f**	**2c**	**4fc**	[a]
12	**1a**	**2d**	**5ad**	71[c]
13	**1a**	**2f**	**4af**	[a]
14	**1a**	**2f**	**5af**	35

[a] Adducts **4** were not isolated, but identified in the crude reaction mixture by ^{1}H and ^{13}C NMR spectroscopy. [b] Retro-Michael adduct (Scheme 2 bottom right, see text and Supporting Information). [c] The yield of the isolated major diastereomer is 47%.



Scheme 2. Addition of the carbanions **2a–f** to the benzylidenemalonates **1a–i** and possible subsequent protonation, elimination, or cyclization paths.

proton transfer with formation of the tautomeric carbanions **4**. Acidic workup of **4** then yields compounds **5**.

Thus, mixing the Michael acceptors **1c–f** with two equivalents of **2b**-K$^+$ in dry DMSO, subsequent workup with aqueous HCl solution, and distillation gave products **5cb–5fb** in moderate to good yields (Table 2, entries 1–4). The NMR spectra of **5db–5fb** (Supporting Information) agree with those previously described in reference [26]. The reactions of **1a–f** with the anion of ethyl cyanoacetate **2c** were studied by NMR spectroscopy and showed the predominant formation of anions **4ac–4fc** (Table 2, entries 5, 6, and 8–11), in accordance with the higher acidity of ethyl cyanoacetate (pK_a(DMSO) = 13.1)[30] relative to diethyl malonate (pK_a(DMSO) = 16.4).[31] Additional signals (<10%) indicate the presence of a second compound, potentially the corresponding anions **3**. Electrophile **1b** and ethyl cyanoacetate **2c**-H reacted in the presence of K_2CO_3 in a dimethoxyethane/DMSO mixture to yield the retro-Michael product shown at the bottom right of Scheme 2 (Table 2, entry 7). The reaction of **1a** with **2d** and subsequent acidic workup as described for entries 1–4 in Table 2 gave the product **5ad** as a mixture of diastereoisomers in a ratio of 2:1 in 71% yield. The malononitrile anion **2f** reacted with electrophile **1a** to yield **4af**, which was converted into **5af** by acidic workup (Table 2, entries 13 and 14). Michael additions of the nitroethyl anion **2a**,[13,14] and the dinitrobenzhydryl anion **2e**[29] to similar electrophiles have recently been shown to proceed analogously. Therefore we have not identified the adducts of **2a** and **2e** with the benzylidenemalonates **1a–i**.

Kinetic measurements: To obtain pseudo-first-order kinetics, solutions of the electrophiles **1a–i** (1.0×10^{-5}–1.0×10^{-3} mol L^{-1}) were mixed with more than ten equivalents of the compounds **2a–d**. (For the reactions of **1a–c** with the green dinitrobenzhydryl anion **2e** the first-order rate constants k_{obs} were determined with **2e** as the minor component). The decay of the absorptions of the electrophiles was then followed spectrophotometrically either with stopped-flow instruments or, for reactions with half-lives of more than ≈15 s, with conventional UV/Vis diode-array spectrometers equipped with fiber optics and a submersible probe. From the fit of the absorbance A_t to the exponential function $A_t = A_0\exp(-k_{obs}t) + C$, the first-order rate constants k_{obs} were derived. Because the UV absorption maxima of the electrophiles **1a–f** are close to those of the carbanions **2a-d**, the combinations of these substrates were not followed at the absorption maxima of the electrophiles, but at shoulders of the absorption bands of the electrophiles, at which neither the carbanions **2** nor the resulting products showed significant absorptions.

Figure S1 (Supporting Information) shows the development of a weak absorption band at $\lambda_{max} \approx 360$ nm during the reaction of the p-cyano-substituted benzylidenemalonate **1b** with **2c**; this observation may be typical for this electrophile, because a comparable weak band ($\lambda_{max}\approx 350$ nm) was formed during the reaction of **1b** with **2a**.

Similar observations were made when the *p*-nitro-substituted benzylidenemalonate **1a** was combined with the nucleophiles **2a**–**d**. Orange products with weak absorptions at $\lambda_{max}=455$–470 nm were formed, and for the reaction of **1a** with the anion of diethyl malonate the rate of the formation of the 455 nm band was found to equal the rate of the decay of the absorption band of **1a** at $\lambda=325$ nm. Though the nature of these colored side products is not clear, it is conceivable that in the presence of *p*-NO_2 or *p*-CN groups (i.e., in the reactions with **1a** and **1b**) the initially-formed adducts **4** undergo cyclization with formation of intramolecular Meisenheimer–Jackson complexes,[32] as shown for the adduct from **2b** and **1a** at the bottom left of Scheme 2.

Generally, plots of the first-order rate constants (k_{obs}) against the concentrations of the carbanions were linear with slopes k_2 and negligible intercepts (Figure 2, Table 3).

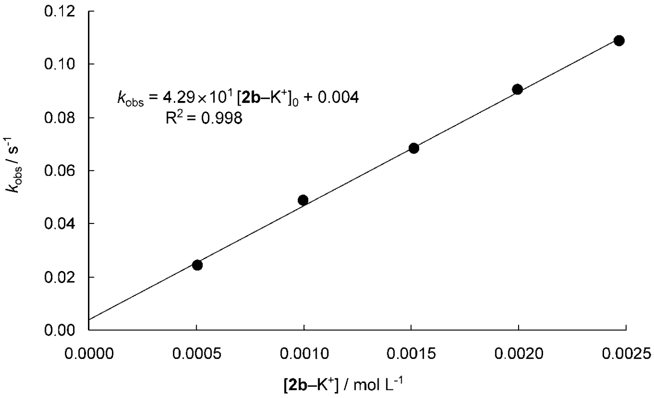


Figure 2. Determination of the second-order rate constant for the reaction of **1a** with **2b**-K in DMSO at 20 °C ($k_2=43.0$ L mol^{-1} s^{-1}).

Table 3. Second-order rate constants k_2 for the reactions of the electrophiles **1a**–**i** with the nucleophiles **2a**–**e** in DMSO at 20 °C.

Electrophile	E[a]	Nucleophile	k_2 [L mol^{-1} s^{-1}]
1a	−17.67	**2a**	2.41×10^{2}
1a		**2b**[b]	4.29×10^{1}
1a		**2c**	2.12×10^{1}
1a		**2c**[c]	2.24×10^{1}
1a		**2d**[c]	6.58
1a		**2e**	1.09×10^{1}
1b	−18.06	**2a**	1.45×10^{2}
1b		**2b**[c]	2.86×10^{1}
1b		**2c**	9.77
1b		**2e**	5.94
1b		**2e**[c]	6.03
1c	−18.98	**2a**	3.71×10^{1}
1c		**2b**[c]	6.81
1c		**2c**	2.68
1c		**2c**[c]	2.51
1c		**2e**	1.67
1d	−20.55	**2b**[c]	5.93×10^{-1}
1d		**2c**	2.43×10^{-1}
1e	−21.11	**2a**	2.99
1e		**2b**[c]	2.37×10^{-1}
1e		**2b**[d]	2.33×10^{-1}
1e		**2c**	1.11×10^{-1}
1f	−21.47	**2a**	1.70
1f		**2b**[c]	1.41×10^{-1}
1f		**2c**	4.27×10^{-2}
1g	−23.1	**2a**	1.68×10^{-1}
1g		**2b**[d]	8.85×10^{-3}
1h	−23.4	**2a**	6.96×10^{-2}
1i	−23.8	**2a**	3.94×10^{-2}

[a] Calculated from Equation (1); see section "Correlation Analysis". [b] From the increase of the absorbance at $\lambda=425$ nm one derives $k_2=42.6$ L mol^{-1} s^{-1}. [c] In the presence of [18]crown-6. [d] Reaction in the presence of the conjugate CH acid **2b**-H.

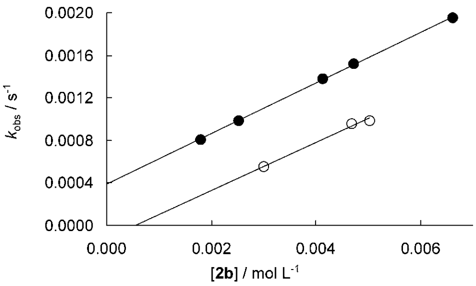


Figure 3. Reaction of the electrophile **1e** (1×10^{-4} mol L^{-1}) with the carbanion **2b** without addition of **2b**-H (●, $k_{obs}=0.237$ [**2b**] + 0.0004) and in the presence of 2–6 equivalents of **2b**-H (○, $k_{obs}=0.223$ [**2b**] - 0.0001) in DMSO at 20 °C.

Equilibrium constants: Although most of the Michael additions listed in Table 3 proceeded quantitatively, as indicated by negligible end absorptions of the solutions at the absorption maxima of the benzylidenemalonates **1**, several reactions of the malonate anion **2b** turned out to be reversible.

Thus, the *p*-dimethylamino-substituted benzylidenemalonate **1g** did not react at all when combined with the carbanion **2b**-K$^+$. However, in the presence of 3–5 equivalents of the conjugate acid **2b**-H ($\approx 2\times10^{-2}$ mol L^{-1}) almost quantitative conversion of **1g** was achieved, and the k_2 value listed in Table 3 refers to these conditions. Similar behavior was expected for other additions of the carbanions **2b**–**f** to the amino-substituted benzylidenemalonates **1g**–**i**. However, because of the expected low reaction rates, these additions have not been investigated.

The reactions of **2b**-K$^+$ with **1e**,**f** also proceeded incompletely, as indicated by significant end absorptions of the mixtures at the absorption maxima of the electrophiles. In line with the assumption of a reversible Michael addition, the linear plot of k_{obs} versus [**2b**] had a positive intercept (Figure 3, upper graph), which equals the rate constant of the reverse reaction.[33] Complete consumption of **1e** was achieved when the reaction of **1e** with **2b**-K$^+$ was performed in the presence of the conjugate CH acid **2b**-H (2–6 equivalents). The linear plot of k_{obs} versus [**2b**] obtained under these conditions had almost the same slope (Figure 3, lower graph) as the one obtained in the absence of **2b**-H, indicating that the rate-determining step is the same in both cases, that is, the proton transfer from **2b**-H to **3** (=**4** for R^1, R^2=CO_2Et) is a fast subsequent reaction. Analogously, the linear plot of k_{obs} versus [**2b**] for the reaction of **2b** with **1f** showed a positive intercept (Supporting Information, Table S23).

By theory,[33] it is now possible to calculate the equilibrium constants K for the reactions of **2b** with **1e** and **1f** as the ratio of the forward (k_2, slope of k_{obs} vs. [**2b**] plot) and backward (k_-, intercept of k_{obs} vs. [**2b**] plot) rate constants [Eq. (2)]. However, because of the uncertainty in the determination of k_- as the intercept of such correlations, the equilibrium constants K have been determined directly from the absorbances of **1e** and **1f** in the presence of variable concentrations of **2b** using Equation (3).

$$K = k_2/k_- \tag{2}$$

$$K = \frac{[\mathbf{3}]_{eq}}{[\mathbf{1}]_{eq}[\mathbf{2b}]_{eq}} = \frac{[\mathbf{1}]_0 - [\mathbf{1}]_{eq}}{[\mathbf{1}]_{eq}([\mathbf{2b}]_0 - [\mathbf{1}]_0 + [\mathbf{1}]_{eq})} \tag{3}$$

The equilibrium constants K derived from Equation (3), which are listed in Table 4, can then be combined with the rate constants k_2 from Table 3 to give the values of k_- listed in the fourth line of Table 4. The values for the reverse reactions derived in the two different ways differ by factors of 1.1 and 1.7, and we consider the values in the fourth line of Table 4 to be more reliable.

Table 4. Equilibrium and rate constants for the reactions of carbanion **2b** with the electrophiles **1e,f** in DMSO at 20 °C.

	1e	**1f**
k_-[a] [s^{-1}]	4×10^{-4}[a]	1×10^{-3} [a]
K [$L\,mol^{-1}$]	5.3×10^{2}[b]	2.3×10^{2} [b]
k_-[c] [s^{-1}]	4.5×10^{-4}[c]	6.0×10^{-4} [c]
ΔG^0 [$kJ\,mol^{-1}$]	−15.3[d]	−13.3[d]
$\Delta G^{\neq}$ [$kJ\,mol^{-1}$]	75.3[e]	76.5[e]
$\Delta G_0^{\neq}$ [$kJ\,mol^{-1}$]	82.8[f]	83.0[f]

[a] Intercept on the Y-axis for the plot of k_{obs} versus [**2b**] (as shown in Tables S20 and S23, Supporting Information). [b] From Equation (3) using the initial absorptions of the electrophiles **1e** and **1f** and the equilibrium absorptions after addition of carbanion **2b** (see Tables S1 and S2, Supporting Information). [c] Calculated on the basis of Equation (2) and the second-order rate constants listed in Table 3. [d] Calculated from the equilibrium constants K. [e] Forward reaction; from second-order rate constants k_2 in Table 3. [f] Calculated on the basis of Equation (4) and ΔG^0 and $\Delta G^{\neq}$ from this table.

Substitution of $\Delta G^{\neq}$ and ΔG^0 for these reactions into the Marcus equation[34][Eq. (4)], in which the work term has been neglected, yields intrinsic barriers of $\Delta G_0^{\neq} = 83\ kJ\,mol^{-1}$.

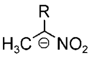
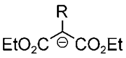
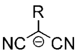
$$\Delta G^{\neq} = \Delta G_0^{\neq} + 0.5\Delta G^0 + (\Delta G^0)^2/(16\Delta G_0^{\neq}) \tag{4}$$

This value is considerably higher than those previously reported for the additions of pyridines[4c] and tertiary alkyl amines[5,6] to structurally related Michael acceptors.

Interestingly, the addition reactions of the carbanion **2c** to the electrophiles **1e,f** proceed quantitatively, although **2c** reacts more slowly ($N = 19.62$) than the reversibly reacting carbanion **2b** ($N = 20.22$). How can this behavior be explained?

Scheme 2 shows that ΔG^0 for the reaction of **1** with **2** to give **4** includes the difference in "carbanion stabilization" of anions **2** and **4**. Because pK_a values for the Michael adducts **5**, the conjugate acids of **4**, are not available, we estimated the influence of alkyl groups on the CH acidities of these compounds from a comparison of the carbanions **2** with their methyl analogues, as illustrated in Table 5.

Table 5. Influence of methyl groups on the basicities of carbanions (DMSO).

Carbanion	pK_{aH} (R=H)	pK_{aH} (R=CH_3)
	16.7[a] (**2a**)	16.8[a]
	16.4[b] (**2b**)	18.7[c]
	11.1[d] (**2f**)	12.4[d]

[a] From reference [35]. [b] From reference [31]. [c] From reference [36]. [d] From reference [37].

Although pK_{aH} values are not available for all methyl analogues of carbanions **2a–f**, the examples shown in Table 5 indicate that introduction of a methyl group leads to a particularly large decrease in carbanion stabilization in the case of malonate **2b**. This effect may account for the observation that the Michael additions of **2b** are less exergonic than the analogous reactions of the other carbanions of Table 1.

Correlation analysis: In Figure 4, the logarithmic second-order rate constants (log k_2) for the reactions of the carbanions **2a–d** with the arylidene malonates **1a–i** and the refer-

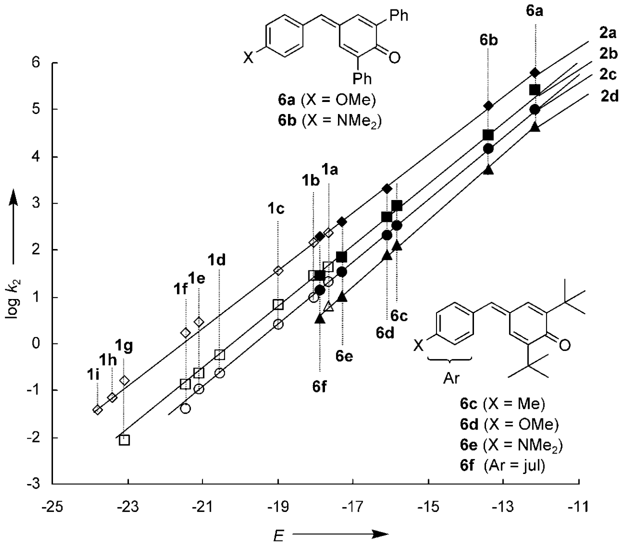


Figure 4. Plot of log k_2 for the reactions of carbanions **2a–d** with electrophiles **1a–i** (open symbols) and with reference electrophiles **6a–f** (filled symbols) in DMSO versus the electrophilicity parameter E of the employed electrophiles.

ence electrophiles **6a**–**f** (quinone methides) are plotted against the corresponding electrophilicity parameters *E*. The *E* parameters of **6a**–**f** were taken from reference [8], and those for **1a**–**i** were calculated from the rate constants for their reactions with the carbanions **2a**–**d** (reference nucleophiles). For that purpose, the nonlinear solver "What's Best!" was used to minimize the square of the deviations (Δ^2) between calculated and experimental rate constants $\Delta^2 = \Sigma(\log k_2 - s(N+E))^2$. Because *N* and *s* of the carbanions are given in Table 1 and the corresponding rate constants k_2 are listed in Table 3, the electrophilicity parameters *E* for **1a**–**i** could be obtained.

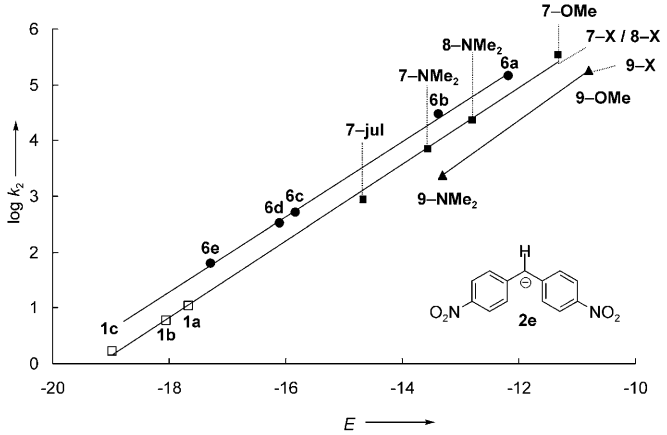
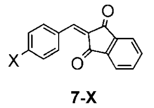
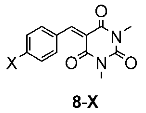
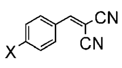


Figure 5. Correlation of log k_2 versus *E* for the reactions of carbanion **2e** with different Michael acceptors in DMSO: structures of **1a**–**c** in Scheme 1; structures of **6a**–**e** in Figure 4; structures of (**7**–**9**)-**X** see text; for "jul"-substituent see **1i** in Scheme 1.

Figure 5 illustrates that the rate constants of the reactions of the dinitrobenzhydryl anion **2e** with various classes of electrophiles follow separate log*k* versus *E* correlations. The upper correlation line for the reactions of **2e** with the quinone methides **6a**–**e** was used for the calculation of the *N* and *s* parameters of **2e**.[29] The benzylidenemalonates **1a**–**c** are on the same, somewhat lower correlation line as the Michael acceptors indandiones **7**-**X** and the barbiturates **8**-**X**.


7-X


8-X


9-X

As a consequence, the logk_2 values for the reactions of **2e** with **1a**–**c**, **7**-**X**, and **8**-**X**, which are calculated using Equation (1), are 2–4 times higher than the experimental values. The benzylidene malononitriles **9**-**X** deviate even more, and the observed rate constants are approximately one order of magnitude smaller than those calculated by Equation (1). Though a similar split-up of the correlation lines for different classes of electrophiles was reported earlier,[14] we resist the temptation to improve the reliability of the correlations by the addition of correction terms. Rather, we keep the correlation simple and unambiguous, and emphasize that the use of Equation (1) implies errors up to factors of 10–100, which we consider acceptable in a reactivity range of more than thirty orders of magnitude.

Figure 6 shows that the electrophilicities of the benzylidenemalonates **1a**–**i** cover a range of more than six orders of magnitude from $-17.7 > E > -23.8$. Hence, the title compounds **1a**–**i** are roughly ten to eleven orders of magnitude less reactive than their cyclic analogues **10a**–**d**. Thus, fixation of the two ester groups of **1** in a six-membered ring has an enormous effect on the reactivity of these Michael acceptors.

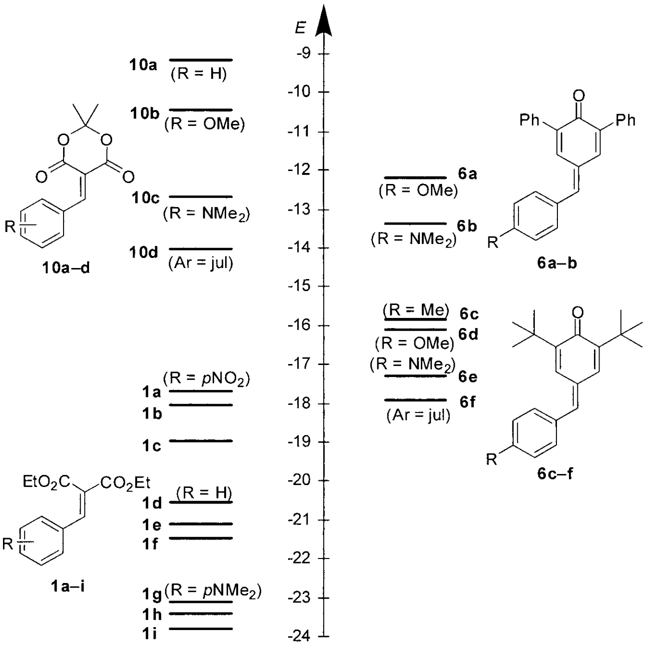


Figure 6. Comparison of the electrophilicity parameters *E* of diethyl benzylidenemalonates **1a**–**i** with those of some reference electrophiles **6a**–**f** and benzylidene Meldrum's acids **10a**–**d**. For "jul"-substituent see **1i** in Scheme 1.

According to Figure 7, the electrophilicity parameters *E* for the benzylidenemalonates **1a**–**i** correlate excellently with Hammett's σ_p values.[38] Comparison with the corresponding Hammett plot for benzylidene Meldrum's acids shows that the electrophilicities of the acyclic Michael acceptors **1a**–**i** are less affected by substituent variation than the electrophilicities of their cyclic analogues **10a**–**d**. For reactions with typical amines and carbanions ($s \approx 0.65$, Table 1) the slopes given in Figure 7 correspond to Hammett reaction constants of $\rho \approx 2.4$ (for **1**) and $\rho \approx 3.5$ (for **10**).

The fact that compound **1i** with the "julolidyl" substituent (for definition see Scheme 1) fits nicely on this correlation line confirms the validity of the Hammett substituent constant $\sigma_p(\text{jul}) = -0.89$, which has recently been derived from related experiments.[14] Analogously, $\sigma_p(\text{thq}) = -0.77$ can be

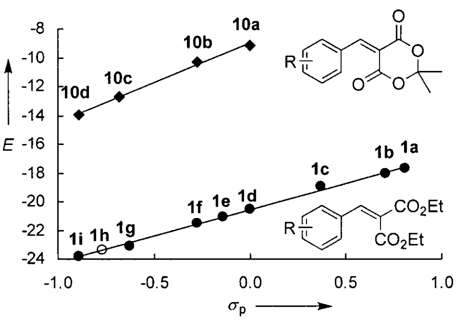


Figure 7. Correlation between the electrophilicity parameters E of electrophiles **1a**–**i** and **10a**–**d** in DMSO with Hammett's σ_p values (for **1a**–**i**: $E=3.68\sigma_p-20.57$; for **10a**-**d**: $E=5.37\sigma_p-9.08$). σ_p for "thq" in **1h** has not been reported but is derived from this correlation.

derived by substituting the E parameter for **1h** into the correlation equation given in Figure 7.

Conclusion

Diethyl benzylidenemalonates **1a**–**i** are more than 10^{10} times less reactive than benzylidene Meldrum's acids **10**, their cyclic counterparts. They extend our electrophilicity scale on the low-reactivity end by more than six orders of magnitude, from $-17.7>E>-23.8$, and are, therefore, recommended as reference electrophiles for determining the nucleophilicities of highly reactive nucleophiles, with N values of $16<N<30$. A report on the use of **1a**–**i** for the characterization of the anions of arylacetonitriles and arylpropionitriles is in preparation.

Experimental Section

Diethyl benzylidenemalonates 1a–**i**: Diethyl benzylidenemalonates **1a**–**i** were prepared following a modified method of Zabicky.[27] Diethyl malonate and the corresponding benzaldehyde (1 equiv) were stirred under reflux in toluene for 3–4 h using piperidine (≈10 mol%) as a catalyst. The product formation was followed by TLC. The reaction mixture was consecutively washed with aqueous HCl, aqueous $NaHCO_3$ solution, and water. After drying the solution, the solvent was evaporated. The residue was either distilled or recrystallized from ethanol to obtain the diethyl benzylidenemalonates. ^{1}H NMR spectra and melting points for the thus obtained compounds **1a**–**g** were in agreement with literature reports (see Supporting Information).

Diethyl 2-(1-methyl-1,2,3,4-tetrahydroquinoline-6-ylmethylene)malonate (1h): Diethyl malonate (1.15 g, 7.18 mmol), 6-formyl-1-methyl-1,2,3,4-tetrahydroquinoline (1.26 g, 7.19 mmol), and piperidine (300 μL) gave a crude product that was washed as described in the general procedure (Supporting Information) and further purified using MPLC (SiO_2, dichloromethane/isohexane = 1/1). The fractions were combined, the solvents evaporated in vacuum, and the residue was crystallized from ethanol/isohexane at −5 °C. Yield: 1.50 g, 4.7 mmol, 65%; yellow solid; m.p. 56.2–56.7 °C; ^{1}H NMR (400 MHz, [D$_6$]DMSO): $\delta=1.22$ (t, $J=7.1$ Hz, 3H; CH_3), 1.26 (t, $J=7.1$ Hz, 3H; CH_3), 1.85 (quint, $J=6.3$ Hz, 2H; CH_2), 2.64 (t, $J=6.3$ Hz, 2H; CH_2), 2.92 (s, 3H; NMe), 3.31 (t, $J=6.3$ Hz, 2H; NCH_2), 4.17 (q, $J=7.1$ Hz, 2H; OCH_2), 4.27 (q, $J=7.1$ Hz, 2H; OCH_2), 6.57 (d, $J=8.7$ Hz, 1H; ArH), 7.02 (s, 1H; ArH), 7.18 (dd, $J=8.8$ Hz, 2.3 Hz, 1H; ArH), 7.45 ppm (s, 1H; C=CH); ^{13}C NMR (100.6 MHz, [D$_6$]DMSO): $\delta=13.7$ (q), 14.0 (q), 21.1 (t), 27.0 (t), 38.2 (q; NCH_3), 50.2 (t; NCH_2), 60.5 (t; OCH_2), 60.9 (t; OCH_2), 110.0 (d), 118.1 (s), 118.5 (s), 121.7 (s), 130.1 (d), 130.5 (d), 141.7 (d; =CH), 148.6 (s), 164.2 (s), 167.1 ppm (s); HR-MS: m/z calcd for $C_{18}H_{23}O_4N$: 317.1627; found: 317.1610; elemental analysis calcd (%) for $C_{18}H_{23}O_4N$: C 68.12, H 7.30, N 4.41; found: C 67.96, H 7.28, N 4.38.

Diethyl 2-{(1,2,3,5,6,7-hexahydropyrido[3,2,1-*ij*]quinolin-9-yl)methylene}-malonate (1i): A mixture of 1,2,3,5,6,7-hexahydropyrido[3.2.1-*ij*]quinoline-9-carbaldehyde (1.00 g, 4.98 mmol), diethyl malonate (0.79 g, 4.93 mmol), and piperidine (350 μL) was stirred in toluene under reflux until TLC indicated full conversion (3 h). After washing the crude reaction mixture as described in the general procedure (Supporting Information), the resulting oily residue was crystallized from EtOAc/isohexane (1:3). The solid was filtered and washed with isohexane. Yield: 1.1 g, 65%; yellow solid; m.p. 83.2–83.4 °C; ^{1}H NMR (600 MHz, $CDCl_3$,): $\delta=1.30$ (t, $J=6.2$ Hz, 3H; CH_3), 1.35 (t, $J=6.2$ Hz, 3H; CH_3), 1.93 (quint, $J=6.2$ Hz, 2×2H; CH_2), 2.69 (t, $^3J=5.6$ Hz, 2×2H; CH_2), 3.23 (t, $J=5.6$ Hz, 2×2H; NCH_2), 4.25 (q, $J=7.2$ Hz, 2H; OCH_2), 4.35 (q, $J=7.2$ Hz, 2H; OCH_2), 6.91 (s, 2H; ArH), 7.52 ppm (s, 1H, 1H; C=CH); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta=14.0$ (q), 14.2 (q), 21.4 (t), 27.6 (t), 49.9 (t; NCH_2), 60.9 (t; OCH_2), 61.2 (t; OCH_2), 118.5 (s), 119.0 (s), 120.6 (s), 129.7 (d), 143.0 (d, =CH), 145.2 (s), 165.3 (s), 168.2 ppm (s); HR-MS: m/z calcd for $C_{20}H_{25}O_4N$: 343.1784; found: 343.1775; elemental analysis calcd (%) for $C_{20}H_{25}O_4N$: C 69.95, H 7.34, N 4.08; found: C 69.66, H 7.35, N 4.09.

Procedure for the reactions of electrophiles 1 with nucleophile 2b: Compound **2b**-K$^+$ (4.0–7.5 mmol) was dissolved in dry DMSO (20 mL), and a solution of **1a**–**f** (2.0–2.5 mmol) in dry DMSO was added under a nitrogen atmosphere. Stirring was continued for 5 h at room temperature, and the solution was diluted with diethyl ether (25 mL). The reaction mixture was then poured on water (50 mL), cooled with ice, and acidified with acetic acid. After extraction with diethyl ether, the combined organic fractions were washed with water and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the crude product was purified by distillation.

Tetraethyl 2-(4-methoxyphenyl)propane-1,1,3,3-tetracarboxylate (5fb): From **1f** (0.56 g, 2.0 mmol) and **2b**-K (0.79 g, 4.0 mmol). Yield: 0.68 g, 78%; colorless oil; b.p. 210–220 °C (1.3×10^{-2} bar); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=1.04$ (t, $J=7.1$ Hz, 2×3H; CH_3), 1.23 (t, $J=7.1$ Hz, 2×3H; CH_3), 3.75 (s, 3H; OCH_3), 3.95 (q, $J=7.1$ Hz, 2×2H; OCH_2), 4.04–4.18 (m, 7H), 6.76–6.79 (m, 2H; ArH), 7.24–7.27 ppm (m, 2H; ArH); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta=13.6$ (q), 13.8 (q), 43.0 (d; C^b), 54.9 (q; OCH_3), 55.1 (d; C^a), 61.1 (t), 61.4 (t), 113.1 (d), 129.0 (s), 130.4 (d), 158.7 (s), 167.4 (s), 167.9 ppm (s); the NMR chemical shifts are in agreement with the data reported in ref. [26].

Kinetics: For fast kinetic experiments ($\tau_{1/2}<15$ s), standard stopped-flow UV/Vis spectrophotometer systems were used in their single mixing mode. Solutions of the electrophiles **1** in DMSO were mixed with solutions of the carbanions **2** in DMSO (either generated by deprotonation of **2**-H with 1.05 equiv KO*t*Bu in DMSO or by dissolving **2**-K$^+$ in DMSO). ***CAUTION:* Because of explosion hazards, the isolation of 2a-K$^+$ should be avoided**.[39] We therefore recommend generating **2a** in situ from the corresponding CH acid **2a**-H. Kinetics of slow reactions ($\tau_{1/2}>15$ s) were determined by UV/Vis spectrometry using a J&M TIDAS diode array spectrophotometer. To obtain pseudo-first-order kinetics, the carbanions **2** were used in large excess (10 to 100 equivalents) over the electrophiles (except for kinetics with nucleophile **2e**, which was used as the minor component, see section "Kinetic Measurements"). The temperature of the solutions was kept constant (20±0.1 °C) by using circulating bath thermostats. Rate constants k_{obs} (s^{-1}) were obtained by fitting the single exponential $A_t=A_0\exp(-k_{obs}t)+C$ to the observed time-dependent electrophile absorbance (the evaluated wavelengths are given in the Supporting Information). As depicted in the Supporting Information, the second-order rate constants k_2 (Table 3) were obtained from the slopes of the linear plots of k_{obs} versus the carbanion concentrations [**2**].

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