

Electrophilicity Parameters for Benzylidenemalononitriles[†]

Tadeusz Lemek and Herbert Mayr*

Department Chemie, Ludwig-Maximilians-Universität München, Butenandtstr. 5-13 (Haus F), D-81377 München, Germany

herbert.mayr@cup.uni-muenchen.de

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Kinetics of the reactions of stabilized carbanions (derived from nitroethane, diethyl malonate, ethyl cyanoacetate, ethyl acetoacetate, acetyl acetone) with benzylidenemalononitriles have been determined in dimethyl sulfoxide solution at 20 °C. The second-order rate constants are employed to determine the electrophilicity parameters E of the benzylidenemalononitriles according to the correlation equation $\log k(20\text{ °C}) = s(E + N)$. Comparison with literature data shows that this equation allows the semiquantitative prediction of the reactivities of benzylidenemalononitriles toward a wide variety of nucleophiles, including carbanions, enamines, amines, water, and hydroxide.

Introduction

Numerous kinetic investigations have shown that the rate constants for the reactions of carbocations and related electrophiles with neutral nucleophiles can be described by the following equation:^{1–4}

$$\log k(20\text{ °C}) = s(N + E) \quad (1)$$

where s = nucleophile-specific parameter, N = nucleophilicity parameter, and E = electrophilicity parameter. Subsequently, we have reported that the reactions of carbanions with quinone methides, which can be considered as stabilized benzhydryl cations (diarylcarbenium ions),⁵ follow similar relationships.⁶ Kinetic investigations of the reactions of benzhydryl cations with stabilized carbanions allowed us to combine the two sets of kinetic data, and we have presented a nucleophilicity scale ranging from methyl-substituted benzenes to stabilized carbanions (Figure 1).⁷

The question arose whether the order of nucleophilic reactivities of carbanions, which has been derived with respect to carbocations and quinone methides as refer-

ence electrophiles, is directly transferable to other Michael acceptors. If this were the case, eq 1 could also be employed for describing the rates of typical Michael additions. We have examined this question by investigating the reactions of representative carbanions with benzylidenemalononitriles.

The reactions of benzylidenemalononitriles with stabilized carbanions have previously been reported to yield a variety of products.^{8,9} Though carbanions generally react with the benzylidenemalononitriles with initial nucleophilic addition, the primarily formed Michael adducts often undergo consecutive reactions and cannot be isolated. The course of transformation of the dicyano-substituted carbanions formed in the initial addition step

[†] Dedicated to Professor Sema L. Ioffe on the occasion of his 65th birthday.

* To whom correspondence should be addressed. Fax: (+49) 89-2180-77717.

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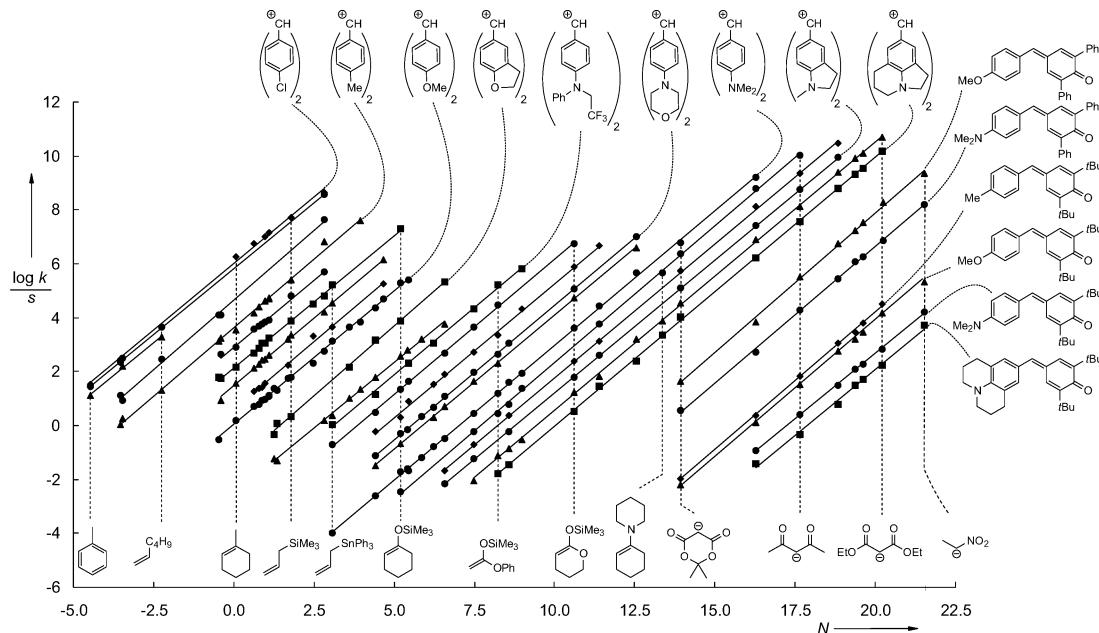


FIGURE 1. Plot of $(\log k)/s$ versus N for the reactions of benzhydryl cations and quinone methides with π -nucleophiles and carbanions.⁷

is controlled by many factors, e.g., the nature of the carbanion, the nature of the aryl group in the arylidene-malononitrile, as well as the reaction conditions.

Results and Discussion

Product Studies. Three types of products for the reactions of the carbanions **2a–e** with the benzylidenemalononitriles **1a–c** were obtained in this investigation (Scheme 1):

(1) The ordinary Michael adduct **4ab** was produced in high yield (89%) from the reaction of **1a** with **2b** in analogy to the previously reported quantitative formation of the Michael adduct **4aa** from **1a** and **2a**.^{8b}

(2) In contrast, the malononitrile anion **2f** along with the benzylidenecyanoacetates **5bc** and **5cc** were obtained by the reactions of **2c** with **1b** and **1c**, respectively. The high acidity of malononitrile and the push–pull-stabilization of **5bc** and **5cc** provide the thermodynamic driving force for the retro-Michael addition of **6**.

(3) In accord with refs 9a,b,d,h, which reported the formation of the 4*H*-pyrans **7** in the reactions of **1a,b** with the acetyl substituted carbanions **2d** and **2e**, we also observed the formation of **7be** when **1b** was combined with **2e**.^{9a,b} We have not been able to isolate the initial Michael adduct **4be** from this combination, even under mild reaction conditions.

Kinetics. The stopped-flow technique was employed to determine the kinetics of these reactions. Since the benzylidenemalononitriles **1a–c** show absorption maxima at 311, 354, and 441 nm, respectively, and the products (except **5**) do not absorb at these wavelengths, the progress of the reactions can be monitored photo-metrically.

Second-order kinetics with complete disappearance of the benzylidenemalononitrile absorptions were observed for the reactions of **1a–c** with the strong bases **2a,b** ($pK_a \approx 16$, DMSO).¹⁰ Analogously, the less basic carbanions

2c and **2d** ($pK_a = 13–14$, DMSO)¹⁰ also underwent irreversible second-order reactions with **1a**, the most reactive electrophile of this series.

In contrast, combination of the weak bases **2c,e** ($pK_a \approx 13$, DMSO)¹⁰ with the weak electrophiles **1b,c** proceeded with incomplete formation of the Michael adducts **3**, which underwent slow consecutive transformations into **5** and **2f** or into **7**. An example for the rapid reversible formation of the initial addition product is shown in Figure 2. Since **3cc** does not absorb at $\lambda = 441$ nm (λ_{max} for **1c**), the combination of **1c** with **2c** results in a rapid initial decay of the absorbance at $\lambda = 441$ nm by approximately 35% (< 0.1 s). The consecutive slow transformation into **5cc** (5 min) with an absorption maximum at $\lambda = 432$ nm then gives rise to a subsequent increase of the absorbance at $\lambda = 441$ nm as shown in the insert of Figure 2.

When the reactions of **2c,e** with **1b,c** were performed with a high excess of the carbanions **2c,e**, pseudo-first-order kinetics for the first reaction step were observed, and the pseudo-first-order rate constants k_{obs} were obtained as the slopes of the plots of $\ln(A_t - A_\infty)$ vs t , where A_t is the absorbance of **1** at t and A_∞ is the absorbance of **1** at the time when the equilibrium between the reactants and the initial adduct **3** is reached. According to ref 11, the pseudo-first-order rate constants of reversible reactions represent the sum of forward and backward reactions (eq 2), and the second-order rate constants k^- can be obtained as the slopes of plots of k_{obs} versus $[2]$ (Figure 3).

$$k_{obs} = ([2]k^- + k^-) \quad (2)$$

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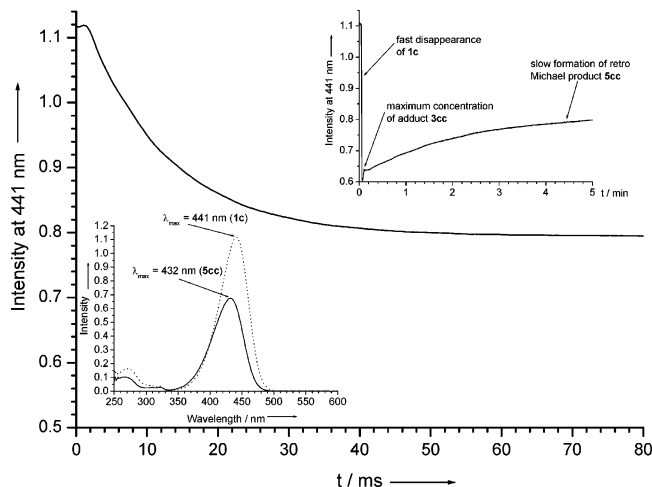
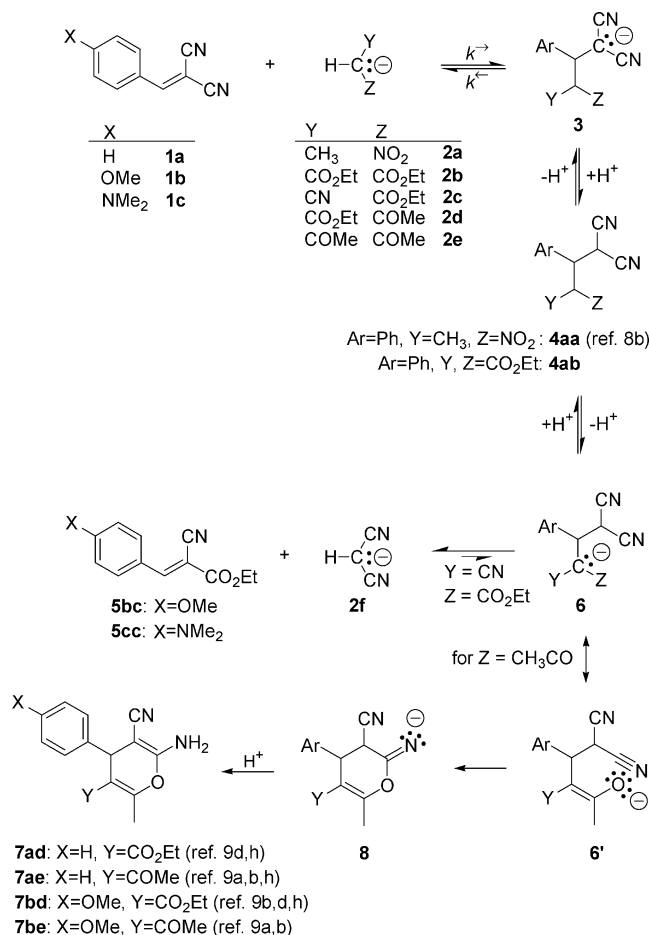


FIGURE 2. Michael addition of **2c** to **1c** and consecutive retro-Michael addition with formation of **5cc** and **2f** monitored at $\lambda = 441$ nm in DMSO, 20 °C.

SCHEME 1. Products of Reactions of Benzylidenemalononitriles 1a–c with Carbanions 2a–e



Reversibility of the nucleophilic attack was a problem in all reactions of the weakly basic anion of dimedone (**2g**). Though the reactions of **2g** proceed with complete

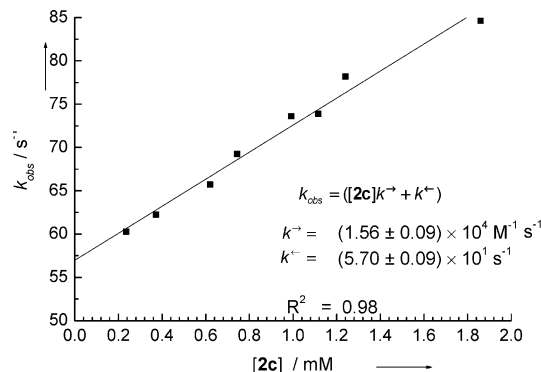


FIGURE 3. Pseudo-first-order rate constant k_{obs} for the reaction of *p*-dimethylaminobenzylidene-malononitrile **1c** with the carbanion of ethyl cyanoacetate **2c** in DMSO at 20 °C as a function of $[2c]$.

SCHEME 2. Formation of 4H-Chromenes in Reactions of Dimedone Anion with Benzylidenemalononitriles^{9c,e,f}

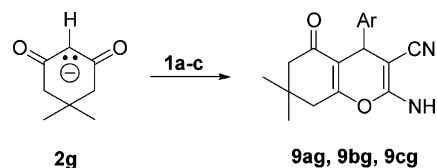


TABLE 1. Rate Constants for Addition Reactions of Carbanions 2a–e with Benzylidenemalononitriles 1a–c in DMSO at 20 °C

carb-anion	cation	pK _a (DMSO) ^a	electro- isolated phile	product	k ₂ (M ⁻¹ s ⁻¹)
2a	N(<i>n</i> Bu) ₄ ⁺	16.7	1a	4aa^b	>2 × 10 ⁷
2b	K ⁺	16.4	1a	4ab	(1.15 ± 0.06) × 10 ⁷
2c	K ⁺	13.1	1a	7ad^c	(5.42 ± 0.11) × 10 ⁶
2d	K ⁺	14.3	1a	7ad^c	(3.52 ± 0.16) × 10 ⁶
2a	N(<i>n</i> Bu) ₄ ⁺	16.7	1b	5bc	(5.17 ± 0.23) × 10 ⁶
2b	K ⁺	16.4	1b	5bc	(2.04 ± 0.06) × 10 ⁶
2c	K ⁺	13.1	1b	7be^e	(8.42 ± 0.11) × 10 ^{5d}
2e	K ⁺	13.3	1b	7be^e	(5.96 ± 0.05) × 10 ^{4d}
2a	N(<i>n</i> Bu) ₄ ⁺	16.7	1c	5cc	(1.85 ± 0.03) × 10 ⁵
2b	K ⁺	16.4	1c	5cc	(3.34 ± 0.13) × 10 ⁴
2c	K ⁺	13.1	1c	5cc	(1.56 ± 0.09) × 10 ^{4d}
2e	K ⁺	13.3	1c	5cc	(1.17 ± 0.07) × 10 ^{3d}

^a From ref 10. ^b From ref 8b. ^c From refs 9d and 9h. ^d Reversible CC bond formation. ^e From refs 9a and 9b.

consumption of **1a–c** due to the formation of the 4H-chromene **9** (Scheme 2),^{9c,e,f} cyclization with irreversible formation of **9** occurs in a slow consecutive reaction, and we have not been able to find conditions under which second-order kinetics was obeyed. The order with respect to carbanion was generally greater than 1, usually close to 2, and addition of dimedone as a proton-source did not simplify the kinetics as in the analogous reactions of **2g** with quinone methides.⁶ For that reason, kinetic data for the reactions of **2g** are not included in Table 1.

Determination of the Electrophilicity Parameters. Equation 1 was used to calculate the *E* parameters of **1a–c** from the rate constants given in Table 1 and the previously reported *N* and *s* parameters of the carbanions **2a–e**.⁷ A least-squares fit of calculated and experimental rate constants (minimization of $\Delta^2 = \sum(\log k - s(N + E))^2$ with What'sBest!'s nonlinear solver) gave the *E* parameters of the benzylidenemalononitriles

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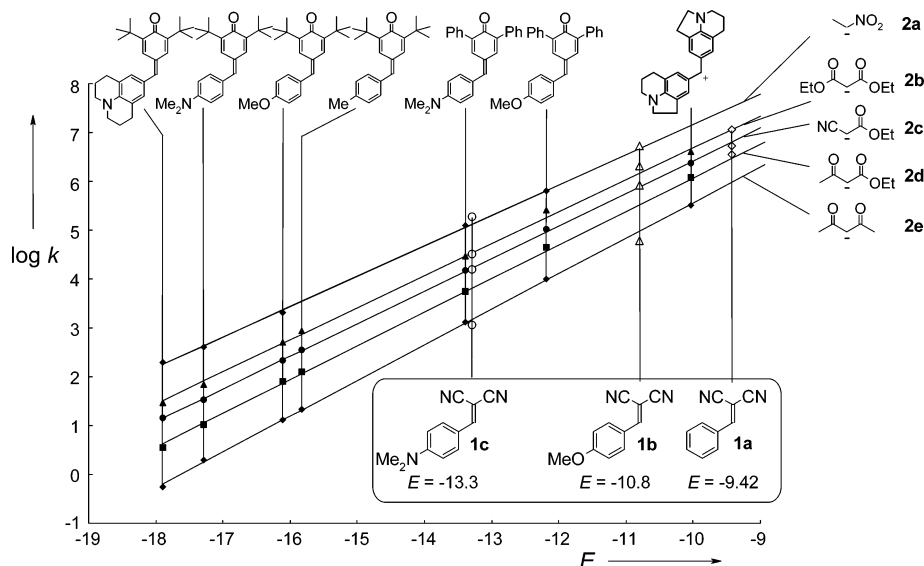


FIGURE 4. Rate constants for the reactions of carbanions **2a–e** with benzylidenemalononitriles **1a–c** compared with the reactivities toward reference electrophiles.⁷ The rate constants for the reactions of **1a–c** with **2a–e** are not used for the construction of the correlation lines.

1a–c, which are close to the arithmetic means of E calculated from k of the individual experiments. A comparison of the electrophilicities of benzylidenemalononitriles **1a–c** with the electrophilicities of benzhydryl cations and quinone methides is given in Figure 4. The good fit demonstrates that the nucleophilic reactivity order of carbanions in DMSO as derived from the reactions with benzhydryl cations and quinone methides, also holds for the reactions with typical Michael acceptors.

Discussion

A three-parameter equation, like eq 1, cannot be expected to reproduce and predict rate constants for electrophile nucleophile combinations of large structural variety with high precision. However, the satisfactory fit of the rate constants determined in this investigation to the previously published correlation lines⁷ in Figure 4 shows the suitability of this approach for a semiquantitative treatment of organic reactivity. From the E parameters given in Figure 4, one can now derive that the noncharged Michael acceptors **1a–c** have electrophilicities comparable to those of amino-substituted benzhydrylium ions or triaryllallyl cations,^{1d,12} allylpalladium complexes,^{1d,13} or tricarbonylcycloheptadienylium cations,^{1d,14} i.e., Figure 5 illustrates the electrophilicity range where highly stabilized carbocations and strongly electron-deficient noncharged π -electrophiles overlap.

To examine the suitability of the electrophilicity parameters determined in this work for generally predicting the electrophilic reactivities of the benzylidenemalononitriles **1a–c**, we have calculated the rate constants of their reactions with other types of nucleophiles by eq 1 and compared these numbers with experimental values (Table 2).

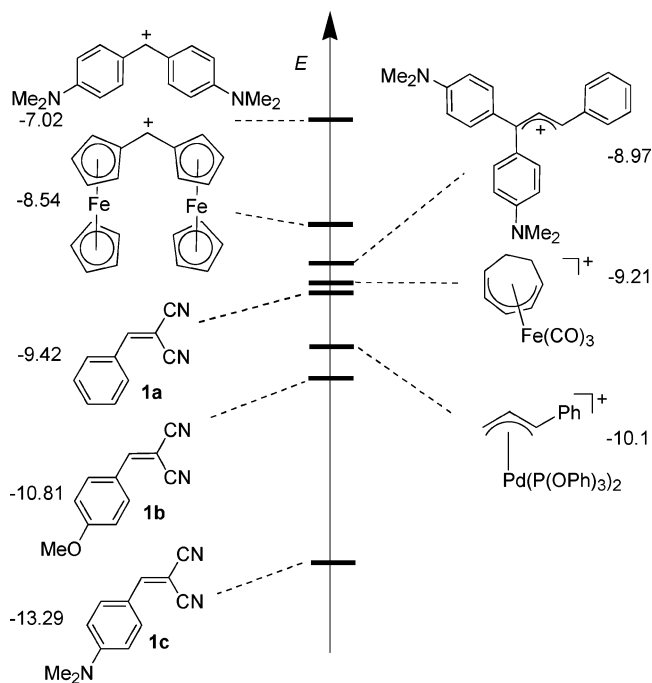


FIGURE 5. Comparison of the electrophilicity parameters E of charged^{1d} and noncharged electrophiles.

The malonodinitrile anion **2f** was found to possess similar nucleophilicity parameters in DMSO and in water,¹⁵ in accord with Bernasconi's report that this carbanion reacts only four times faster in 50% aqueous DMSO than in pure water.¹⁶ The rate constant calculated for the reaction of **2f** with **1a** is 1.3 times larger than that measured by Bernasconi.¹⁶ In view of the approximate character of the N and s parameters for CN^-

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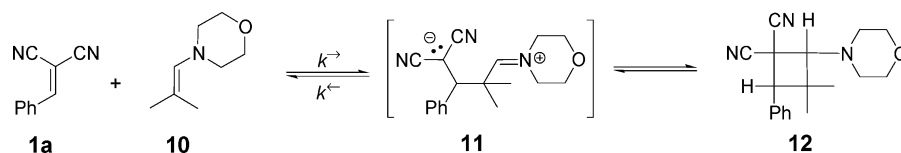
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TABLE 2. Comparison of Experimental Second-Order Rate Constants k_{exp} and k_{calc} Calculated (from eq 1) for Reactions of Benzylidenemalononitriles **1a–c** with Various Nucleophiles

electrophile (E parameter)	nucleophile	N	s	$k^{20^\circ\text{C}}_{\text{calc}}$ ($\text{M}^{-1} \text{s}^{-1}$)	k_{exp} ($\text{M}^{-1} \text{s}^{-1}$) (conditions)
1a (−9.42)	CH(CN) $_2^-$	19.58 ^a	0.54 ^a	3.1×10^5 (H $_2$ O)	2.3×10^5 (20 °C, H $_2$ O) ^b
		19.36 ^c	0.67 ^c	4.6×10^6 (DMSO)	9.5×10^5 (20 °C, H $_2$ O/DMSO 1/1 v/v) ^b
	CN $^-$	9.19 ^d	0.60 ^d	0.73 (H $_2$ O)	0.50 (25 °C, H $_2$ O/EtOH 4/1 v/v) ^e
	benzylamine	14.7 ^f	0.44 ^f	2.3×10^2 (MeCN)	2.6×10^2 (20 °C, MeCN) ^g
	piperidine	20.9 ^h	0.38 ^h	2.30×10^4 (H $_2$ O-DMSO 1/1 v/v)	1.8×10^5 (20 °C, H $_2$ O/DMSO 1/1 v/v) ⁱ
	morpholine	16.96 ^j	0.67 ^j	1.1×10^5 (DMSO)	1.6×10^5 (20 °C, DMSO/H $_2$ O 7/1 v/v) ^k
	H $_2$ O	5.11 ^l	0.89 ^l	$1.5 \times 10^{-4} \text{ s}^{-1}$ (H $_2$ O)	$1.2 \times 10^{-4} \text{ s}^{-1}$ (20 °C, H $_2$ O) ^m
	OH $^-$ /H $_2$ O	10.47 ⁿ	0.61 ⁿ	4.4 (H $_2$ O)	1.3×10^2 (20 °C, H $_2$ O) ^m
	10	10.04 ^o	0.82 ^o	3.2 (CH $_2$ Cl $_2$)	1.2×10^{-2} (20 °C, CH $_2$ Cl $_2$) ^p
	1b (−10.8)	piperidine	20.9 ^h	0.38 ^h	6.9×10^3 (H $_2$ O-DMSO 1/1 v/v)
OH $^-$ /H $_2$ O		10.47 ⁿ	0.61 ⁿ	0.63 (H $_2$ O)	2.1×10^1 (20 °C, H $_2$ O) ^m
1c (−13.3)	piperidine	20.9 ^h	0.38 ^h	7.7×10^2 (H $_2$ O-DMSO 1/1 v/v)	5.6×10^3 (20 °C, H $_2$ O/DMSO 1/1 v/v) ^k

^a N and s for CH(CN) $_2^-$ /H $_2$ O (from ref 15). ^b From ref 16. ^c N and s for CH(CN) $_2^-$ /DMSO (from ref 7). ^d For approximate values for CN $^-$ /H $_2$ O see ref 4. ^e From ref 17. ^f N and s for *n*-PrNH $_2$ in MeCN (from ref 18). ^g From ref 19. ^h N and s in 50% aqueous DMSO (see Supporting Information); the plot of log k vs E as shown in Figure S7 has an unusually low correlation coefficient that we do not recommend to use these numbers for further calculations. ⁱ From ref 20. ^j N and s for morpholine in DMSO (from ref 4). ^k From ref 21. ^l N and s refers to first-order rate constants (see ref 4). ^m From ref 22. ⁿ From ref 4. ^o For N and s of **10** in CH $_2$ Cl $_2$, see ref 23. ^p Extrapolated value, see Supporting Information.

SCHEME 3. Reversible Stepwise [2 + 2] Cycloaddition of Morpholinoisobutylene **10** with Benzylidenemalononitrile **1a**



H $_2$ O,⁴ the excellent agreement between calculated and experimental numbers for the reactions of **1a** with CN $^-$ in water has to be considered as accidental. Entry 3 of Table 2 shows that the calculated rate constant for the reaction of *n*-propylamine with **1a** in acetonitrile is almost identical to the published experimental value¹⁹ for the reaction of benzylamine with **1a** in the same solvent.

Nucleophilicity parameters N and s for piperidine and morpholine have previously only been established for the solvent DMSO.⁴ To compare predictions by eq 1 with the published rate constants for the reactions of piperidine with **1a–c** in 50% aqueous DMSO,²¹ we have now determined $N = 20.9$ and $s = 0.38$ for piperidine in 50% aqueous DMSO as described in the Supporting Information. With these numbers, we can now calculate the rate constants for the reactions of piperidine with **1a–c** in 50% aqueous DMSO, and as shown in Table 2, the three calculated rate constants are 7–13 times smaller than those measured by Bernasconi.^{20,21}

It must again be considered as a fortuity that the rate constant calculated for the reaction of morpholine with **1a** in DMSO differs by only a factor of 1.4 from the one measured in 70% DMSO/30% H $_2$ O. While the first-order rate constant calculated for the reaction of **1a** with water is exactly matching the one measured by Bernasconi,²²

TABLE 3. Rate and Equilibrium Constants for [2 + 2] Cycloaddition of Benzylidenemalononitrile **1a** with *N*-Morpholinoisobutene **10** (CH $_2$ Cl $_2$)

T (°C)	k^+ ($\text{M}^{-1} \text{s}^{-1}$)	k^- (s^{-1})	K^a (M^{-1})	K^b (M^{-1})
−20.0	2.81×10^{-3}	2.0×10^{-4}	14	19 (from two runs)
−30.5	2.03×10^{-3}	4.4×10^{-5}	46	48 (from three runs)
−41.0	1.19×10^{-3}	(7.3×10^{-6})	(163)	103 (from three runs)
−50.0	7.10×10^{-4}	(3.5×10^{-6})	(205)	

^a Calculated from $K = k^+/k^-$. ^b Calculated from $K = (A_0 - A_\infty)/(A_\infty[\mathbf{10}])$ at λ_{max} .

OH $^-$ in water was reported to react 30 times faster with **1a** and **1b** than predicted by eq 1.

Because rate constants for the reactions of benzylidenemalononitriles with π -nucleophiles of known N and s parameters have not been available in the literature, we have studied the kinetics of the reaction of **1a** with the enamine **10** in this work (Scheme 3). In accord with literature reports, the previously characterized cyclobutane **12** is formed,²⁴ presumably via the dipolar intermediate **11**.

The incomplete disappearance of the absorbance of **1a** indicated the existence of an equilibrium, and when **10** was used in high excess, it was possible to derive k^+ and k^- from a plot of the pseudo-first-order rate constant k_{obs} versus $[\mathbf{10}]$ in analogy to the procedure described above (cf. Figure 3). Table 3 compares the equilibrium constants derived as the ratio of forward over backward rate constants with those derived from the UV-spectroscopy.

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cally determined concentrations of **1a**. Though the two methods give somewhat different results, it is obvious that the cyclobutane is favored at low temperature, whereas dissociation is preferred at higher temperature. From a van't Hoff plot, $\Delta_r H^\ddagger = -39.2 \text{ kJ mol}^{-1}$ and $\Delta_r S^\ddagger = -130 \text{ J mol}^{-1} \text{ K}^{-1}$ (K from concentrations) can be derived.

An Eyring plot for the reaction of **1a** with **10** yields $\Delta_r H^\ddagger = 19.8 \text{ kJ mol}^{-1}$ and $\Delta_r S^\ddagger = -214 \text{ J mol}^{-1} \text{ K}^{-1}$, in agreement with Huisgen's reports that stepwise [2 + 2] cycloadditions via zwitterionic intermediates generally proceed with highly negative entropies of activation.²⁵

We can now use the Eyring parameters to calculate the combination rate constant for **1a** + **10** at 20 °C ($0.0124 \text{ M}^{-1} \text{ s}^{-1}$) and compare it with the value derived from eq 1 ($3.2 \text{ M}^{-1} \text{ s}^{-1}$). Though the two numbers differ by a factor of 250, it is remarkable that eq 1 is even able to predict the correct order of magnitude for stepwise [2 + 2] cycloadditions. A better agreement cannot be expected because of the Coulomb interactions in the intermediate 1,4-dipole, which strongly depend on solvent polarity.²⁶

We therefore conclude that the E parameters of the benzylidenemalononitriles **1a–c** derived in this work are a useful tool for predicting the reactivities of these electrophiles. It should be noted, however, that this statement cannot be generalized for all types of Michael acceptors. The relative reactivities of different nucleophiles toward tetracyanoethylene,²⁷ for example, are not properly reproduced by eq 1, probably because of destabilization of the zwitterionic intermediates by the inverse anomeric effect of two geminal cyano groups, which strongly depends on the nature of the additional substituents.²⁸ Despite of this limitation, the results of this investigation suggest to systematically analyze the potential of eq 1 for predicting the rates of nucleophilic additions to electron-deficient olefins.²⁹ In view of the previously reported relationship between eq 1 and Ritchie's N_+ relationship^{4,30} and the finding by Hoz³¹ that the rate constants for nucleophilic additions to acceptor-substituted 9-methylene-fluorenes correlate with Ritchie's N_+ values, one may expect that many more types of electrophile nucleophile combinations can be described by the linear free energy relationship (eq 1).

Experimental Section

Instruments and Materials. ¹H and ¹³C NMR spectra were recorded on 300 and 75.5 MHz instruments, respectively. Chemical shifts are expressed in ppm and refer to Me₄Si ($\delta_{\text{H}} = 0.00 \text{ ppm}$), coupling constants are in Hz, and melting points are uncorrected. The yields refer to isolated products without optimization of the procedures. DMSO 99.5% ($\text{H}_2\text{O} < 0.01\%$)

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was used. The benzylidenemalononitriles **1b–c** were prepared according to literature procedures³² and recrystallized from EtOH. Potassium or tetra-*n*-butylammonium salts of carbanions **2b–f** were prepared according to published procedures.³³

Product Studies. Reaction of 1a with 2b. Diethyl malonate **2b** (305 μL , 2.00 mmol) was added to a solution of freshly sublimated *t*BuOK (225 mg, 2.00 mmol) in DMSO (1 mL) at room temperature. After 2 min of stirring, a solution of **1a** (154 mg, 1.00 mmol) in DMSO (1 mL) was added. After 10 min, trifluoroacetic acid (200 μL , 2.60 mmol) was added, and the mixture was poured into water (50 mL). A white solid precipitated, which was filtered, washed with water, and dried in the air. The crude product was dissolved in 2 mL of methanol and crystallized to give 280 mg (89%) of 2-(2,2-dicyano-1-phenyl-ethyl)-malonic acid diethyl ester (**4ab**): mp 79–79.5 °C; ¹H NMR (CDCl₃) δ 0.93 (t, $J = 7.1$, 3 H, CH₂CH₃), 1.28 (t, $J = 7.1$, 3 H, CH₂CH₃), 3.89 (dd, $J = 11.4$, $J = 5.0$, 1 H, PhCH), 3.92 (q, $J = 7.1$, 2 H, CH₂CH₃), 4.07 (d, $J = 11.4$, 1 H, CH(CN)₂), 4.27 (q, $J = 7.1$, 2 H, CH₂CH₃), 4.88 (d, $J = 5.0$, 1 H, CH(CO₂Et)₂), 7.38 (s, 5 H, Ph); ¹³C NMR (CDCl₃) δ 13.5 (CH₃), 13.8 (CH₃), 27.6 (CH(CN)₂), 44.8 (PhCH), 53.4 (CH(CO₂Et)₂), 62.1 (CH₂), 62.8 (CH₂), 111.2 (CN), 111.2 (CN), 128.5 (C_m Ph, tentatively), 129.1 (C_o Ph, tentatively), 129.6 (C_p Ph), 133.4 (C_i Ph), 165.8 (CO₂Et), 167.5 (CO₂Et). Anal. Calcd for C₁₇H₁₈N₂O₄ (314.34): H 5.77 C 64.96 N 8.91. Found: H 5.78 C 65.15 N 8.98.

Reaction of 1b with 2c. Ethyl cyanoacetate (340 mg, 3.00 mmol) was added to a vigorously stirred solution of freshly sublimated *t*BuOK (337 mg, 3.00 mmol) in DMSO (1 mL). After 1 min of stirring, a solution of **1b** (184 mg, 1.00 mmol) in DMSO (2 mL) was added. After 15 min, trifluoroacetic acid (250 μL , 3.25 mmol) was added, and the mixture was poured into water (100 mL). The product was extracted with AcOEt (3 \times 20 mL), and the organic layer was separated, washed with brine, and dried with CaCl₂. The solvent was removed, and the crude product (a yellow oil, 500 mg) was dried in vacuo. Crystallization from MeOH and recrystallization from hexane/AcOEt yielded 100 mg (43%) of 2-cyano-3-(4-methoxy-phenyl)-acrylic acid ethyl ester **5bc** (the isolation of the product was not quantitative): mp 80–81 °C (lit.³⁴ 82–83 °C). The ¹H NMR spectrum was consistent with that reported in ref 34.

Reaction of 1c with 2c. Ethyl cyanoacetate (340 mg, 3.00 mmol) was added to a vigorously stirred suspension of K₂CO₃ (690 mg, 5.00 mmol) in DMSO (2 mL). After addition of **1c** (99 mg, 0.500 mmol) the mixture was stirred for 45 min at room temperature and diluted with 20 mL of AcOEt and 10 mL of aqueous HCl (1 M). The organic layer was separated, washed with water and brine, dried with Na₂SO₄, and purified by column chromatography on silica gel 60 F₂₅₄ (eluent hexane/AcOEt). Recrystallization from hexane/AcOEt yielded 110 mg (90%) of 2-cyano-3-(4-(dimethylamino)-phenyl)acrylic acid ethyl ester (**5cc**): mp 125–126 °C (lit.³⁴ 127–128 °C). The ¹H NMR spectrum of **5cc** was consistent with that reported in ref 34. The UV spectrum shows $\lambda_{\text{max}} = 432 \text{ nm}$ in DMSO at 20 °C.

Reaction of 1b with 2e. Triethylamine (50 μL , 0.36 mmol) was added to a solution of **1b** (92 mg, 0.50 mmol) and acetyl acetone (100 mg, 1 mmol) in DMSO (2 mL). The mixture was stirred for 1 h at room temperature and diluted with AcOEt (20 mL) and aqueous HCl (5 mL, 1 M). The organic layer was separated, washed with water and brine, dried with Na₂SO₄,

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and purified by column chromatography on silica gel 60 F₂₅₄ with hexane/AcOEt solvent system. Recrystallization from hexane/CHCl₃ yielded 125 mg (88%) of 5-acetyl-2-amino-4-(4-methoxyphenyl)-6-methyl-4*H*-pyran-3-carbonitrile **7be**: mp 158–159 °C (lit.^{9a,b} 157–159 °C). The ¹H NMR spectrum was in agreement with the spectrum reported in ref 9a.

Kinetic Measurements. The kinetic measurements were performed as previously reported.³⁵

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Supporting Information Available: Details of the kinetic experiments and NMR spectra of 2,6-di-*tert*-butyl-4-(piperidin-1-yl-(4-tolyl)methyl)phenol. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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