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Electrophilic Reactivities of Azodicarboxylates

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Dedicated to Professor Günter Schäfer on the occasion of his 75th birthday

Abstract: The kinetics of the reactions of the azodicarboxylates **1** with the enamines **2** have been studied in CH_3CN at 20 °C. The reactions follow a second-order rate law and can be described by the linear free energy relationship $\log k_2(20\,°C) = s(N+E)$ (E = electrophilicity parameter, N = nucleophilicity parameter, and s = nucleophile-specific slope parameter). With E parameters from −12.2 to −8.9, the electrophilic reactivities of **1** turned out to be comparable to those of α,β-unsaturated iminium ions, amino-substituted benzhydrylium ions, and ordinary Michael acceptors. While the E parameters of the azodicarboxylates **1** determined in this work also hold for their reactions with triarylphosphines, they cannot be used for estimating rate constants for their reactions with amines. Comparison of experimental and calculated rate constants for cycloadditions and ene reactions of azodicarboxylates provides information on the concertedness of these reactions.

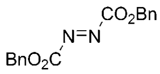
Keywords: electrophilic amination · kinetics · organocatalysis · pericyclic reaction · reaction mechanisms

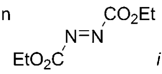
Introduction

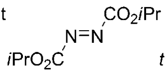
Azodicarboxylates **1** have been used as strong electrophiles in numerous synthetic transformations,[1] for example, electrophilic aminations of carbonyl compounds,[2] which have first been described in 1954 by Huisgen and Jakob.[2a] They have been reported to be highly reactive dienophiles and enophiles in Diels–Alder and ene reactions,[3] and their reaction with phosphines represents the first step of the synthetically important Mitsunobu reaction.[4] In recent years, organocatalytic enantioselective α-aminations of aldehydes and ketones with azodicarboxylates attracted great attention,[5] in which the electrophiles **1** are attacked by intermediate enamines. Electrophiles used for enamine-activated reactions of carbonyl compounds should react fast with the enamine intermediates but not with the enols, which are present in equilibrium with the tautomeric carbonyl compounds. As the reactions of azodicarboxylates with enamines represent the key step of organocatalytic α-aminations of carbonyl compounds,[5] we have now quantified the electrophilic reactivities of the four azodicarboxylates **1a–d** using the linear free energy relationship [Eq. (1)].

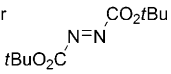
$$\log k(20\,°C) = s(N + E) \tag{1}$$

In numerous investigations we have shown that the reactions of carbocations and Michael acceptors with σ, n, and π nucleophiles follow Equation (1), in which electrophiles are described by E (electrophilicity parameter) and nucleophiles are described by N (nucleophilicity parameter) and s (nucleophile-specific slope parameter).[6]


1a


1b


1c


1d

Bn = CH_2Ph

In this way, we were able to set up comprehensive electrophilicity and nucleophilicity scales, which allow us to predict the rates of polar organic reactions with an accuracy of better than a factor of 10^2 in a reactivity range of 40 orders of magnitude.[7]

The nucleophile-specific parameters N and s of the enamines **2a–e** have recently been derived from the rates of their reactions with benzhydrylium ions (Table 1).[7a,8] These en-

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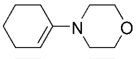
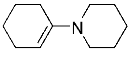
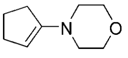
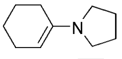
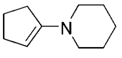
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201001598. It contains preparative procedures, product characterization, and details of the individual runs of the kinetic experiments.

Table 1. Enamines **2** used as reference nucleophiles in this study and their reactivity parameters *N* and *s* in dichloromethane.

Enamine		N (s)[a]
	**2a**	11.40 (0.83)
	**2b**	13.36 (0.81)
	**2c**	13.41 (0.82)
	**2d**	14.91 (0.86)
	**2e**	15.06 (0.82)

[a] References [7a] and [8].

amines have now been employed as reference nucleophiles for determining the electrophilicities *E* of **1a–d**.

Results and Discussion

Reactions of azodicarboxylates 1 with enamines 2: Treatment of the azodicarboxylates **1b–d** with the enamines **2c** and **2d** yielded the α-hydrazino-substituted ketones **3**[2a,9] after aqueous workup (Scheme 1). Initial attack of the nucleophilic carbon of the enamine **2** at the azo functionality of **1** leads to zwitterionic intermediates, which are hydrolyzed with formation of the final products **3**.

The rates of the reactions of the azodicarboxylates **1** with the enamines **2** were determined photometrically in CH_3CN at 20 °C. For the kinetic studies, the nucleophiles **2** were used in high excess over the electrophiles **1** to achieve first-order conditions. The reaction progress was monitored by following the decrease of the absorbances of the electrophiles **1** at 405 nm. From the observed monoexponential decays the first-order rate constants, k_{obs}, were obtained (Figure 1). Details are given in the Supporting Information.

As shown for the reaction of diethyl azodicarboxylate (**1b**) with morpholinocyclopentene (**2c**) in Figure 1, plots of k_{obs} versus the enamine concentrations were linear as required by Equation (2):

$$k_{obs} = k_2[\mathbf{2}] \qquad (2)$$

The slopes of these plots yielded the second-order rate constants k_2, which are listed in Table 2.

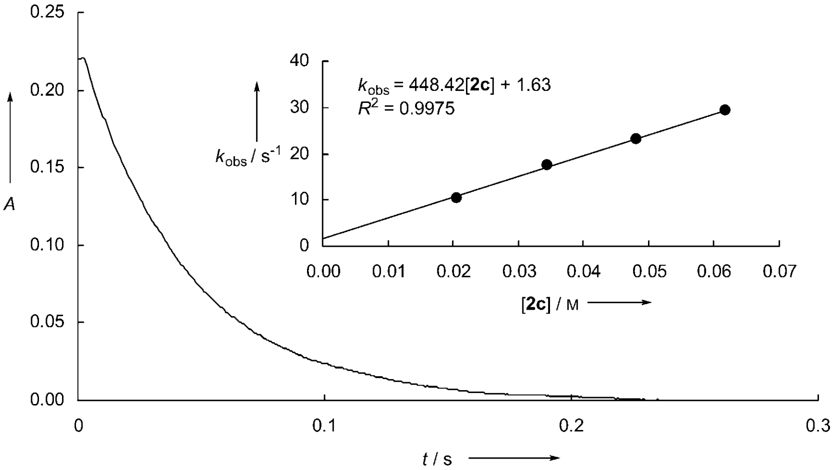
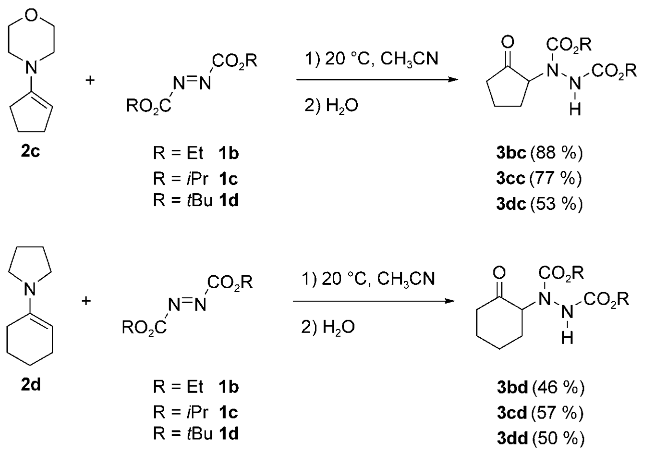


Figure 1. Exponential decay of the absorbance at 405 nm during the reaction of **1b** with **2c** ([**1b**] = 6.52×10^{-3} M; [**2c**] = 4.81×10^{-2} M; $k_{obs} = 2.32\times10^{1}\,s^{-1}$). Inset: Determination of the second-order rate constant k_2 ($k_2 = 4.48\times10^{2}\,M^{-1}s^{-1}$) as the slope of the correlation between the first-order rate constants k_{obs} and the concentration of the enamine **2c**.



Scheme 1. Reactions of **1b–d** with the enamines **2c** and **2d**.

Table 2. Second-order rate constants k_2 for the reactions of the azodicarboxylates **1a–d** with the enamines **2a–e** in acetonitrile at 20 °C.

Azodicarboxylate (E)	Enamine	k_2^{exptl} [$M^{-1}s^{-1}$]	k_2^{calcd} [$M^{-1}s^{-1}$][a]	k_2^{exptl}/k_2^{calcd}
1a (−8.89)	**2a**	1.72×10^{2}	1.21×10^{2}	1.4
	2b	3.02×10^{3}	4.17×10^{3}	0.72
	2c	4.88×10^{3}	5.08×10^{3}	0.96
1b (−10.15)	**2a**	1.84×10^{1}	1.09×10^{1}	1.7
	2b	3.04×10^{2}	3.97×10^{2}	0.76
	2c	4.48×10^{2}	4.70×10^{2}	0.95
	2e	8.52×10^{3}	1.06×10^{4}	0.80
1c (−10.71)	**2a**	4.98	3.73	1.3
	2b	1.13×10^{2}	1.40×10^{2}	0.81
	2c	1.47×10^{2}	1.63×10^{2}	0.90
	2d	5.95×10^{3}	4.08×10^{3}	1.5
	2e	2.54×10^{3}	3.68×10^{3}	0.69
1d (−12.23)	**2a**	2.86×10^{-1}	2.06×10^{-1}	1.4
	2b	5.07	8.28	0.61
	2c	1.02×10^{1}	9.34	1.1
	2d	2.99×10^{2}	2.03×10^{2}	1.5
	2e	1.50×10^{2}	2.11×10^{2}	0.71

[a] Calculated by using Equation (1), *N* and *s* parameters from Table 1, and *E* from this table.

Application of Equation (1) implies slopes of 1.0 for the plots of $(\log k_2)/s$ versus N. Figure 2 shows that this condition is roughly fulfilled for the reactions of **1** with the enamines **2**, in which a new C–N bond is formed. Therefore, electrophilicity parameters, E, of **1** were determined by a least-squares fit, that is, by minimization of $\Delta^2 = \Sigma(\log k_2 - s(N+E))^2$. The last column of Table 2 shows that calculated and experimental rate constants agree within a factor of 2, which is within the confidence limit of Equation (1). It is remarkable that the N and s parameters of **2a–e**, which have been derived from their reactivities toward benzhydrylium ions, also hold for their reactions with the nitrogen electrophiles **1**. In line with this interpretation, we have previously reported that the N and s parameters of carbon nucleophiles can also be used to calculate rates of reactions with diazonium ions.[10]

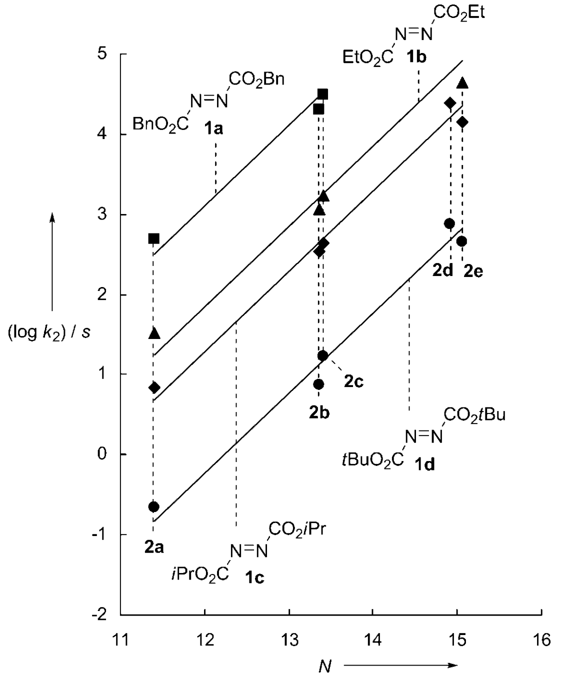


Figure 2. Correlation of $(\log k_2)/s$ against the corresponding nucleophilicity parameters N of the enamines **2a–e** for the reactions of azodicarboxylates **1a–d** with **2** [the slopes are fixed to 1.0 as required by Eq. (1)].

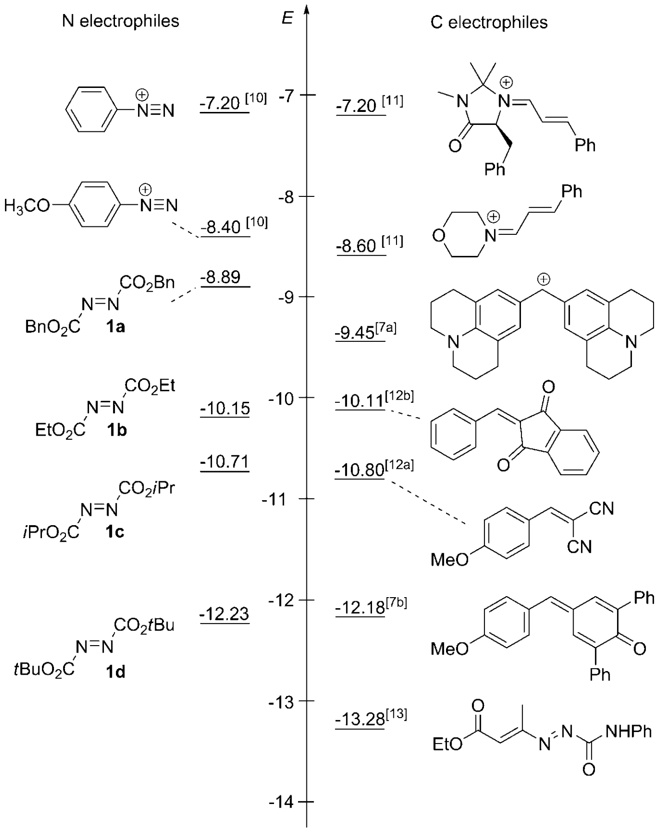


Figure 3. Comparison of the electrophilicity parameters of azodicarboxylates **1** with other electrophiles.

The electrophilicities of the azodicarboxylates **1a–d** cover three orders of magnitude. They are only slightly less reactive than arenediazonium ions,[10] comparable to α,β-unsaturated iminium ions,[11] amino-substituted benzhydrylium ions,[7a] and ordinary Michael acceptors (Figure 3).[7b,12] The slightly less electrophilic, structurally related 1,2-diaza-1,3-dienes react with nucleophiles at the alkenyl and not at the azo group.[13]

The origin of the remarkably large effect of the different ester groups on the electrophilicities of the azodicarboxylates in the order of Bn > Et > *i*Pr > *t*Bu, as shown in Figures 2 and 3, is not known. With electrophilicity parameters between −9 and −12, azodicarboxylates are not attacked by typical enols, but react fast with enamines, comparable to other Michael acceptors, which proved to be suitable for enamine-activated reactions of carbonyl compounds.

To compare these reactivities with rate constants determined in dichloromethane, we have also studied the influence of solvent on some of the reactions of **1** with **2**. Table 3 shows that the second-order rate constants for the reactions of **1** with **2** in acetonitrile (dielectric constant $\varepsilon = 35.94$)[14] and dichloromethane ($\varepsilon = 8.93$)[14] differ by less than a factor of 3. It is, therefore, not necessary to consider the effect of

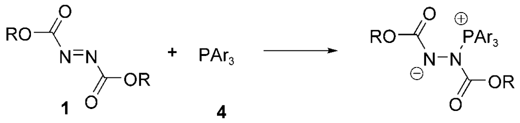
Table 3. Comparison of second-order rate constants k_2 for the reactions of the azodicarboxylates **1a–d** with the enamines **2a–e** in acetonitrile and dichloromethane at 20 °C.

1	2	k_2^{MeCN} [$\mathrm{M^{-1}s^{-1}}$]	$k_2^{\mathrm{CH_2Cl_2}}$ [$\mathrm{M^{-1}s^{-1}}$]	$k_2^{\mathrm{MeCN}}/k_2^{\mathrm{CH_2Cl_2}}$
1a	**2c**	4.88×10^3	1.81×10^3	2.7
1b	**2a**	1.84×10^1	1.08×10^1	1.7
	2c	4.48×10^2	2.38×10^2	1.9
1c	**2a**	4.98	2.21	2.3
	2c	1.47×10^2	8.36×10^1	1.8
1d	**2a**	2.86×10^{-1}	1.24×10^{-1}	2.3
	2b	5.07	2.48	2.0
	2c	1.02×10^1	3.98	2.6
	2e	1.50×10^2	1.03×10^2	1.5

solvent on E when applying Equation (1) on reactions of **1** with nucleophiles in dichloromethane.

Reactions with triarylphosphines: To check whether the electrophilicity parameters E of **1a–d** (Figure 3) derived from the rates of their reactions with enamines **2** (carbon nucleophiles) are also suitable for the prediction of the rates of the reactions of azodicarboxylates with heteronucleophiles, we studied the kinetics of the reactions of **1a–d** with the triarylphosphines **4** and the amines **5**, the N and s parameters of which have previously been derived from the rates of their reactions with benzhydrylium ions.[15,16]

Nucleophilic additions of the triarylphosphines **4** to dialkyl azodicarboxylates **1**, which correspond to the first step of the Mitsunobu reaction, yield the so-called Huisgen zwitterions, as depicted in Scheme 2.[17]



Scheme 2. Reactions of **1** with phosphines **4**.

The kinetics of the reactions of **1** with triarylphosphines in CH_2Cl_2 were determined photometrically, as described above for the reactions of **1** with enamines **2**. Linear plots of k_{obs} versus $[PAr_3]$ confirmed second-order rate laws for these reactions, and the resulting second-order rate constants for the attack of PAr_3 at the N=N unit are summarized in Table 4.

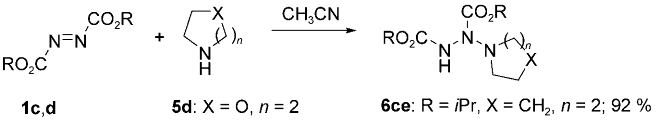
As shown in the last column of Table 4, the experimental rate constants for the reactions of **1** with the phosphines **4** generally agree within a factor of 10 with those calculated by Equation (1). This agreement is surprising: Since E parameters are generally derived from reactions with a series of C-centered nucleophiles (E of **1** from reactions with enamines, Table 2, Figure 2) and N and s parameters are generally derived from the rates of reactions with a series of C-centered electrophiles (N and s of **4** from reactions with benzhydrylium ions), Equation (1) can only be expected to hold for the formation of C–X bonds, that is, for reactions in which at least one of the reaction centers in the electrophile or nucleophile is carbon.[15] The unexpected observation that Equation (1) also holds for the formation of an N–P bond reminds one of the observation that Equation (1), as well as the Ritchie Equation, were also found to work for the combinations of diazonium ions with several heteronucleophiles.[10,18] The comparable magnitudes of the P–N (290 kJ mol^{-1}) and C–N (305 kJ mol^{-1}) bond energies may account for this finding.[19]

Table 4. Experimental and calculated second-order rate constants for the reactions of the azodicarboxylates **1** with the phosphines **4** in dichloromethane at 20 °C.

1	Phosphine **4** (N/s)[a]	k_2^{exptl} [$M^{-1}s^{-1}$]	k_2^{calcd} [$M^{-1}s^{-1}$][b]	k_2^{calcd}/k_2^{exptl}
1a	**4a** ($(4\text{-}ClC_6H_4)_3P$) (12.58/0.65)	6.41×10^{1}	2.50×10^{2}	3.9
1a	**4b** (Ph_3P) (14.33/0.65)	4.83×10^{2}	3.44×10^{3}	7.1
1a	**4c** ($(4\text{-}MeC_6H_4)_3P$) (15.44/0.64)	2.42×10^{3}	1.56×10^{4}	6.4
1a	**4d** ($(4\text{-}OMeC_6H_4)_3P$) (16.17/0.62)	1.07×10^{4}	3.26×10^{4}	3.0
1b	**4b** (14.33/0.65)	1.45×10^{2}	5.21×10^{2}	3.6
1b	**4c** (15.44/0.64)	6.13×10^{2}	2.43×10^{3}	3.8
1b	**4d** (16.17/0.62)	2.36×10^{3}	5.40×10^{3}	2.3
1c	**4a** (12.58/0.65)	4.28	1.64×10^{1}	3.8
1c	**4b** (14.33/0.65)	4.51×10^{1}	2.25×10^{2}	5.0
1c	**4c** (15.44/0.64)	2.16×10^{2}	1.06×10^{3}	4.9
1c	**4d** (16.17/0.62)	7.25×10^{2}	2.43×10^{3}	3.3
1d	**4a** (12.58/0.65)	4.83×10^{-1}	1.69	3.5
1d	**4b** (14.33/0.65)	2.14	2.32×10^{1}	11
1d	**4c** (15.44/0.64)	1.11×10^{1}	1.13×10^{2}	10

[a] N/s-parameters from reference [15]. [b] Calculated by using Equation (1), N and s parameters from reference [15], and the E parameters from Table 2.

Reactions with amines: The reactions of azodicarboxylates **1** with amines **5** have been reported to yield triazanes **6** in petroleum ether.[20] Scheme 3 shows that triazanes **6** are also formed in acetonitrile, that is, the solvent in which the kinetic investigations were performed. Though N–N single bonds are generally rather weak, the triazanes **6** are stabilized by two electron-withdrawing ester groups and can be isolated without problem.[20a]



1c,d

5d: X = O, n = 2
5e: X = CH_2, n = 2
5f: X = CH_2, n = 1

6ce: R = *i*Pr, X = CH_2, n = 2; 92 %
6dd: R = *t*Bu, X = O, n = 2; 93 %
6de: R = *t*Bu, X = CH_2, n = 2; 81 %
6df: R = *t*Bu, X = CH_2, n = 1; 76 %

Scheme 3. Reactions of **1c** and **1d** with amines **5d–f**.

Nevertheless, the thermodynamic driving force for these additions seems to be rather low. As shown below, the relative reactivities of the azodicarboxylates **1** toward amines are the same as toward enamines **2** and phosphines **4**. For that reason, one can expect that **1a** should even react faster with amines than the azodicarboxylates **1b–d**. The fact, that no conversion was observed when **1a** was combined with morpholine **5d** and pyrrolidine **5f** must, therefore, be due to unfavorable thermodynamics (fast reverse reactions).

The reactions of **1** with the secondary amines **5a–f** were studied in CH_3CN by following the decay of the electrophiles' absorbances. When the amines were used in large excess, first-order kinetics were observed with exponential decays of the absorbances of the azodicarboxylates **1**. However, linearity of the k_{obs} versus [**5**] plots was only observed for the reactions of **1c** with **5c** and **5e**. For all other reactions of the azodicarboxylates **1** with the secondary amines **5a–f**, the plots of the k_{obs} values versus the amine concentrations showed concave curvatures (Figure 4), indicating that

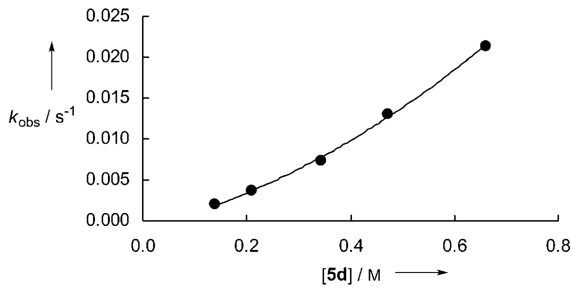
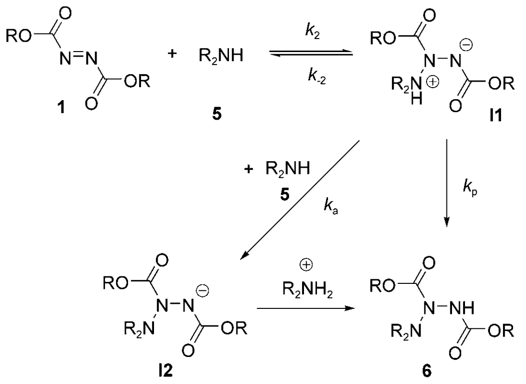


Figure 4. Plots of k_{obs} versus [**5d**] for the reaction of **5d** with the azodicarboxylate **1b** (CH_3CN, 20 °C).

a second molecule of amine is involved in the rate-determining step, which acts as a base catalyst (Scheme 4).



Scheme 4. Reactions of the azodicarboxylates **1** with the amines **5**.

The assumption that the formation of the intermediate **I1** is a reversible process is in line with the observation that tertiary amines [for example, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) or 1,4-diazabicyclo[2.2.2]octane (DABCO)] do not react with the azodicarboxylates **1**.

According to Scheme 4, the change of the concentration of the betaine intermediate **I1** can be expressed by Equation (3).

$$d[\mathbf{I1}]/dt = k_2[\mathbf{1}][\mathbf{5}] - k_{-2}[\mathbf{I1}] - k_a[\mathbf{I1}][\mathbf{5}] - k_p[\mathbf{I1}] \quad (3)$$

With the assumption of a steady-state concentration for the intermediate **I1** ($d[\mathbf{I1}]/dt = 0$), the rate law can be expressed by Equations (4) and (5).

$$-d[\mathbf{1}]/dt = k_2[\mathbf{1}][\mathbf{5}]\ (k_a[\mathbf{5}] + k_p)/(k_{-2} + k_a[\mathbf{5}] + k_p) \quad (4)$$

$$k_{obs} = k_2[\mathbf{5}]\ (k_a[\mathbf{5}] + k_p)/(k_{-2} + k_a[\mathbf{5}] + k_p) \quad (5)$$

Let us first neglect the direct proton transfer (k_p) from NH^+ to N^- in the zwitterionic intermediate **I1**. Equation (5) is then reduced to Equation (6), which can be transformed into Equation (7).

$$k_{obs} = k_2[\mathbf{5}]^2 k_a/(k_{-2} + k_a[\mathbf{5}]) \quad (6)$$

$$[\mathbf{5}]/k_{obs} = 1/k_2 + k_{-2}/(k_2[\mathbf{5}]k_a) \quad (7)$$

$$k_{obs} = k_2[\mathbf{5}] \quad (8)$$

If $k_{-2} \ll k_a[\mathbf{5}]$, Equation (6) is transformed into Equation (8), that is, a second-order reaction [Eq. (2)] with rate-determining formation of the N–N bond. As mentioned before, this situation was only observed for the reaction of **1c** with **5c** and **5e**. At high amine concentrations, the second-order rate law [Eq. (8)] also holds for the reactions of **1b** with **5b** and **5c**, and for **1d** with **5b**. As exemplified in Figure 5a for the reaction of **1d** with **5b**, the k_{obs}/[**5b**] value increases with increasing amine concentration [**5b**], because the proton transfer (k_a[**5b**]) is getting faster. At high amine concentrations, where k_{obs}/[**5b**] is constant, the attack of the amine at the azodicarboxylate is rate limiting and k_{obs}/[**5b**] = k_2 [Eq. (8)]; the second-order rate constant equals the intercept on the *y* axis. The whole range of amine concentrations can be evaluated by using Equation (7). The linear plot of [**5**]/k_{obs} against 1/[**5**], as shown in Figure 5b, provides $1/k_2$ as the intercept. The second-order rate constants for the reaction of **1c** with **5d**, determined by the different evaluations, are thus in fair agreement. Equation (7) has analogously been used to determine the second-order rate constants k_2 for the first step of the reactions of **1b** with **5b** and **5c**.

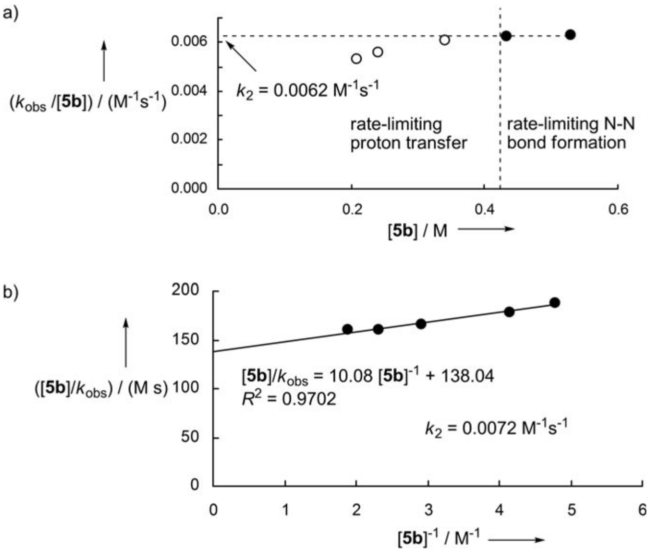


Figure 5. Plots of k_{obs}/[**5b**] versus [**5b**] (a) and [**5b**]/k_{obs} versus 1/[**5b**] (b) for the reaction of **5b** with the azodicarboxylate **1d**.

In all other combinations of **1** and **5**, rate-limiting N–N bond formation was never observed, not even at high amine concentrations. The second-order rate constants for the first step of the reactions were also determined by plotting [**5**]/k_{obs} against 1/[**5**]. Deviations from these linear plots occur only at very low amine concentrations, probably due to the operation of k_p. If the k_{obs} values at low amine concentrations are neglected (open circles in Figure 6), the

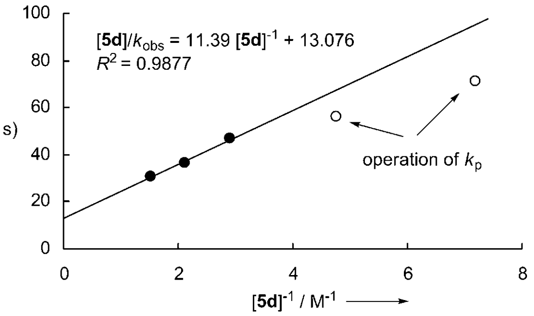


Figure 6. Plot of [**5d**]/k_{obs} versus 1/[**5d**] for the reaction of **5d** with the azodicarboxylate **1b** (filled circles: included for the determination of k_2; $k_2 = 1/(13.076\,\text{M}\,\text{s}) = 7.65 \times 10^{-2}\,\text{M}^{-1}\text{s}^{-1}$; open circles: not included for the evaluation of k_2, because at the low concentration of **5d** the assumption that $k_p \ll k_a$[**5d**] seems to be invalid).

second-order rate constants k_2 can be obtained from the intercepts ($1/k_2$) of the linear correlations [Figure 6 and Eq. (7)].

Analogous changes of the reaction order of amines have previously been reported for the reactions of secondary amines with quinone methides,[16] thiocarbonates,[21] thionobenzoates,[22] and activated esters of indole-3-acetic acid.[23] Table 5 shows the second-order rate constants, k_2, for the reactions of **1** with **5** obtained by these evaluations.

Table 5. Experimental and calculated second-order rate constants for the reactions of azodicarboxylates **1** with amines **5** in acetonitrile at 20 °C.

1	Amine **5** (N/s)[a]	k_2^{exptl} [$\text{M}^{-1}\text{s}^{-1}$]	k_2^{calcd} [$\text{M}^{-1}\text{s}^{-1}$][b]	$k_2^{\text{calcd}}/k_2^{\text{exptl}}$
1b	**5a** (bis(2-methoxy)ethylamine) (13.24/0.93)	1.58×10^{-2}	7.48×10^{2}	4.7×10^{4}
1b	**5b** (di-*n*-propylamine) (14.51/0.80)	3.34×10^{-1}	3.08×10^{3}	9.2×10^{3}
1b	**5c** (diethylamine) (15.10/0.73)	1.00	4.11×10^{3}	4.1×10^{3}
1b	**5d** (morpholine) (15.65/0.74)	7.65×10^{-2}	1.17×10^{4}	1.5×10^{5}
1b	**5e** (piperidine) (17.35/0.68)	1.72	7.87×10^{4}	4.6×10^{4}
1b	**5f** (pyrrolidine) (18.64/0.60)	2.94×10^{1}	1.24×10^{5}	4.2×10^{3}
1c	**5a** (13.24/0.93)	5.52×10^{-3}	2.25×10^{2}	4.1×10^{4}
1c	**5b** (14.51/0.80)	9.52×10^{-2}	1.10×10^{3}	1.2×10^{4}
1c	**5c** (15.10/0.73)	3.27×10^{-1}[c]	1.60×10^{3}	4.9×10^{3}
1c	**5d** (15.65/0.74)	1.86×10^{-2}	4.52×10^{3}	2.4×10^{5}
1c	**5e** (17.35/0.68)	4.59×10^{-1}[c]	3.27×10^{4}	7.1×10^{4}
1c	**5f** (18.64/0.60)	1.55×10^{1}	5.73×10^{4}	3.7×10^{3}
1d	**5a** (13.24/0.93)	3.22×10^{-4}	8.70	2.7×10^{4}
1d	**5b** (14.51/0.80)	7.24×10^{-3}	6.67×10^{1}	9.2×10^{3}
1d	**5c** (15.10/0.73)	2.60×10^{-2}	1.24×10^{2}	4.8×10^{3}
1d	**5d** (15.65/0.74)	1.06×10^{-3}	3.39×10^{2}	3.2×10^{5}
1d	**5e** (17.35/0.68)	3.07×10^{-2}	3.03×10^{3}	9.9×10^{4}
1d	**5f** (18.64/0.60)	8.09×10^{-1}	7.01×10^{3}	8.7×10^{3}

[a] N/s-parameters from reference [16]. [b] Calculated by using Equation (1), N and s parameters from reference [16], and the E parameters from Table 2. [c] Derived from plots of k_{obs} versus [**5**].

The experimental rate constants are 10^3 to 10^6 times smaller than the values calculated by Equation (1). As described above, Equation (1) can only be expected to hold when at least one of the reaction centers in either electrophile or nucleophile is carbon. Table 5 clearly shows that Equation (1) cannot be applied to the N–N bond-forming reactions in the first step shown in Scheme 4. The considerably smaller N–N bond energy (159 kJ mol^{-1}) compared with the C–N bond energy (305 kJ mol^{-1}) may account for the fact, why N parameters of amines that have been derived from the reactivities of amines with C electrophiles give values that are far too low in reactions with N electrophiles.

Figure 7 illustrates that acyclic and cyclic secondary amines **5** are on different correlation lines, considerably below that for enamines **2**, from which the phosphines **4** deviate only marginally. Nevertheless, the internal consistency of the second-order rate constants k_2 for the reactions of the amines **5** with the azodicarboxylates **1b–d** is beautifully demonstrated by Figure 8 in which the reactivities of the amines **5a–f** towards the azodicarboxylates **1c** and **1d** are plotted against the corresponding reactivities toward diethyl azodicarboxylate (**1b**).

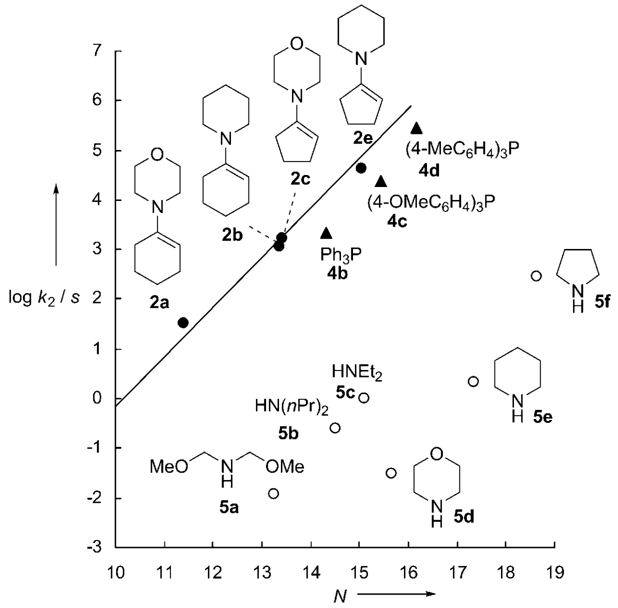


Figure 7. Plots of ($\log k_2$)/s versus the N parameters of the enamines **2a–c** and **2e** (filled circles), the phosphines **4b–d** (filled triangles), and the amines **5a–f** (open circles) for the reactions of the azodicarboxylate **1b** with **2**, **4**, and **5** at 20 °C. The linear graph refers to the plot of ($\log k_2$)/s against the N parameters of the enamines **2a–c** and **2e** and the slope is fixed to unity.

Pericyclic reactions: Rate constants for the [2+2] cycloaddition of **1b** with ethyl vinyl ether,[4d] for the Diels–Alder reactions of **1b** with cyclohexa-1,3-diene[4b] and 2,3-dimethyl-1,3-butadiene,[4a] and for the ene reaction of diethyl azodicarboxylate (**1b**) with 2-methyl-but-2-ene[4c] have previously been reported (Table 6). Though the conditions (solvent, temperature) were not in all cases identical to those for which the reactivity parameters E, N, and s have been derived, they are similar enough that a comparison between

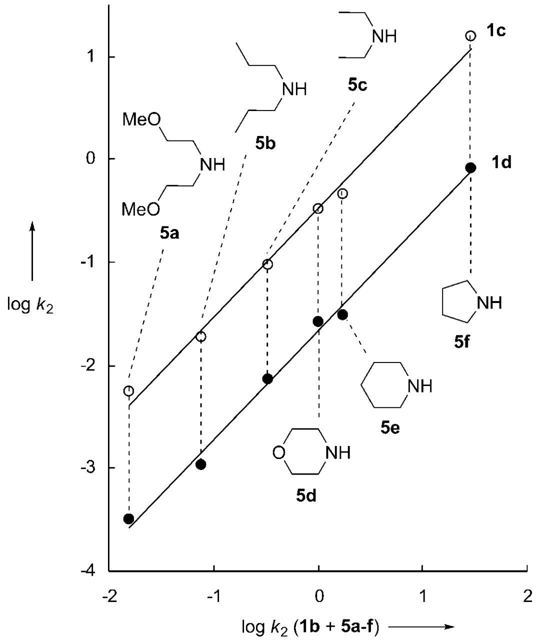
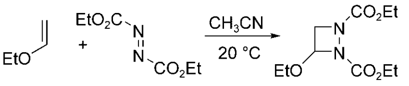
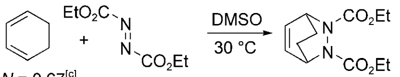
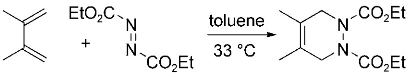
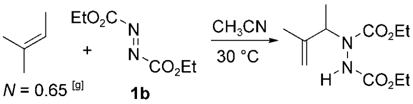


Figure 8. Correlation of the rate constants ($\log k_2$) for the reactions of **1c** and **1d** with the amines **5a–f** against the rate constants ($\log k_2$) for the reaction of **1b** with the amines **5a–f** (in CH_3CN, 20 °C).

Table 6. Comparison of experimental and calculated second-order rate constants k_2 for pericyclic reactions of **1b** with different nucleophiles.

Reaction	k_2^{exptl} [$M^{-1}s^{-1}$][a]	k_2^{calcd} [$M^{-1}s^{-1}$][b]	$k_2^{\text{exptl}}/k_2^{\text{calcd}}$
 N = 3.92[c] **1b** s = 0.90	8.38×10^{-5}[d]	2.3×10^{-6}	36
 N = 0.67[c] **1b** s = 1.10	7.6×10^{-5}[e]	3.4×10^{-11}	2.2×10^{6}
 N = 1.17[c] **1b** s = 1.00	9.46×10^{-5}[f]	9.6×10^{-10}	9.9×10^{4}
 N = 0.65[g] **1b** s = 1.17	5.7×10^{-4}[h]	6.9×10^{-12}	8.3×10^{7}

[a] If more than one rate constant was reported for a certain reaction, we selected that which was determined under conditions most similar to those we used for deriving the reactivity parameters (acetonitrile, 20 °C, 1013 mbar). [b] Calculated by using Equation (1). [c] Reference [7c]. [d] Reference [3d]. [e] Reference [3b]. [f] Reference [3a]. [g] Reference [7a]. [h] Reference [3c].

experimental and calculated rate constants appears to be justified.

Table 6 shows that the reaction of **1b** with ethyl vinyl ether at 30 °C is only 36 times faster than that calculated for 20 °C, that is, the rate of the [2+2] cycloaddition is in agreement with the predictions of Equation (1). As [2+2] cycloadditions proceed stepwise and only one new σ bond is formed in the rate-limiting step, Equation (1) appears to be applicable.

On the other hand, the Diels–Alder reactions as well as the ene reaction (entries 2–4 in Table 6) proceed 10^5 to 10^8 times faster than calculated by Equation (1). In these cases, the concerted formation of two new σ bonds stabilizes the transition state and gives rise to a higher reaction rate. In cases in which pericyclic processes are feasible, Equation (1) gives only a lower limit for the rate constant. If calculated and experimental rate constants refer to the same reaction conditions, the deviation between the two values may even be considered as a measure for the energy of concertedness.[24]

Conclusion

The π systems of azodicarboxylates and enamines combine with the formation of only one new C–N bond, which allows us to derive electrophilicity parameters, E, for the azodicarboxylates **1a–d**. They are slightly less electrophilic than ordinary arenediazonium ions, comparable to α,β-unsaturated iminium ions and benzylidenemalononitriles. The E parameters of the azodicarboxylates determined herein can be used to predict rate constants not only for the reactions of these electrophiles with carbon nucleophiles, but unexpectedly also for the reactions with phosphines, though none of the reaction centers is carbon, a prerequisite for the application of Equation (1). The reported rate constants for Diels–Alder and ene reactions of diethyl azodicarboxylate are 10^5 to 10^8 times higher than those calculated by using Equation (1), indicating concerted pericyclic reactions.

Experimental Section

General: Azodicarboxylates **1a–d**, phosphines **4a–d**, and amines **5a–f** were purchased, and the amines **5** were purified by distillation prior to use. The enamines **2a–e** were synthesized by literature procedures.[25]

Reactions of azodicarboxylates 1 with enamines 2: A solution of the azodicarboxylate **1b–d** in dry acetonitrile was added dropwise to a stirred solution of the enamine **2c** or **2d** (1 equiv) in acetonitrile. The mixture was stirred at 20 °C until the yellow color of **1** had disappeared. The reaction mixture was quenched by water and the separated organic layer was dried over $MgSO_4$. The solvent was removed in vacuo and the crude product was purified by column chromatography.

Reactions of azodicarboxylates 1 with amines 5: The amines **5d**–**f** (2 equiv) was added to a solution of the azodicarboxylate **1c** or **1d** in acetonitrile at 20 °C and the mixture was stirred until the yellow color of the azodicarboxylate had disappeared. The solvent was evaporated in vacuo.

Kinetics: The kinetics of the reactions of the azodicarboxylates **1** with the nucleophiles **2**, **4**, or **5** were followed by UV/Vis spectroscopy by using work stations similar to those described previously.[7a,f,26] For slow reactions ($\tau_{1/2} > 10$ s) the UV/Vis spectra were collected at different times by using a J&M TIDAS diode array spectrophotometer that was connected to a Hellma 661.502-QX quartz Suprasil immersion probe (5 mm light path) by fiber optic cables with standard SMA connectors. All kinetic measurements were carried out in Schlenk glassware under the exclusion of moisture. The temperature of the solutions during the kinetic studies was maintained at 20 °C within ±0.1 °C by using circulating bath cryostats and monitored with thermocouple probes that were inserted into the reaction mixture. Stopped-flow spectrophotometer systems (Applied Photophysics SX.18MV-R or Hi-Tech SF-61DX2) were used for the investigation of fast reactions of azodicarboxylates with nucleophiles ($10\,\text{ms} < \tau_{1/2} < 10\,\text{s}$). The kinetic runs were initiated by mixing equal volumes of solutions of the azodicarboxylates and the nucleophiles. Concentrations and rate constants for the individual kinetic experiments are given in the Supporting Information.

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