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Nucleophilic Reactivities of Sulfur Ylides and Related Carbanions: Comparison with Structurally Related Organophosphorus Compounds

Roland Appel and Herbert Mayr*[a]

Dedicated to Professor Helmut Vorbrüggen on the occasion of his 80th birthday

Phosphorus and sulfur ylides are two important classes of reagents in organic chemistry. While phosphorus ylides and related phosphoryl stabilized carbanions are used in the most common olefination reactions, that is, Wittig, Wittig–Horner, and Horner–Wadsworth–Emmons reactions,[1] sulfur ylides have been introduced as versatile reagents for the syntheses of three-membered carbo- and heterocyclic rings (Corey–Chaykovsky reaction).[2]

In contrast to their phosphorus-stabilized analogues, sulfinyl- and sulfonyl-stabilized carbanions react with aldehydes to form β-hydroxysulfines and -sulfones,[3] respectively, or undergo Knoevenagel condensation reactions.[4] Acylation and subsequent reductive elimination transfers β-hydroxysulfones into olefins (Julia and related olefinations).[5]

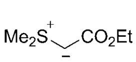
Previous investigations on structure–reactivity relationships of sulfur and phosphorus ylides were focused on their basicities[6] and the different leaving group abilities of R_2S and R_3P.[7] Owing to the poor correlation between basicities and reactivities of carbon-centered nucleophiles,[8] a quantitative comparison of the reactivities of sulfur and phosphorus ylides as well as their related carbanions has so far not been possible.

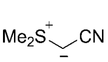
In recent years, we have shown that the rates of the reactions of carbocations and Michael acceptors with n-, π-, and σ-nucleophiles can be described by Equation (1), where $k_{20^\circ C}$ is the second-order rate constant in $M^{-1}\,s^{-1}$, s is a nucleophile-specific slope parameter, N is a nucleophilicity parameter, and E is an electrophilicity parameter.

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

By using this methodology, we have developed the most comprehensive nucleophilicity scale presently available and, therefore, were able to directly compare many different classes of nucleophiles.[8,9] With the rule of thumb that electrophile–nucleophile combinations at room temperature only take place when $(E + N > -5)$, we have been able to establish a rough ordering principle of polar organic reactivity.[9c]

After determining the nucleophilicities of phosphorus ylides and phosphoryl-stabilized carbanions,[8c] we have now studied the kinetics of the reactions of the sulfur ylides **1a** and **1b**, the sulfonyl-stabilized carbanion **1c**, and the sulfinyl-stabilized carbanion **1d** with the benzhydrylium ions **2a**–**e** and the structurally related quinone methides **2f**–**k** (Table 1) in DMSO, to derive the nucleophilicity parameters N and s for the nucleophiles **1** and to compare them with those of analogous phosphorus compounds.


1a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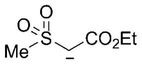
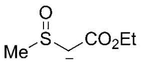

1c


1d

As shown in Scheme 1, the reference electrophiles **2a** and **2h** were employed to elucidate the course of these reactions. Because of the low stability of the addition products **3a**,**b** obtained from **2a** and the sulfur ylides **1a**,**b**, the adducts **3a**,**b** were not isolated but immediately treated with thiophenolate to afford the non-charged products **4a**,**b**, which were fully characterized. For identifying the products formed from the nucleophiles **1c**,**d** and the quinone methide **2h**, solutions of the carbanions **1c**,**d** were generated by deprotonation of the corresponding CH acids (**1c**,**d**)-H with KO*t*Bu in DMSO, subsequent addition of **2h**, and aqueous acidic workup. The addition products **5a** and **5b** were obtained as mixtures of two and four diastereomers, respectively (^1H and ^{13}C NMR spectroscopy).

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[a] R. Appel, Prof. Dr. H. Mayr
Department Chemie, Ludwig-Maximilians-Universität München
Butenandtstrasse 5-13 (Haus F), 81377 München (Germany)
Fax: (+49) 89-2180-77717
E-mail: herbert.mayr@cup.uni-muenchen.de

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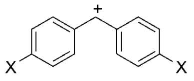
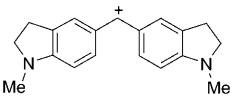
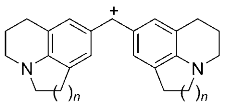
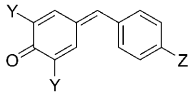
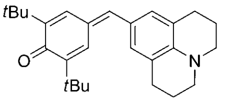
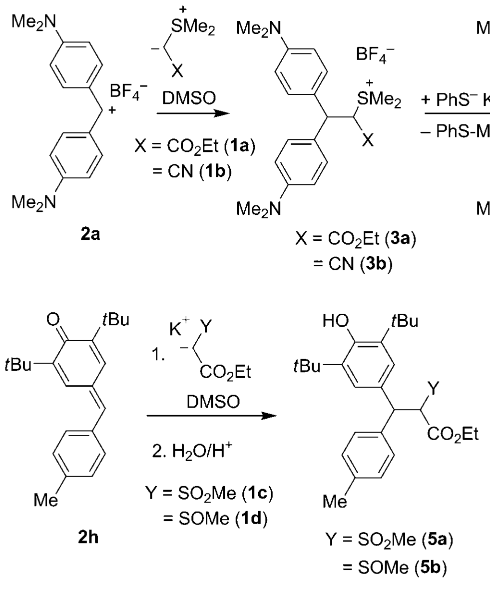
Table 1. Benzhydrylium ions **2a**–**e** and quinone methides **2f**–**k** employed as reference electrophiles in this work.

Electrophile			E[a]
2a	X=NMe$_2$		−7.02
2b	X=N(CH$_2$)$_4$		−7.69
2c			−8.76
2d (n=2) **2e** (n=1)			−9.45 −10.04
Electrophile			E[a]
2f	Y=Ph	Z=OMe	−12.18
2g	Y=Ph	Z=NMe$_2$	−13.39
2h	Y=tBu	Z=Me	−15.83
2i	Y=tBu	Z=OMe	−16.11
2j	Y=tBu	Z=NMe$_2$	−17.29
2k			−17.90

[a] Electrophilicity parameters E for **2a**–**e** from reference [9b], for **2f**–**k** from reference [9c].



Scheme 1. Characterization of the reaction products.

All kinetic investigations were monitored photometrically by following the disappearance of the colored electrophiles **2** in the presence of more than 10 equivalents of the nucleophiles **1** (first-order conditions). Solutions of the ylides **1a**,**b** in DMSO were freshly prepared before the kinetic experiments; the carbanions **1c**,**d** were generated by deprotonation of the corresponding CH acids (**1c**,**d**)-H with 1.00–1.05 equivalents of KOtBu in DMSO solution. To prove that (**1c**,**d**)-H were quantitatively deprotonated under these conditions, several kinetic experiments have been repeated by using only 0.5–0.6 equivalents of KOtBu for the deprotonation of (**1c**,**d**)-H. In these experiments, where the concentrations of the carbanions **1c**,**d** correspond to the amount of KOtBu used, second-order rate constants were obtained, which agreed within 1–2 % with those obtained with a slight excess of KOtBu (see Table 2). As the presence of [18]crown-6 did not affect the reactivities of (**1c**,**d**)-K, one can conclude that the reactivities of the free carbanions **1c**,**d** were observed.

From the exponential decays of the UV/Vis absorbances of the electrophiles, the first-order rate constants k_{obs} were obtained. Plots of k_{obs} (s^{-1}) against the concentrations of the nucleophiles **1** were linear with negligible intercepts as required by Equation (2) (Figure 1).

$$-d[\mathbf{2}]/dt = k_2[\mathbf{1}]\ [\mathbf{2}]\ \text{for}[\mathbf{1}] \gg [\mathbf{2}]\ \Rightarrow\ k_{\mathrm{obs}} = k_2\,[\mathbf{1}] \tag{2}$$

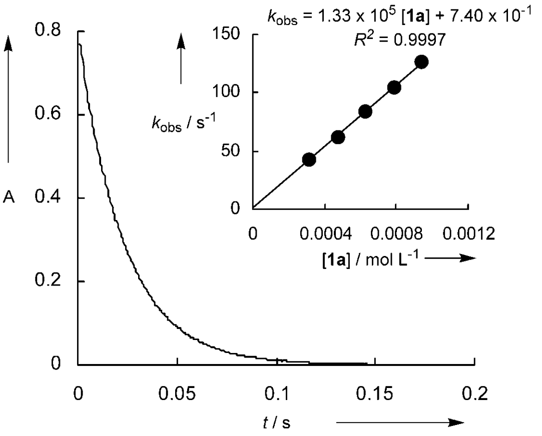
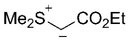
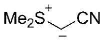
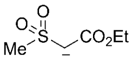
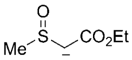


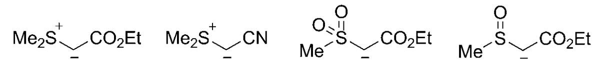
Figure 1. Exponential decay of the absorbance at 624 nm during the reaction of **1a** (3.14×10^{-4} M) with **2b** (2.23×10^{-5} M) at 20 °C in DMSO. Insert: Determination of the second-order rate constant $k_2 = 1.33\times10^{5}$ M^{-1}s^{-1} from the dependence of the first-order rate constant k_{obs} on the concentration of **1a**.

According to Table 2, the quinone methide **2f** is the only electrophile for which rate constants with all four nucleophiles **1a**–**d** have been determined. The corresponding rate constants can, therefore, be employed for a direct structure–reactivity analysis. As shown in Scheme 2, the cyano-substituted sulfur ylide **1b** is marginally more reactive than the ethoxycarbonyl-substituted analogue **1a**. However, the methylsulfonyl-stabilized carbanion **1c** is 45 times and the methylsulfinyl-stabilized carbanion **1d** 990 times more reactive than the ylide **1a**. Comparison of the two carbanions **1c**,**d** moreover shows that the methylsulfinyl-stabilized spe-

Table 2. Second-order rate constants for the reactions of the sulfur-stabilized nucleophiles **1** with the reference electrophiles **2** in DMSO at 20°C.

Nucleophile	N/s[a]	Electrophile	k_2 [$\mathrm{M^{-1}s^{-1}}$]
 **1a**	15.85/0.61	**2a**	2.70×10^{5}
		2b	1.33×10^{5}
		2c	1.34×10^{4}
		2d	7.30×10^{3}
		2e	2.56×10^{3}
		2f	2.32×10^{2}
 **1b**	16.23/0.60	**2a**	3.47×10^{5}
		2b	2.08×10^{5}
		2c	1.95×10^{4}
		2d	9.06×10^{3}
		2e	3.07×10^{3}
		2f	4.00×10^{2}
 **1c**	18.00/0.66	**2d**	3.38×10^{5}
		2e	1.61×10^{5}
		2f	1.04×10^{4}
		2f	1.02×10^{4}[b]
		2g	1.17×10^{3}
		2h	2.72×10^{1}
		2i	1.65×10^{1}
		2j	2.54
 **1d**	20.61/0.64	**2f**	2.29×10^{5}
		2g	3.42×10^{4}
		2g	3.44×10^{4}[b]
		2h	1.34×10^{3}
		2i	8.12×10^{2}
		2j	1.30×10^{2}[b]
		2k	4.43×10^{1}

[a] Nucleophilicity parameters N and s derived by using Equation (1); determination see below. [b] Deprotonation of the conjugate CH acids (**1c**,**d**)-H with 0.5–0.6 equivalents of KO*t*Bu.



	1a	**1b**	**1c**	**1d**
k_{rel}	1.0	1.7	45	990

Scheme 2. Relative reactivities of the nucleophiles **1a**–**d** toward the quinone methide **2f** (DMSO, 20°C).

cies **1d** is 22 times more reactive than the analogously substituted methylsulfonyl compound **1c**.

To include compounds **1a**–**d** in our comprehensive nucleophilicity scale, we determined their nucleophilicity parameters N and s. For that purpose, log k_2 for the reactions of the nucleophiles **1** with the electrophiles **2** (Table 2) were plotted against their electrophilicity parameters E as shown in Figure 2. The linearity of the correlations shows the applicability of Equation (1), which allows one to derive the nucleophile-specific parameters N and s for the nucleophiles **1a**–**d**, which are listed in Table 2 and Figure 3.

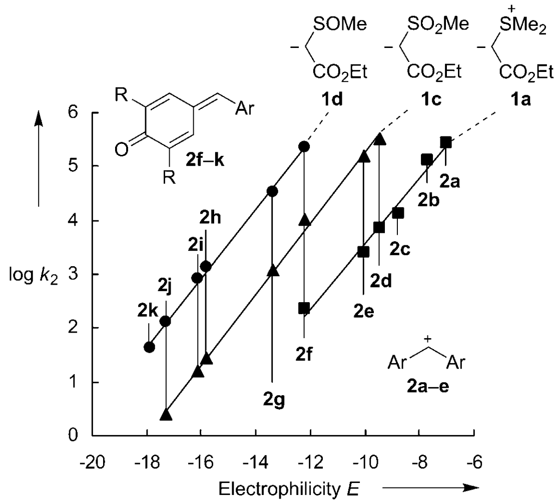


Figure 2. Plots of log k_2 for the reactions of the sulfur ylide **1a** and the sulfur-stabilized carbanions **1c**,**d** with the reference electrophiles **2a**–**k** at 20°C in DMSO versus their electrophilicity parameters E. For the sake of clarity, the correlation line for **1b** is not shown (see the Supporting Information).

Among the many comparisons, which are now possible on the basis of N, we will restrict the following discussion on the comparison with the recently investigated phosphoryl-stabilized carbanions and phosphorus ylides (Figure 3).[8c]

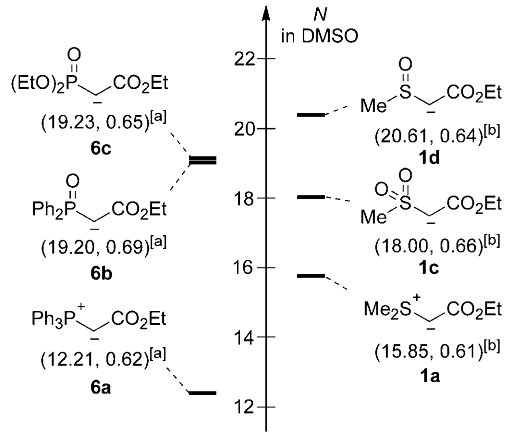
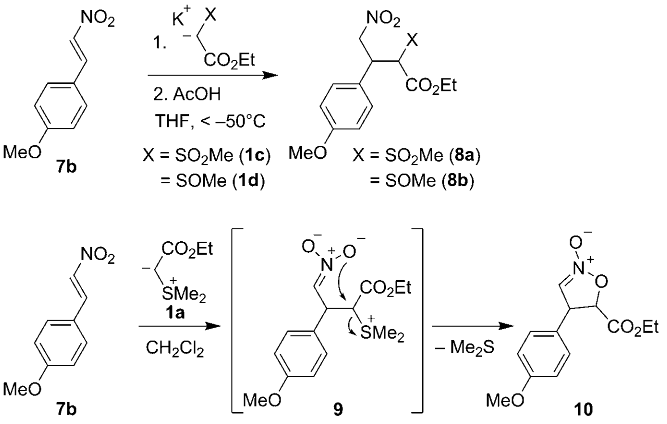


Figure 3. Comparison of the nucleophilicity parameters (N, s) in DMSO of the sulfur-stabilized nucleophiles **1a**,**c**,**d** with those of phosphorus ylide **6a** and phosphoryl-stabilized carbanions **6b**,**c**. [a] Values (N, s) taken from reference [8c]. [b] Values (N, s) taken from Table 2.

Figure 3 reveals a difference of nucleophilic reactivity of $\Delta N \approx 3.6$ between the triphenylphosphonium ylide **6a** and the structurally analogous dimethylsulfonium ylide **1a**. For an s value of 0.62, this difference implies that the phosphorus ylide **6a** is 170 times less reactive than the sulfur ylide **1a**. On the other hand, the phosphoryl-stabilized carbanions **6b**,**c** show nucleophilic reactivities, which lie in between those of the sulfinyl- and sulfonyl-stabilized carbanions **1c**,**d**. From the nucleophilicities of diethyl malonate anions (N=20.22), ethyl cyanoacetate anions (N=19.62), and ethyl acetoacetate anions (N=18.82),[9c] one can derive that the ethoxycarbonyl-, cyano-, and acetyl groups have stabilizing abilities, which are also in between those of a methylsulfinyl and a methylsulfonyl group.

To examine the applicability of the *N* and *s* parameters of the sulfur-stabilized nucleophiles **1** for reactions with other electrophiles, we have investigated their reactions with *trans*-β-nitrostyrene (**7a**) and *trans*-4-methoxy-β-nitrostyrene (**7b**), whose electrophilicity parameters *E* have recently been determined.[10] Whereas the reactions of the carbanions **1c**,**d** with nitrostyrene **7b** yield the Michael addition products **8a** and **8b**, respectively, the zwitterion **9** initially generated from the sulfur ylide **1a** and **7b**, underwent a subsequent intramolecular nucleophilic displacement of dimethyl sulfide to yield the dihydroisoxazole *N*-oxide **10** (Scheme 3). The latter compound was not isolated but intercepted by a 1,3-dipolar cycloaddition with dimethyl maleate according to previous reports[11] and as specified in the Supporting Information.



Scheme 3. Reactions of the nucleophiles **1a**,**c**,**d** with nitroolefin **7b**.

In line with these mechanisms, the experimental second-order rate constants for the reactions of **1a**,**c**,**d** with the nitrostyrenes **7a**,**b** agree within a factor of 1.1 to 4.3 with those calculated by using Equation (1) (Table 3). This remarkable agreement demonstrates that rates of the reactions of the nucleophiles **1** with electrophiles of known electrophilicity *E* can be efficiently predicted by Equation (1) using the *N*/*s* parameters reported in Table 2.

Table 3. Experimental and calculated second-order rate constants ($M^{-1}s^{-1}$) for the reactions of the nucleophiles **1a**,**c**,**d** with the nitrostyrenes **7** in DMSO at 20°C.

Nucleophile	Electrophile	k_2^{exp}	k_2^{calcd}[a]	k_2^{exp}/k_2^{calcd}
1a	**7b**	5.46	5.03	1.1
1c	**7a**	1.25×10^2	5.48×10^2	0.23
	7b	3.98×10^1	1.51×10^2	0.26
1d	**7a**	1.21×10^4	2.12×10^4	0.57
	7b	3.48×10^3	6.06×10^3	0.57

[a] Calculated by Equation (1) using the electrophilicity parameters $E(\mathbf{7a}) = -13.85$ and $E(\mathbf{7b}) = -14.70$ (from reference [10]) as well as the *N* and *s* values for **1a**,**c**,**d** (from Table 2).

As the formation of oxaphosphetanes from phosphorus ylides and carbonyl compounds generally proceeds via concerted [2+2] cycloaddition reactions,[1a–d,12] the *N* and *s* parameters of phosphorus ylides cannot be employed to determine the *E* parameters of aldehydes.[8c] On the other hand, sulfur ylides have been demonstrated to react with aldehydes by a stepwise mechanism.[13] It should, therefore, be possible to use the kinetics of the formation of epoxides via the Corey–Chaykovsky reaction to derive electrophilicity parameters of carbonyl compounds.

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Keywords: carbanions · kinetics · linear free energy relationships · nucleophilicity · ylides

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