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PAPER

Characterization of the nucleophilic reactivities of thiocarboxylate, dithiocarbonate and dithiocarbamate anions†

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The kinetics of the reactions of thiocarboxylate and thiocarbonate anions with benzhydrylium ions have been determined in acetonitrile solution using laser-flash photolytic techniques. The second-order rate constants (k) correlate linearly with the electrophilicity parameters E of the benzhydrylium ions, as required by the correlation $\log k$ (20 °C) = $s_N(N + E)$ (*J. Am. Chem. Soc.*, 2001, **123**, 9500–9512), allowing us to calculate the nucleophile-specific parameters N and s_N for these anions. With these parameters, a direct comparison of the reactivities of thiocarboxylate, dithiocarbonate and dithiocarbamate anions with other nucleophiles becomes possible.

Introduction

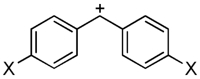
Salts of thiocarboxylic acids, as well as of thiocarbonic acids and their derivatives, are important reagents in organic synthesis.[1] While it is well-known that S-centered nucleophiles are generally more reactive than O-centered nucleophiles of equal Brønsted basicity,[2] systematic investigations of the nucleophilicities of thiocarboxylate, dithiocarbonate and dithiocarbamate anions have not yet been reported.[3]

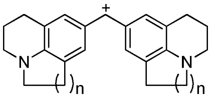
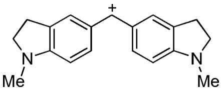
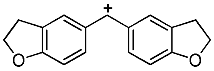
In previous work, we have shown that the rate constants ($\log k$) for the reactions of a large variety of nucleophiles including π-systems (alkenes, arenes, allylsilanes, enol ethers, enamines), n-nucleophiles (amines, alcohols, phosphanes), and hydride donors with benzhydrylium ions correlate linearly with the empirical electrophilicity parameters E of benzhydrylium ions (Table 1), which are defined as solvent-independent.[4,5] The negative intercepts of these correlations on the abscissa ($\log k$ = 0) correspond to the solvent-dependent nucleophilicity parameters N and the slopes are the nucleophile-specific sensitivity parameters s_N.

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

It has been demonstrated that the calculated rate constants (eqn (1)) for the reactions of nucleophiles with the reference benzhydrylium ions agree with the experimental values, with a standard deviation of a factor of 1.26.[4b] The reliability of the predictions decreases significantly when other classes of electrophiles are employed. However, also for the reactions of nucleophiles with other types of carbocations, cationic metal-π-complexes, or Michael acceptors the agreement between the calculated and experimental rate constants is generally better than a factor of 10–100, which is quite remarkable for a three-parameter equation covering a reactivity range of 40 orders of magnitude.[4]

Table 1 Abbreviations and electrophilicity parameters E of the benzhydryliumions (Ar_2CH^+)



X	Abbreviations	E^a	$PR_3{}^b$
	n = 1 $(lil)_2CH^+$ n = 2 $(jul)_2CH^+$	−10.04 −9.45	$P(nBu)_3$ $P(nBu)_3$
	$(ind)_2CH^+$	−8.76	$P(nBu)_3$
$N(CH_2)_4$	$(pyr)_2CH^+$	−7.69	$P(ani)_3$
$N(CH_3)_2$	$(dma)_2CH^+$	−7.02	$P(ani)_3$
$N(Ph)CH_3$	$(mpa)_2CH^+$	−5.89	$P(tol)_3$
$N(CH_2CH_2)_2O$	$(mor)_2CH^+$	−5.53	$P(tol)_3$
NPh_2	$(dpa)_2CH^+$	−4.72	PPh_3
$N(CH_3)CH_2CF_3$	$(mfa)_2CH^+$	−3.85	PPh_3
$N(Ph)CH_2CF_3$	$(pfa)_2CH^+$	−3.14	PPh_3
	$(fur)_2CH^+$	−1.36	PPh_3
OMe	$(ani)_2CH^+$	0	PPh_3

[a] Electrophilicity parameters E for benzhydrylium ions from ref. 4 [b] Photoleaving group for the photolytic generation of Ar_2CH^+ from $Ar_2CH–PR_3{}^+BF_4{}^-$; ani = p-anisyl, tol = p-tolyl.

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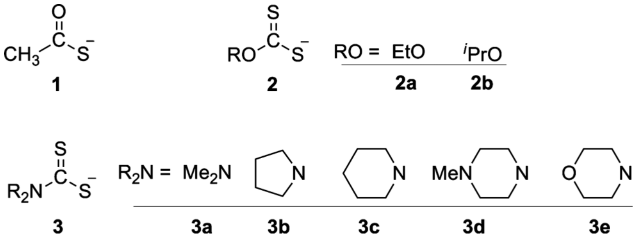
† Electronic supplementary information (ESI) available: Synthetic procedures and product characterization, details of the determination of rate constants. See DOI: 10.1039/c1ob06245j

In this article, we will demonstrate that the benzhydrylium methodology, which has been employed to construct the most comprehensive nucleophilicity scale presently available,[4] can also be used to characterise the nucleophilic reactivities of thiocarboxylate (**1**), *O*-alkyldithiocarbonate (**2**) and *N*,*N*-dialkyldithiocarbamate anions (**3**) (Scheme 1).

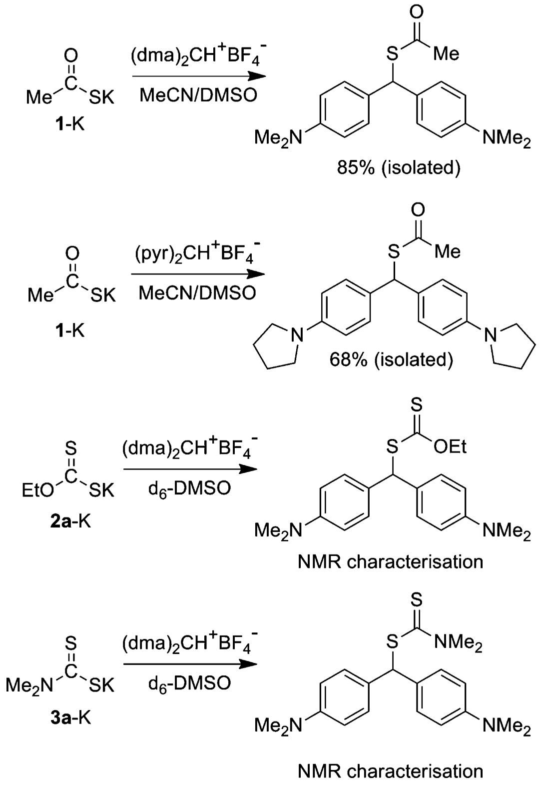


Scheme 1 The sulfur-centered nucleophiles studied in this work.

Results and discussion

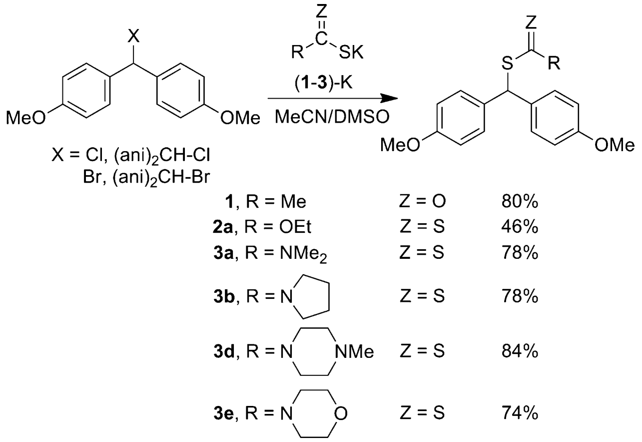
Reaction products

The combination of potassium thioacetate (**1**–K) with one equivalent of $(dma)_2CH^+BF_4^-$ or $(pyr)_2CH^+BF_4^-$ in MeCN/DMSO solution at room temperature and aqueous workup gave the thioacetic acid esters shown in entries 1 and 2 of Scheme 2 in 85% and 68% isolated yield, respectively. The addition of potassium *O*-ethyl dithiocarbonate (**2a**–K) or potassium *N*,*N*-dimethyldithiocarbamate (**3a**–K) to a blue solution of $(dma)_2CH^+BF_4^-$ in DMSO-d$_6$ in an NMR tube led to decolourisation, and the NMR spectra revealed the exclusive formation of the addition products shown in entries 3 and 4 of Scheme 2. Details are given in the ESI.†



Scheme 2 Products from the reactions of the potassium salts **1**, **2a** and **3a** with benzhydrylium tetrafluoroborates.

Analogous benzhydryl esters were obtained in moderate to good yields when the dimethoxy substituted benzhydryl halides $(ani)_2CH$–Cl or $(ani)_2CH$–Br were combined with the potassium salts (**1–3**)–K (Scheme 3). Detailed procedures and characterisations of the resulting products are reported in the ESI.†



Scheme 3 Products and isolated yields from the reactions of the potassium salts (**1–3**)–K with 4,4′-dimethoxybenzhydryl halides.

Kinetics

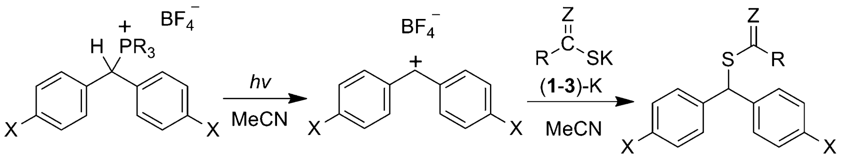
All anions **1–3** reacted so fast with the benzhydryl cations listed in Table 1 ($k > 2 \times 10^6$ M^{-1}s^{-1} at 20 °C) that conventional UV-vis spectroscopy, even in combination with stopped-flow techniques, could not be used to follow the course of these reactions. Therefore, laser-flash photolytic techniques were employed to study the rates of the reactions of **1–3** with Ar_2CH^+.

As tertiary phosphanes have previously been reported to be good photo-leaving groups,[6] freshly prepared solutions of the benzhydrylphosphonium tetrafluoroborates were irradiated with 6.5-ns laser pulses (266 nm, 40–60 mJ) in the presence of a high excess of the nucleophiles **1–3** at 20 °C (Scheme 4). The intermediate benzhydrylium ions Ar_2CH^+ (Table 1) were identified by their UV-vis spectra. Their decay, which was monitored at λ_{max}, followed an exponential function, indicating first-order conditions.

The corresponding first-order rate constants k_{obs} (s^{-1}) were obtained by least-squares fitting of the absorbances (averaged from at least five kinetic runs at each nucleophile concentration) to the single-exponential $A_t = A_0e^{-k_{obs}t} + C$. From the slopes of the linear plots of k_{obs} *vs.* [nucleophile] (Fig. 1), the second-order rate constants k (M^{-1} s^{-1}) were derived and are listed in Table 2. The intercepts of these plots reflect the background reaction (*e.g.*, recombination with PR_3). They are small for highly stabilised benzhydrylium ions and increase with increasing electrophilicities of the benzhydrylium ions.

Structure reactivity relationships

Benzhydrylium ion $(lil)_2CH^+$, the least reactive electrophile of this series, will now be employed to investigate structure reactivity relationships.



Scheme 4 Laser-flash photolysis for determining the rates of the reactions of (**1–3**)–K with benzhydrylium ions.

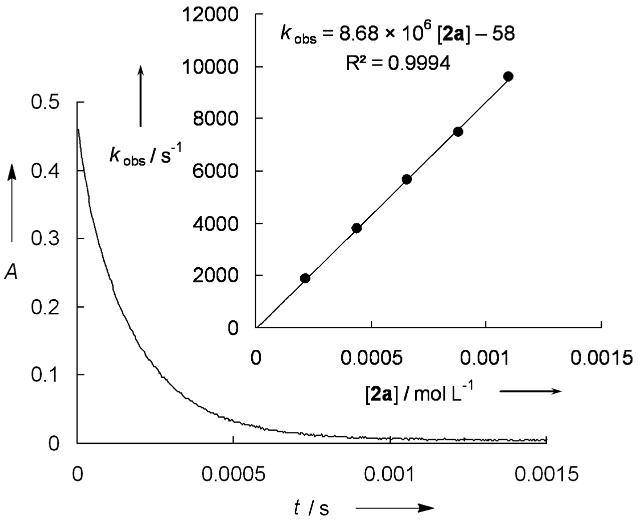
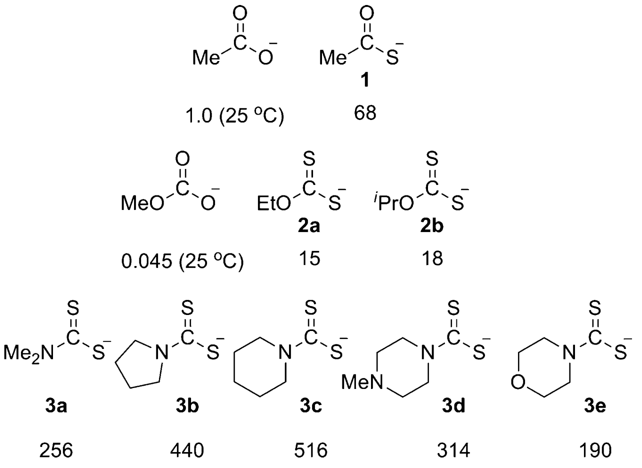


Fig. 1 Exponential decay of the absorbance A at 640 nm during the reaction of **2a** [6.60×10^{-4} mol L^{-1}] with (jul)$_2$CH$^+$ at 20 °C in CH$_3$CN. Insert: Determination of second-order rate constant $k = 8.68 \times 10^6$ M^{-1} s^{-1} from the dependence of k_{obs} on the concentration of **2a**.

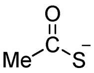
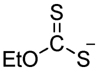
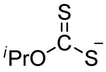
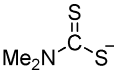
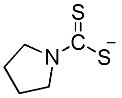
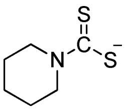
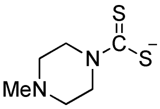
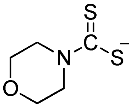
Though the rate constants of the reactions of the acetate and methyl carbonate ion with (lil)$_2$CH$^+$ (1.51×10^5 and 6.72×10^3 M^{-1} s^{-1}) refer to 25 °C,[7] the relative reactivities in Scheme 5 are not corrected for the different temperature, because bimolecular reactions of that rate have only a very small temperature coefficient due to the small value of $\Delta H^{\ddagger}$.



Scheme 5 The relative reactivities of carboxylate and carbonate ions and of their thio analogues **1–3** toward (lil)$_2$CH$^+$ in acetonitrile. Data for **1–3** from Table 2. Acetate and methyl carbonate from ref. 7.

One can see that the change from acetate to thioacetate (**1**) increases the nucleophilicity by a factor of 68. Similarly, a 330-fold enhancement of the nucleophilicity is observed when

Table 2 Second-order rate constants (k) for the reactions of anions **1–4** with the benzhydrylium ions (Ar$_2$CH$^+$) in CH$_3$CN at 20 °C

Nucleophile		N, s_N[a]	Ar$_2$CH$^+$	k/M^{-1} s^{-1}
	**1**	21.20, 0.63	(lil)$_2$CH$^+$	1.03×10^7
			(jul)$_2$CH$^+$	2.36×10^7
			(ind)$_2$CH$^+$	5.74×10^7
			(pyr)$_2$CH$^+$	3.11×10^8
			(dma)$_2$CH$^+$	6.24×10^8[b]
			(mor)$_2$CH$^+$	2.70×10^9[b]
			(dpa)$_2$CH$^+$	6.01×10^9[b]
			(mfa)$_2$CH$^+$	1.28×10^{10}[b]
			(pfa)$_2$CH$^+$	1.01×10^{10}[b]
			(fur)$_2$CH$^+$	2.44×10^{10}[b]
			(ani)$_2$CH$^+$	3.10×10^{10}[b]
	**2a**	19.30, 0.69	(lil)$_2$CH$^+$	2.27×10^6
			(jul)$_2$CH$^+$	8.68×10^6
			(ind)$_2$CH$^+$	1.47×10^7
			(pyr)$_2$CH$^+$	1.27×10^8
			(dma)$_2$CH$^+$	2.89×10^8
			(mor)$_2$CH$^+$	1.94×10^9[b]
			(dpa)$_2$CH$^+$	7.72×10^9[b]
			(mfa)$_2$CH$^+$	7.08×10^9[b]
			(pfa)$_2$CH$^+$	1.22×10^{10}[b]
			(ani)$_2$CH$^+$	2.55×10^{10}[b]
	**2b**	18.27, 0.78	(lil)$_2$CH$^+$	2.77×10^6
			(jul)$_2$CH$^+$	7.67×10^6
			(ind)$_2$CH$^+$	2.54×10^7
			(pyr)$_2$CH$^+$	1.90×10^8
			(dma)$_2$CH$^+$	2.39×10^8[b]
	**3a**	20.93, 0.69	(lil)$_2$CH$^+$	3.87×10^7
			(jul)$_2$CH$^+$	8.00×10^7
			(ind)$_2$CH$^+$	2.96×10^8
			(pyr)$_2$CH$^+$	1.74×10^9[b]
			(dma)$_2$CH$^+$	3.35×10^9[b]
	**3b**	22.40, 0.63	(lil)$_2$CH$^+$	6.64×10^7
			(jul)$_2$CH$^+$	1.57×10^8
			(ind)$_2$CH$^+$	4.29×10^8
			(pyr)$_2$CH$^+$	2.06×10^9[b]
	**3c**	23.84, 0.57	(lil)$_2$CH$^+$	7.79×10^7
			(jul)$_2$CH$^+$	2.01×10^8
			(ind)$_2$CH$^+$	4.26×10^8
			(pyr)$_2$CH$^+$	2.04×10^9[b]
	**3d**	23.61, 0.57	(lil)$_2$CH$^+$	4.74×10^7
			(jul)$_2$CH$^+$	1.07×10^8
			(ind)$_2$CH$^+$	2.52×10^8
			(pyr)$_2$CH$^+$	1.40×10^9[b]
	**3e**	21.72, 0.64	(lil)$_2$CH$^+$	2.87×10^7
			(jul)$_2$CH$^+$	7.08×10^7
			(ind)$_2$CH$^+$	1.89×10^8
			(pyr)$_2$CH$^+$	1.08×10^9[b]
n-Hex–S$^-$	**4**		(lil)$_2$CH$^+$	$\approx 8 \times 10^7$
			(jul)$_2$CH$^+$	$\approx 1 \times 10^8$

[a] Nucleophilicity parameters N/s_N according to eqn (1). [b] Because of the proximity of the diffusion limit, not used for the calculation of N and s_N.

one compares methyl carbonate with ethyl dithiocarbonate (**2a**). While a change of the alkoxy group has little influence on the nucleophilicity (*cf* **2a**/**2b**) the dithiocarbamate anions **3a–e** are approximately one order of magnitude more nucleophilic than the dithiocarbonate ions **2a** and **2b** due to the smaller electronegativity and larger +M effect of nitrogen compared to oxygen.

The lower line of Scheme 5 shows that cyclic dithiocarbamates **3b,c** are approximately two times more nucleophilic than **3a** and the series **3c**/**3d**/**3e** shows the expected slight reduction in the nucleophilicity due to the different electronegativity of the atom in position 4 of the heterocycle ring.

As previous investigations on the nucleophilicities of alkyl thiolates (dianions of cysteine and mercaptoacetic acid) were performed in aqueous solution,[8] we now attempted to measure the rate constants of the reactions of potassium hexane-1-thiolate **4** with benzhydrylium ions in acetonitrile. For unknown reasons, the decay of the benzhydrylium ions was not monoexponential, despite the use of a large excess of **4**-K/18-crown-6. As a consequence, only approximate rate constants could be derived for the reactions with **4**. Table 2 shows that thiocarboxylate anion **1** and thiocarbamate anions **2** are approximately 7 and 30 times less reactive than **4** and that the nucleophilicity of **4** is comparable to that of the dithiocarbamates **3**.

Nucleophilicity parameters

When values of log k for the reactions of **1–3** with the benzhydrylium ions (Table 2) were plotted against the previously published electrophilicity parameters E, linear correlations were observed for log k < 8.5, indicating the applicability of eqn (1) (Fig. 2). The slopes of these correlation lines yield the nucleophile-specific sensitivity parameters s_N and the intercepts on the abscissa give the nucleophilicity parameters N, which are listed in Table 2.

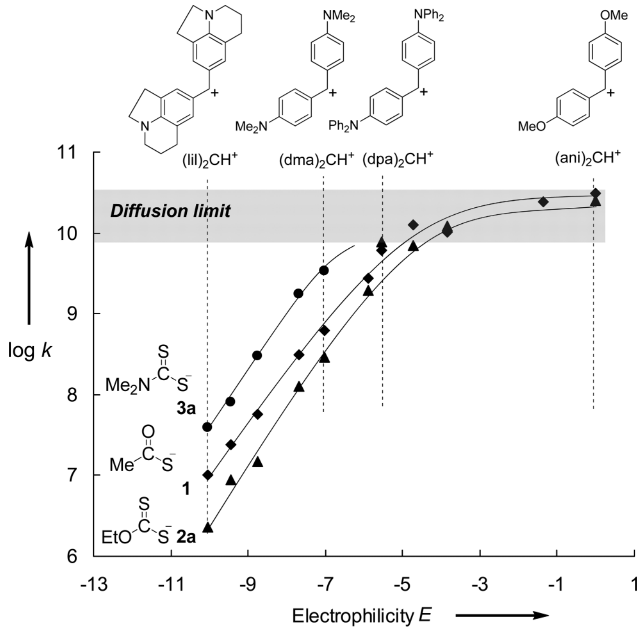


Fig. 2 Plots of log k for the reactions of **1–3** with benzhydrylium ions (Table 2) *versus* their electrophilicity parameters E (Table 1) in acetonitrile at 20 °C.

Conclusions

The reactivities of thiocarboxylate **1**, dithiocarbonate **2** and dithiocarbamate ions **3** toward benzhydrylium ions were found to follow correlation (1), which enables us to include these ions in our comprehensive nucleophilicity scale.[4] Though they are much weaker Brønsted bases than the corresponding oxygen analogues, they are considerably more nucleophilic (Fig. 3).

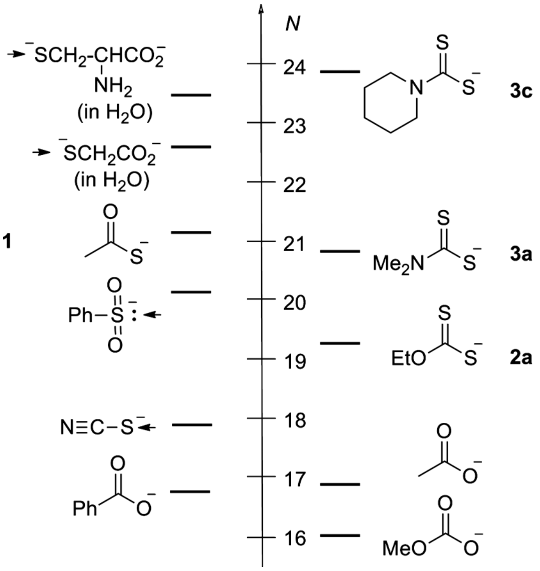


Fig. 3 A comparison of the nucleophilicities of **1–3** with other types of nucleophiles in acetonitrile (N values from ref. 5).

The poor correlation between the nucleophilic reactivities and pK_a values, particularly when nucleophiles with different central atoms are compared, has so far inhibited quantitative predictions of the rates of additions and substitutions involving sulphur nucleophiles. Since, on the other hand, numerous examples have shown that the benzhydrylium-derived N and s_N parameters are applicable to Michael additions and also to S_N2 reactions, it has now become possible to estimate the rates of numerous reactions involving the synthetically important S-nucleophiles **1–3** using eqn (1) and the reactivity parameters given in Table 2.

Acknowledgements

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5 For a comprehensive list of nucleophilicity parameters N and electrophilicity parameters E, see http://www.cup.uni-muenchen.de/oc/mayr/DBintro.html.

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