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VIP Ambident Reactivity

Ambident Reactivities of Methylhydrazines[**]

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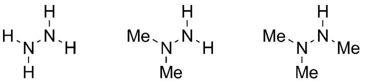
Dedicated to Professor Günter Szeimies on the occasion of his 75th birthday

Hydrazines are an important class of compounds which find considerable technical and commercial applications.[1] Furthermore, numerous biological activities of hydrazine derivatives have been discovered which make them potent drugs, peptidomimetics, and pesticides.[1,2]

Besides their synthetic relevance, hydrazines are also interesting from a mechanistic point of view, as they have two adjacent nucleophilic nitrogen centers. Unsymmetrically substituted hydrazines are, therefore, ambident nucleophiles, and the factors that determine the regioselectivities of their reactions have been studied intensively.[1] Typically, protonations as well as alkylations of alkyl-substituted hydrazines take place at the more-substituted nitrogen atom. Thus, in the case of 1,1-dialkyl hydrazines, quaternary ammonium salts are formed.[1,3] Kinetic investigations focused on the parent hydrazine[4] and little is known about the nucleophilic reactivities of substituted hydrazines[5] though this information is crucial for predicting the regioselectivities in a variety of heterocyclic syntheses.

To investigate the factors which control relative reactivities of the different sites of unsymmetrical hydrazines we have studied the reactions of the hydrazines **1**–**3** (Scheme 1) with the quinone methides **4a**,**b** and the benzhydrylium ions **4c**–**l** (Table 1). The electrophiles **4** have been used as reference compounds for the construction of comprehensive nucleophilicity scales based on Equation (1), which characterizes nucleophiles by two parameters (nucleophilicity N and the sensitivity parameter s_N) and electrophiles by one parameter (electrophilicity E).[6]

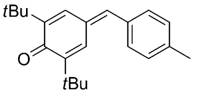
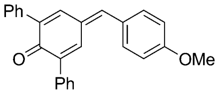
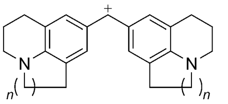
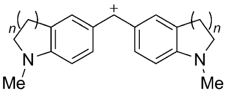
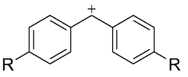
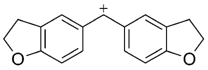
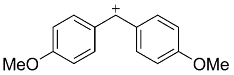


1 **2** **3**

Scheme 1. Structures of hydrazines **1**–**3**.

$$\lg k_2(20\,^\circ\mathrm{C}) = s_\mathrm{N}(N + E) \tag{1}$$

Table 1: Reference electrophiles **4** used in this study.

Reference electrophile			E[a]
		**4a**	−15.83
		**4b**	−12.18
	$n=1$	**4c**	−10.04
	$n=2$	**4d**	−9.45
	$n=1$	**4e**	−8.76
	$n=2$	**4f**	−8.22
	R = *N*-pyrrolidino	**4g**	−7.69
	R = NMe_2	**4h**	−7.02
	R = *N*-morpholino	**4i**	−5.53
	R = $N(Me)CH_2CF_3$	**4j**	−3.85
		**4k**	−1.36
		**4l**	0.00

[a] Electrophilicity parameters E from Ref. [6b,c].

The rate constants of the reactions of **1**–**3** with the reference electrophiles **4b**–**h** were determined spectrophotometrically in acetonitrile at 20 °C using conventional and stopped-flow methods as described elsewhere.[6] For the fast reactions ($k_2 > 10^6\,\mathrm{M}^{-1}\,\mathrm{s}^{-1}$), benzhydrylium ions **4g**–**k** were generated by laser-flash photolysis (7 ns pulse, 266 nm) of substituted benzhydryl phosphonium tetrafluoroborates in the presence of hydrazines.[7] In all cases, the hydrazines **1**–**3** were used in large excess (over 8 equivalents) relative to the electrophiles to ensure first-order conditions.

Mono-exponential decays of the absorbances of the electrophiles were observed for all reactions with the unsubstituted hydrazine (**1**), and the first-order rate constants k_obs were obtained by least-squares fitting of the exponential function $A = A_0 e^{-k_\mathrm{obs} t} + C$ to the absorbance; a typical example is shown in Figure S1 of the Supporting Information. Plots of k_obs versus the hydrazine concentrations were linear and the second-order rate constants k_2 listed in Table 2 were obtained from the slopes of these plots [Eq. (2)]. Theoretically, k_0 corresponds to the sum of all first-order side

$$k_\mathrm{obs} = k_2[\mathbf{1}] + k_0 \tag{2}$$

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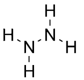
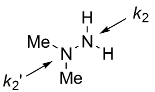
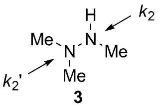
Table 2: Second-order rate constants k_2 and k_2' for the reactions of the reference electrophiles **4** with the primary, secondary, and tertiary amine functions of the hydrazines **1**–**3** in acetonitrile at 20 °C.

Hydrazine	Electrophile[a]	k_2 [$\text{M}^{-1}\,\text{s}^{-1}$]	k_2' [$\text{M}^{-1}\,\text{s}^{-1}$]
 **1**	**4b**	2.23×10^{2}[b]	
	4c	3.41×10^{3}[c]	
	4d	8.74×10^{3}[b]	
	4e	2.04×10^{4}[b]	
	4e	2.14×10^{4}[c]	
	4g	1.58×10^{5}[b]	
	4h	2.95×10^{5}[c]	
	4i	1.22×10^{6}[c]	
	4j	9.90×10^{6}[c]	
 **2**	**4b**	5.69×10^{-1}	
	4c	1.18×10^{1}	
	4e	1.27×10^{2}	
	4g	1.44×10^{3}	3.78×10^{6}
	4h	2.46×10^{3}	8.06×10^{6}
	4i		3.46×10^{7}
	4j		2.04×10^{8}
 **3**	**4e**	6.15×10^{2}	
	4f	1.26×10^{3}	
	4g	3.74×10^{3}	
	4h	1.17×10^{4}	
	4i		3.00×10^{6}
	4j		1.81×10^{7}
	4k		4.58×10^{8}

[a] Counterion of the benzhydryl cations: BF_4^-. [b] Determined using a 1:2 mixture of $N_2H_4{\cdot}2\,HCl$ and 1,8-diaza-bicyclo[5.4.0]undec-7-ene. [c] Determined using $N_2H_4{\cdot}H_2O$.

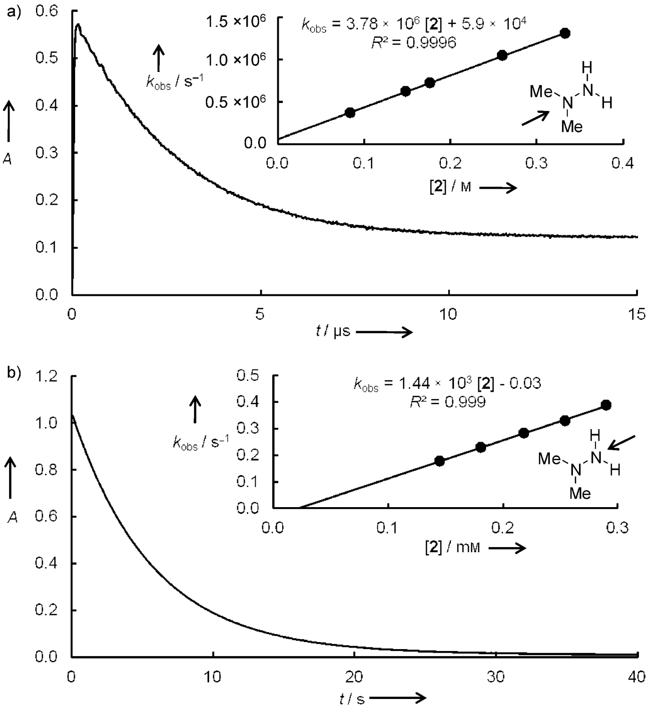


Figure 1. a) Fast exponential decay of the absorbance at 611 nm during the reaction of **4g** (generated from [**4g**-PBu_3] $=1.47\times10^{-5}$ M) with 1,1-dimethylhydrazine ([**2**] $=8.43\times10^{-2}$ M; $k_{obs}=3.71\times10^{5}$ s^{-1}). b) Slow exponential decay of the absorbance at 611 nm during the reaction of **4g** ([**4g**] $=1.80\times10^{-5}$ M) with 1,1-dimethylhydrazine ([**2**] $=1.45\times10^{-4}$ M; $k_{obs}=1.78\times10^{-1}$ s^{-1}). Insets: Plots of k_{obs} versus [**2**] yield the second-order rate constants $k_2'=3.78\times10^{6}$ M^{-1} s^{-1} and $k_2=1.44\times10^{3}$ M^{-1} s^{-1}.

reactions of the benzhydrylium ions and the reverse reaction. As it is very small compared with k_2[**1**], it is dominated by inaccuracies in k_{obs} and will, therefore, not be discussed in the following.

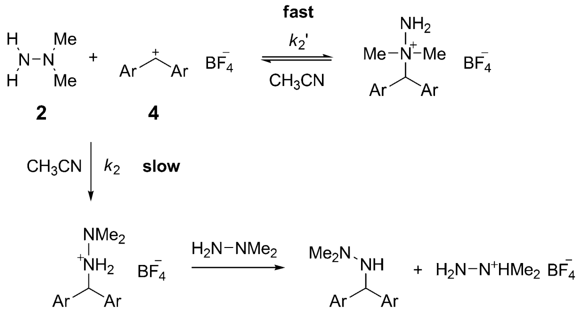
The situation is more complicated for 1,1-dimethylhydrazine (**2**) and trimethylhydrazine (**3**) which contain tertiary amine groups. With these systems, we observed different kinetic behavior depending on the concentration of the hydrazines and the nature of the electrophile. For the reactions of **2** with **4g** and **4h** we could even observe two separate exponential decays on different time scales when different concentrations of **2** were employed. Figure 1 a shows the decay of the absorbance of **4g** which was generated by laser-flash photolysis of the phosphonium salt **4g**-PBu_3 in acetonitrile at 20 °C in the presence of **2** (8.43×10^{-2} M). A mono-exponential decay of the absorbance of the carbocation was observed within 15 µs (approximately 80 % conversion), while the remaining absorbance disappeared within around 100 ms. With increasing hydrazine concentrations, the conversion arising from the fast reaction increased, and eventually the fast decay was observed almost exclusively. From the linear increase of k_{obs} with the concentration of **2**, we obtained the second-order rate constant $k_2'=3.78\times10^{6}$ M^{-1} s^{-1} (Table 2).

At lower concentrations of the hydrazine, the slower decay became more dominant, and for [**2**] $<3\times10^{-4}$ M, the initial fast decay of the absorbance was almost absent and a mono-exponential decay on a longer timescale was observed. Figure 1 b shows the decay of **4g** in the presence of 1.45×10^{-4} M **2** determined with the stopped-flow technique. Again, a mono-exponential decay of the absorbance of the carbocation was observed and a linear correlation of k_{obs} with the hydrazine concentration was obtained, the slope of which yielded another significantly lower second-order rate constant of $k_2=1.44\times10^{3}$ M^{-1} s^{-1} (Table 2).

Analogous observations were made for the reaction of **2** with **4h**, where we obtained second-order rate constants of $k_2'=8.06\times10^{6}$ M^{-1} s^{-1} at high concentrations of **2** and $k_2=2.46\times10^{3}$ M^{-1} s^{-1} at low concentrations (Table 2).

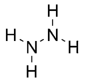
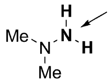
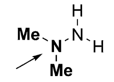
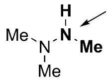
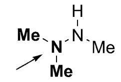
This behavior can be explained by the mechanism depicted in Scheme 2. The fast and reversible reaction corresponds to the attack at the tertiary nitrogen while the slower reaction, which becomes irreversible by deprotonation with a second molecule of the hydrazine, corresponds to the attack at the NH_2 group of **2**. At low concentrations of 1,1-dimethylhydrazine (**2**), the equilibrium for the fast reaction, which leads to the kinetically controlled product, is almost completely on the side of the starting material, and the slow process (reaction at the NH_2 group) is observed exclusively.

When we investigated the reactions of **2** with other reference electrophiles, one of the two modes of attack was always predominant, so that we obtained only one second-order rate constant for each reaction: For the weak electrophiles **4b**–**e**, the equilibrium of the fast reaction is on the side of the reactants and we observed only the slow decay. For the stronger electrophiles **4i**,**j**, we observed exclusively the fast



Scheme 2. Ambident reactivity of 1,1-dimethylhydrazine (**2**) in reactions with **4**.

Table 3: N and s_N parameters of **1**–**3** in CH$_3$CN.

	Hydrazine	N	s_N		N	s_N
1		16.45[a]	0.56[a]			
2		11.72	0.73		22.41	0.45
3		12.43	0.75		17.75	0.53

[a] Nucleophilicity parameters in methanol/acetonitrile (91:9 v/v): $N = 13.47$; $s_N = 0.70$.[10]

reaction because the formation of the quaternary hydrazinium ions is almost quantitative even at low hydrazine concentrations (Table 2).[8]

Figure 2 shows that the rate constants measured for the parent hydrazine (**1**) with the three different methods all correlate linearly with the electrophilicity parameter E as required by Equation (1), while two correlation lines are found for 1,1-dimethylhydrazine (**2**) which are assigned to the two sites of attack. It can be seen that the methyl substituents increase the nucleophilicity of the substituted nitrogen by more than one order of magnitude and decrease the reactivity of the neighboring site by more than two orders of magnitude.

An analogous behavior was found for the reactions of trimethylhydrazine (**3**; Table 2). Though we did not find systems where the two competing reactions could be observed separately, Figure S2 in the Supporting Information clearly shows two correlation lines, the higher one for the reaction at the tertiary nitrogen and the lower one for the reaction at the NHMe position. Again, methyl substitution increases the nucleophilicity of the substituted center while it reduces that of the adjacent nitrogen: The NHMe group of **3** is approximately four-times more nucleophilic than the NH$_2$ group in **2** (reactions with **4e**–**h**, Table 2), while the tertiary nitrogen of **3** is 11-times less nucleophilic than the corresponding nitrogen in **2** (reactions with **4i**,**j**, Table 2).

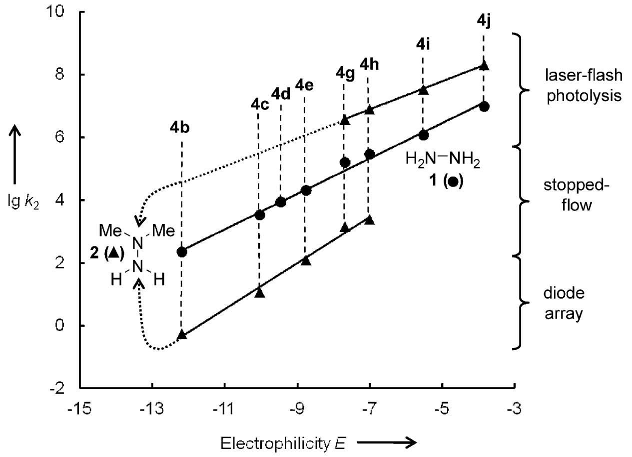


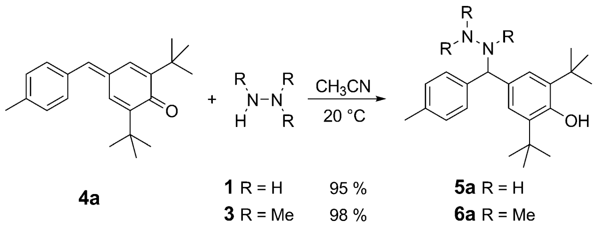
Figure 2. Plots of the second-order rate constants lgk_2 and lgk_2' for the reactions of hydrazine (**1**) and 1,1-dimethylhydrazine (**2**) with benzhydrylium ions and quinone methides in CH$_3$CN at 20 °C versus the E parameters of **4**.

This information is also given by the nucleophilicity parameters N and s_N in Table 3, which have been derived from the correlations in Figure 2 and in Figure S2 (Supporting Information). The different values of s_N for the two sites in **2** and **3** imply, however, that the positional selectivities decrease with increasing reactivity of the electrophiles.

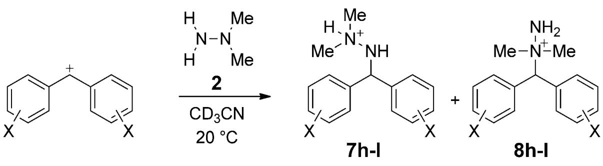
The reaction mechanism, derived from the kinetic experiments (Scheme 2) is in line with structural investigations by NMR spectroscopy.[9] Scheme 3 shows that the quinone methide **4a** reacts exclusively with the NHMe center of **3** to the 1:1 adduct **6a** in analogy to the reaction of the parent hydrazine **1** (→**5a**).

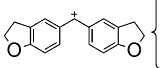
Similarly, NMR spectroscopic analysis of the product obtained from **4h** and **2** showed the exclusive formation of **7h**, which arises from electrophilic attack at the NH$_2$ group of **2** (Scheme 4).[11] In contrast to the interpretation of the kinetic data, NMR analysis of the product obtained from **4j** and **2** also showed exclusive attack at the NH$_2$ group of **2** (→**7j**).[12] We, therefore, assumed that the initial formation of the quaternary hydrazinium ion **8j**, which was derived from the correlation in Figure 2, is followed by re-ionization and eventual formation of the thermodynamically favored product **7j**. To confirm this hypothesis, we have also studied the reactions of the more electrophilic benzhydrylium ions **4k** and **4l** with **2**. At short reaction times we observed the predominant formation of the quaternary hydrazinium ions **8k** and **8l**, which subsequently rearranged to **7k** and **7l**, respectively (Scheme 4).

We have thus shown that the tertiary nitrogen in 1,1-dimethylhydrazine (**2**) is approximately 3000 times (!) more reactive than the NH$_2$ group and that methyl groups generally activate the substituted and deactivate the adjacent nitrogen center. In line with these conclusions, the unsymmetrical hydrazine **2** has been reported to yield quaternary hydrazi-



Scheme 3. Products of the reactions of hydrazines **1** and **3** with **4a** in acetonitrile at 20 °C.



4h	X = 4-NMe$_2$	4 min	quant.	—
4j	X = 4-NMe(CH$_2$CF$_3$)	4 min	quant.	—
4k		4 min	< 5 %	> 95 %
		400 min[a]	> 97 %	< 3 %
4l	X = 4-OMe	4 min	5 %	95 %
		440 min[a]	23 %	77 %

Scheme 4. Reactions of 1,1-dimethylhydrazine (**2**) with **4h–l** in CD$_3$CN. [a] Formation of **7k** and **7l** is accompanied by some decomposition.

nium salts in alkylations which proceed by irreversible S$_N$2 reactions.[13] In reversible reactions, for example, acylations, the thermodynamically more-favored product is formed, however, which results from attack at the NH$_2$ group and subsequent deprotonation.[14] As shown for many other ambident nucleophiles, the observed regioselectivity does not depend on the hardness of the reaction partner, whereas the reversibility of the electrophilic attack plays a decisive role.[15]

Experimental Section

The kinetics of the reactions of the benzhydrylium ions with the hydrazines **1–3** were monitored by UV/Vis spectroscopy. For slow reactions ($\tau_{1/2} > 10$ s), the spectra were collected by using a diode-array spectrophotometer. Stopped-flow spectrophotometer systems were used for the investigation of faster reactions (10 ms $< \tau_{1/2} <$ 10 s). Reactions with $\tau_{1/2} <$ 10 ms were analyzed by laser-flash photolytic generation of **4g–j** from phosphonium ions in the presence of excess hydrazine. The sample solutions were irradiated with 7 ns pulses from a quadrupled Nd:YAG laser (266 nm, 40–60 mJ/pulse). For details of the kinetic experiments, syntheses and product characterization see the Supporting Information.

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Keywords: ambident nucleophiles · correlation analysis · hydrazines · kinetics · linear-free energy relationships

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[7] J. Ammer, M. Baidya, S. Kobayashi, H. Mayr, *J. Phys. Org. Chem.* **2010**, *23*, 1029–1035.

[8] For the reaction of **2** with **4j**, we only observed the fast decay ($k_2' = 2.04 \times 10^8\,\text{M}^{-1}\,\text{s}^{-1}$) even at concentrations as low as $[\mathbf{2}] = 1.58 \times 10^{-5}\,\text{M}$. That we observed > 90% conversion even at such low concentrations (only ca. sixfold excess over **4j**) proves that the large rate constants measured for **4g–j** at high concentrations of **2** do not result from impurities in the hydrazine but reflect the nucleophilic reactivity of **2**.

[9] The regioselectivities of the reactions of **2** and **3** with the reference electrophiles were determined from the ^3J couplings of the methyl groups with the Ar$_2$*CH* group in HMBC NMR spectra (see Supporting Information).

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[11] Deprotonated **7h** was isolated in 66% yield after treatment of **4h** with an excess of **2** (see Supporting Information).

[12] Reaction of the less-substituted nitrogen center was also detected in the reaction of **4j** with **3** (see Supporting Information).

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