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Nucleophilic Reactivities of Hydrazines and Amines: The Futile Search for the α-Effect in Hydrazine Reactivities

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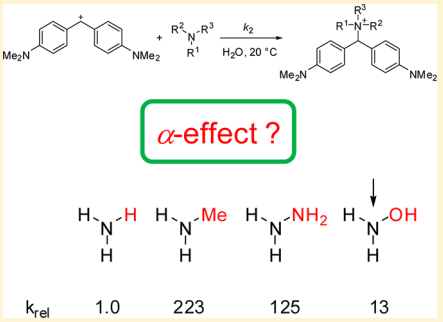
Supporting Information

ABSTRACT: The kinetics of the reactions of amines, hydrazines, hydrazides, and hydroxylamines with benzhydrylium ions and quinone methides were studied in acetonitrile and water by UV−vis spectroscopy, using conventional spectrometers and stopped-flow and laser-flash techniques. From the second-order rate constants k_2 of these reactions, the nucleophilicity parameters N and s_N were determined according to the linear free energy relationship $\log k_2 = s_N(N + E)$. While methyl groups increase the reactivities of the α-position of hydrazines, they decrease the reactivities of the β-position. Despite the 10^2 times lower reactivities of amines and hydrazines in water than in acetonitrile, the relative reactivities of differently substituted amines and hydrazines are almost identical in the two solvents. In both solvents hydrazine has a reactivity similar to that of methylamine. This observation implies that replacement of one hydrogen in ammonia by Me increases the nucleophilicity more than introduction of an amino group, if one takes into account that hydrazine has two reactive centers. Plots of $\log k_2$ versus the corresponding equilibrium constants ($\log K$) or Brønsted basicities (pK_{aH}) do not show enhanced nucleophilicities (α-effect) for either hydrazines or hydroxylamine relative to alkylamines.



INTRODUCTION

In 1962, Pearson and Edwards created the term α-effect to account for the enhanced reactivity of nucleophiles, which bear an unshared pair of electrons at the atom adjacent to the nucleophilic center.[1] This definition was adopted by the 1979 version of the IUPAC Glossary of Terms used in Physical Organic Chemistry and exemplified by the higher nucleophilicity of HOO^- compared to that of HO^-.[2a] Because of the problem in specifying a reference nucleophile with which the α-effect nucleophile should be compared, Hoz and Buncel defined the α-effect as the positive deviation from a Brønsted plot.[3] This definition has been accepted by the 1994 version of the IUPAC glossary.[2b] Um, Im, and Buncel have later introduced the additional criterion that the α-effect nucleophiles and the reference nucleophiles should react by the same mechanisms.[4] They pointed out that the classical assessment of the α-effect fails for reactions of HOO^- with substituted phenyl methanesulfonates, because the mechanisms differ from those of the corresponding reactions with HO^-.

The α-effect, which has been investigated for various reactions of nucleophiles including acylations, Michael additions, S_N2 reactions, and nucleophilic aromatic substitutions has been the topic of several reviews,[3,5] but its origin and extent are still discussed controversially.[5,6] Over the years, several factors have been specified, which are supposed to contribute to the magnitude of the α-effect. The α-effect was claimed to depend on the hybridization of the reaction center of the electrophilic reaction partner[5] and to increase in the order $sp^3 < sp^2 < sp$. Large slopes β_{nuc} in Brønsted correlations, which are attributed to a large extent of bond formation in the transition state, have been claimed to be associated with large α-effects.[5,6i,l,o] Fina and Edwards emphasized, however, that the magnitude of β_{nuc} can only be related to the α-effect when similar substrates are compared.[5c] Buncel, Um, and co-workers concluded that the magnitude of the α-effect strongly depends on the nature of the solvent system.[5a,6e,i]

Several theories on the origin of the α-effect have emerged, which include the destabilization of the ground state by electron repulsions, the stabilization of the transition state, thermodynamic stabilization of the products, and solvent effects.[5] In order to properly elucidate the influence of the product stabilities, Ren and Yamataka proposed to compare the reaction rates with the equilibrium constants for the reactions under consideration rather than with the corresponding Brønsted basicities.[7]

In recent years, a renewed interest in the topic arose with the newly established mass-spectrometric techniques[8] and the progress in quantum chemical methods,[7,9] which reveal the intrinsic reactivities of the unsolvated α-effect nucleophiles. However, experimental studies in the gas-phase also showed that the α-effect depends on the system investigated. For example, an α-effect was found for the nucleophilic substitution reactions of the hydroperoxide anion with methyl fluoride, anisoles, and dimethyl methylphosphonate,[8a,c] but not for its reactions with methyl formate and alkyl chlorides.[8b,d]

Ren and Yamataka investigated the activation energies of S_N2 reactions of alkyl halides and of E2 reactions of ethyl chloride

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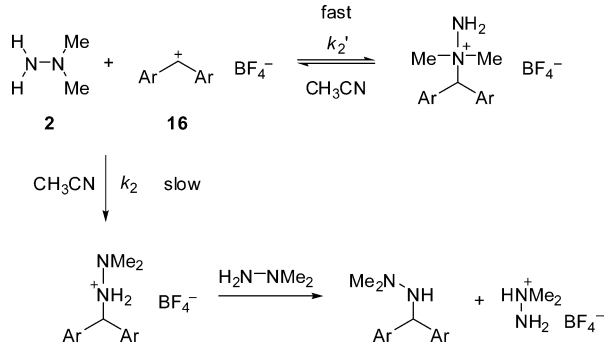
with a series of anionic bases in the gas phase using the G2(+) level of theory.[7,9c,d,f] They found that α-effect nucleophiles deviated significantly from plots of the activation barriers of both reactions versus the proton affinities and claimed that α-effect nucleophiles react with lower deformation energies. However, the hydrazide anion H_2NNH^- has been calculated to react more slowly with methyl chloride than expected from the correlation with the proton affinities, though it has been calculated to react faster than the more basic amide anion NH_2^-.[9f]

The relative reactivities of hydrazines and hydroxylamines depend strongly on the electrophilic reaction partners and the reaction conditions, and the magnitude of the α-effect is much smaller than for other typical α-effect nucleophiles, such as oximates and hydroperoxide anions.[5] Bernasconi and Murray found that the rates of nucleophilic attack of hydrazine, hydroxylamine, and semicarbazide at benzylidene Meldrum's acid correlated well with those of normal primary amines in the Brønsted plot.[6l] On the other hand, the equilibrium constants for the formation of the zwitterionic adducts from benzylidene Meldrum's acid with hydrazine, semicarbazide, and methoxyamine were significantly larger than those with isobasic amines.[6l] Dixon and Bruice reported that hydrazines add to malachite green faster and with greater equilibrium constants than primary amines of the same Brønsted basicities.[6s] The linear correlation between the rate and equilibrium constants with a slope of 1.0 shows that the different product stabilities are fully reflected by the transition states.

As part of our program to include the N-nucleophiles **1**–**15** in our comprehensive nucleophilicity scales,[10] we have recently investigated the reactions of hydrazine (**1**), 1,1-dimethylhydrazine (**2**), and trimethylhydrazine (**3**) with benzhydrylium ions and quinone methides in acetonitrile.[11] We observed that methylation increases the nucleophilicity of the substituted nitrogen and decreases the reactivity of the adjacent center. As a result, the tertiary nitrogen atoms of the asymmetric hydrazines **2** and **3** are the more reactive sites under conditions of kinetic control, while substitutions of the less substituted nitrogen atoms were observed under conditions of thermodynamic product control (Scheme 1, Figure 1).

These results were in contrast to theoretical predictions (DFT) by Hocquet and co-workers based on the principle of maximum hardness.[12] While the nucleophilic Fukui function $f^-(r)$ predicted similar reactivities of the two centers, the "dual descriptor" (second-order Fukui function) $\Delta f(r)$[13] and the calculated charge densities indicated a higher nucleophilicity for the NH_2 terminus in 1,1-dimethylhydrazine (**2**) and methylhydrazine (**4**), respectively.

Scheme 1. Ambident Reactivity of 1,1-Dimethylhydrazine (2) in Reactions with Benzhydrylium Ions (16)[a]



[a]Scheme modified from ref 11.

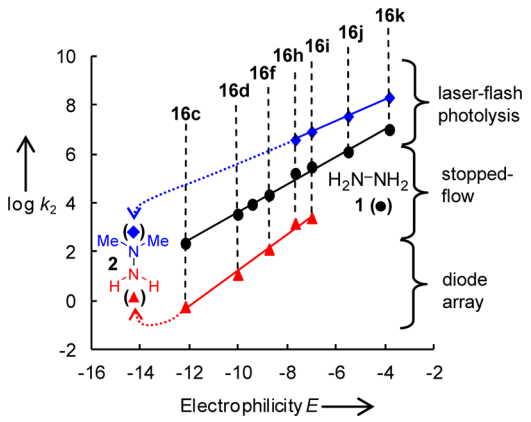
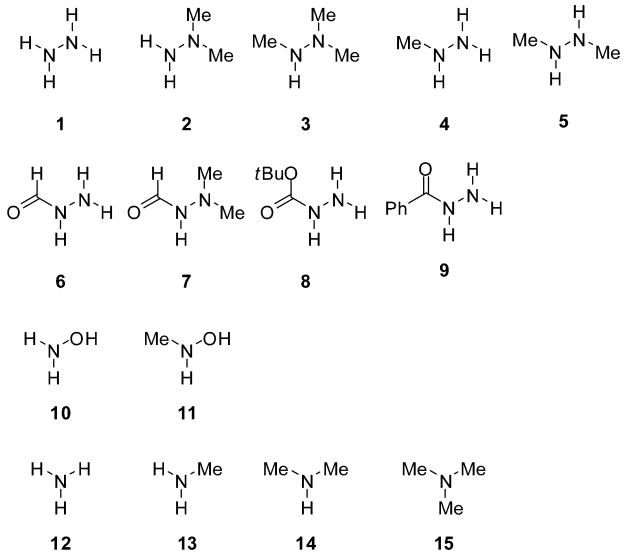


Figure 1. Plots of the second-order rate constants log k_2 or log k_2' for the reactions of hydrazine (**1**) and 1,1-dimethylhydrazine (**2**) with benzhydrylium ions and quinone methides in CH_3CN at 20 °C versus the E parameters of **16** (for structures of **16c**–**k** see Table 1). Figure modified from ref 11.



In order to clarify the influence of substituents on the nucleophilic reactivities and regioselectivities of potential α-effect nucleophiles, we have now studied the kinetics of the reactions of the hydrazines **1**–**5**, hydrazides **6**–**9**, hydroxylamines **10** and **11**, ammonia (**12**), and methylamines **13**–**15** with quinone methides **16a**–**c** and benzhydrylium ions **16d**–**n** as reference electrophiles (Table 1) in acetonitrile and water and evaluated their N and s_N parameters according to the linear free energy relationship eq 1.[14]

$$\log k_2\ (20\ ^\circ\mathrm{C}) = s_N(N + E) \qquad (1)$$

In eq 1, electrophiles are characterized by one solvent-independent parameter (E), and nucleophiles are characterized by two solvent-dependent parameters, N and s_N.[10]

RESULTS AND DISCUSSION

Product Characterization. Complementary to previous studies of **1**–**3**,[11] we characterized the products of representative combinations of the nucleophiles **4**–**15** with quinone methides **16a**–**c** and benzhydrylium ions **16d**–**n**.

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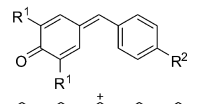
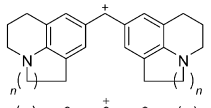
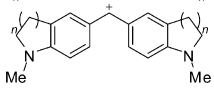
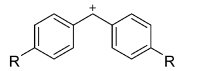
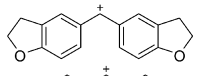
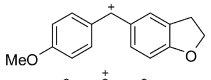
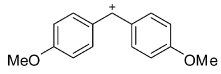
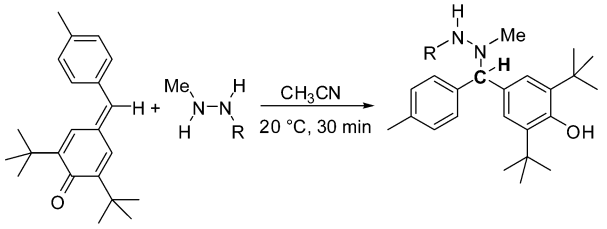
Table 1. List of the Reference Electrophiles 16 Used in this Study

Reference Electrophile[a]			E[b]
	R^1 = *t*Bu, R^2 = OMe	ani(*t*Bu)$_2$QM (**16a**)	–16.11
	R^1 = *t*Bu, R^2 = Me	tol(*t*Bu)$_2$QM (**16b**)	–15.83
	R^1 = Ph, R^2 = OMe	ani(Ph)$_2$QM (**16c**)	–12.18
	n = 1	(lil)$_2$CH$^+$ (**16d**)	–10.04
	n = 2	(jul)$_2$CH$^+$ (**16e**)	–9.45
	n = 1	(ind)$_2$CH$^+$ (**16f**)	–8.76
	n = 2	(thq)$_2$CH$^+$ (**16g**)	–8.22
	R = *N*-pyrrolidino	(pyr)$_2$CH$^+$ (**16h**)	–7.69
	R = NMe$_2$	(dma)$_2$CH$^+$ (**16i**)	–7.02
	R = *N*-morpholino	(mor)$_2$CH$^+$ (**16j**)	–5.53
	R = N(Me)CH$_2$CF$_3$	(mfa)$_2$CH$^+$ (**16k**)	–3.85
		(fur)$_2$CH$^+$ (**16l**)	–1.36
		(ani)(fur)CH$^+$ (**16m**)	–0.81[c]
		(ani)$_2$CH$^+$ (**16n**)	0.00

[a]Counterion of the benzhydryl cations: BF_4^-. [b]Electrophilicity parameters E from refs 10c, 10d, and 10f. [c]Revised electrophilicity parameter from ref 15.

Methylhydrazine (**4**) and 1,2-dimethylhydrazine (**5**) reacted smoothly with the quinone methide tol(*t*Bu)$_2$QM (**16b**) in acetonitrile at 20 °C to form the 1:1 addition products **17** or **18**, respectively (Scheme 2), as recently described for the

Scheme 2. Products of Reactions of Hydrazines 4 and 5 with 16b and ^{1}H and ^{13}C NMR Chemical Shifts (ppm) of the Ar$_2$CH Group

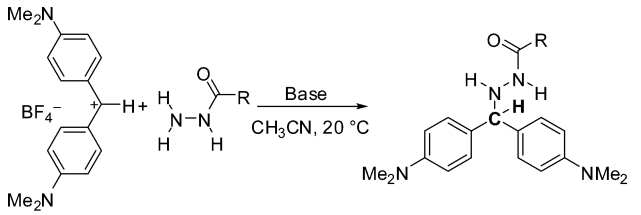


16b **4** R = H — **17** (94%; δ_H = 4.08; δ_C = 82.3)
5 R = Me — **18** (98%; δ_H = 4.35; δ_C = 78.1)

parent hydrazine (**1**) and trimethylhydrazine (**3**).[11] While **5** has two equivalent nucleophilic centers, **4** could, in principle, attack the quinone methide with either the primary or the secondary amino function. We obtained only the product from regioselective reaction at the NHMe group in 94% yield, which was identified by heteronuclear multiple-bond correlation spectroscopy (HMBC-NMR).[16]

Regioselective reactions at the NH$_2$ groups were found for the reactions of the benzhydrylium salt (dma)$_2$CH$^+$BF$_4^-$ (**16i**) with formohydrazide (**6**), *tert*-butyl hydrazinecarboxylate (**8**), and benzohydrazide (**9**). After alkaline workup, the products **19**–**21** were obtained (Scheme 3). Like formohydrazide (**6**), the product **19** exists as a mixture of (*Z*)- and (*E*)-isomers (2:1 in CDCl$_3$). These results are in agreement with those of other researchers who showed a large preference for attack at the NH$_2$ group of hydrazides under various reaction conditions.[17]

Scheme 3. Products of Reaction of 6, 8, and 9 with 16i and ^{1}H and ^{13}C NMR Chemical Shifts (ppm) of the Ar$_2$CH Group



16i **6** R = H — NMe$_3$ — **19** (quant.[a]; δ_H = 5.09/4.81 (*Z*/*E*); δ_C = 69.1/67.6 (*Z*/*E*))
8 R = O*t*Bu — NaOH — **20** (quant.; δ_H = 5.11; δ_C = 67.2)
9 R = Ph — NaOH — **21** (93%; δ_H = 5.10; δ_C = 68.3)

[a]^{1}H NMR spectroscopic analysis of the crude product showed the exclusive formation of **19** as a 2:1 mixture of (*Z*)- and (*E*)-isomers.

The regioselectivity can only be reversed when the more acidic acylated NH group is deprotonated.[18] No reaction was observed when *N*′,*N*′-dimethylformohydrazide (**7**) was combined with equimolar amounts of 4,4′-dimethoxybenzhydryl chloride (**16n**-Cl) at 20 °C, which can be explained by the low equilibrium constant for attack of **16n** at the NMe$_2$ group of **7** (see below).

Combination of **16i** with 5.5 equiv of hydroxylamine (**10**), which was generated by treatment of its hydrochloride with 1.7 equiv of trimethylamine (**15**), yielded a 9:1 mixture of the mono- and double-alkylation products **22** and **23** (Scheme 4). On the other hand, the combination of **10** with an equimolar amount of **16e** yielded the monoalkylated hydroxylamine **25** selectively. Regioselective monoalkylation of the nitrogen to give **24** was also found for the combination of **16i** with 2.4 equiv of *N*-methylhydroxylamine (**11**), which was generated from the corresponding hydrochloride with 1 equiv of trimethylamine (Scheme 4). In line with these results, N-alkylation of hydroxylamine has previously been observed.[6z,19] Only derivatives of hydroxamic acid, i.e., hydroxylamines carrying electron-withdrawing groups at nitrogen, were found to react at oxygen in transition-metal-catalyzed allylic substitution reactions[20] and in S$_N$2 reactions when the hydroxyl group was deprotonated with NaH.[21]

When **16i** was added to 18 equiv of ammonia (**12**) in acetonitrile at 20 °C, we observed the exclusive formation of the secondary amine **27** (Scheme 5). Unlike ammonia (**12**), methylamine (**13**) and dimethylamine (**14**) reacted with **16i** to yield the 1:1 products **28** and **29** exclusively.

Treatment of (ani)$_2$CHCl (**16n**-Cl) with an ethanolic solution of 5 equiv of trimethylamine (**15**) in acetonitrile at 20 °C resulted in the formation of the quaternary ammonium salt **30** (Scheme 6). Less reactive carbocations, such as **16i**, reacted reversibly with trimethylamine (**15**), and products could not be isolated (detailed discussion below).

Kinetics of Reactions of 1–15 with Reference Electrophiles 16. The rates of the reactions of the amines, hydrazines, hydrazides, and hydroxylamines **1**–**15** with the reference electrophiles **16** were determined spectrophotometrically in acetonitrile or water at 20 °C using conventional and stopped-flow methods as described previously.[10] The nucleophiles **1**–**15** were used in large excess (over 8 equiv) relative to the electrophiles **16** to ensure first-order conditions. For the fast reactions (k_2 > 10^6 M^{-1} s^{-1}), benzhydrylium ions **16h**–**n** were

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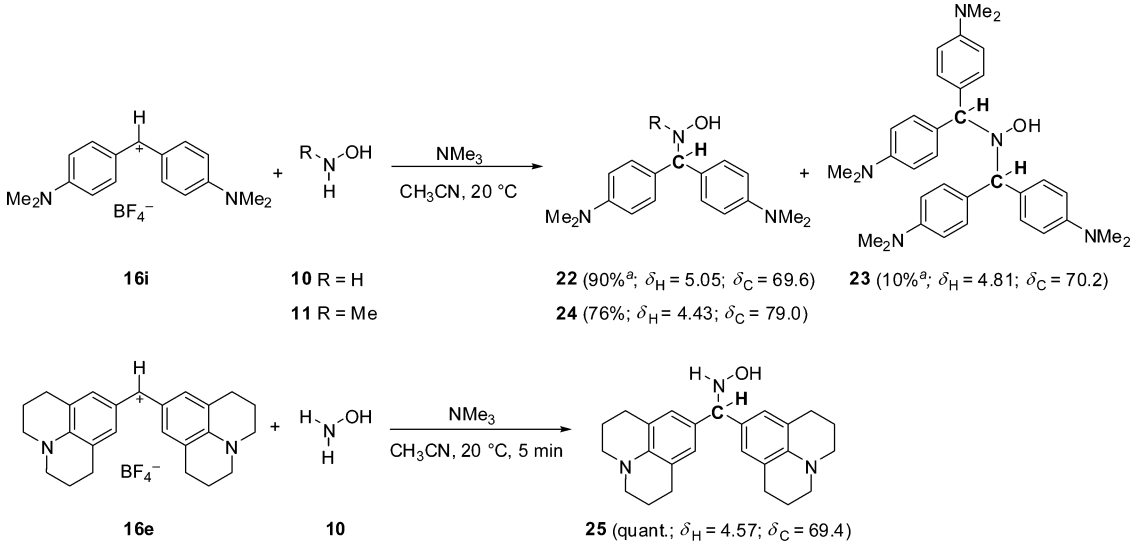
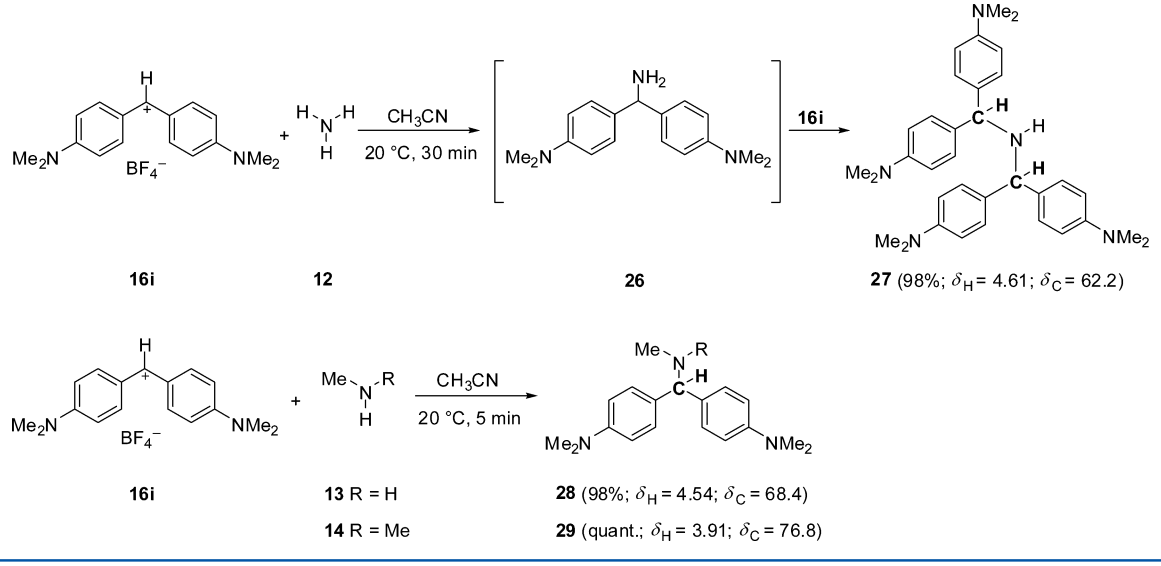
Scheme 4. Products of the Reactions of 10 and 11 with 16i or 16e and ^{1}H and ^{13}C NMR Chemical Shifts (ppm) of the Ar_2CH Group

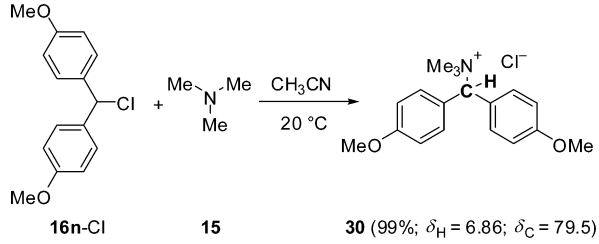


[a]The ratio **22**/**23** was determined by ^{1}H NMR spectroscopic analysis of the crude product.

Scheme 5. Products of Reactions of 12−14 with 16i and ^{1}H and ^{13}C NMR Chemical Shifts (ppm) of the Ar_2CH Group



Scheme 6. Formation of Quaternary Ammonium Salt 30 by Treatment of 16n-Cl with Trimethylamine (15) and ^{1}H and ^{13}C NMR Chemical Shifts (ppm) of the Ar_2CH Group



generated by laser-flash photolysis (7 ns pulse, 266 nm) of substituted benzhydryl triphenyl or tributyl phosphonium tetrafluoroborates in acetonitrile in the presence of excess nucleophile.[11,14a]

Monoexponential decays of the absorbances of the electrophiles were observed for all reactions, and the first-order rate constants k_{obs} (s^{-1}) were obtained by least-squares fitting of the exponential function $A = A_0\ e^{-k_{obs}t} + C$ to the decays of the absorbances; a typical example is shown in Figure 2. Plots of k_{obs} versus the nucleophile concentrations were linear for all reactions of **6**−**15** with the reference electrophiles **16**. According to eq 2, the second-order rate constants k_2 ($M^{-1}\ s^{-1}$) were obtained as the slopes of these plots (Table 2).

$$k_{obs} = k_2[Nu] + k_0 \quad (2)$$

For the determination of the kinetics of the reactions of hydroxylamine (**10**), *N*-methylhydroxylamine (**11**), methylamine (**13**), and dimethylamine (**14**) with benzhydrylium ions and quinone methides **16**, the nucleophiles were generated by partial deprotonation of the corresponding hydrochlorides with 0.50−0.95 equiv of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as recently reported for analogous studies of hydrazine (**1**).[11]

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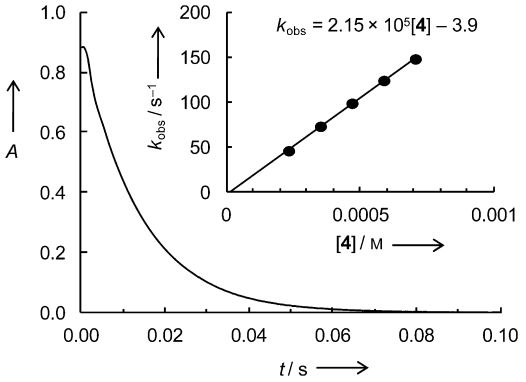


Figure 2. Exponential decay of the absorbance at 616 nm during the reaction of **16f** (1.74×10^{-5} M) with methylhydrazine ([4] = 3.56×10^{-4} M; k_{obs} = 73.2 s^{-1}) in acetonitrile at 20 °C. Inset: The plot of k_{obs} versus [4] yielded the second-order rate constant $k_2 = 2.15 \times 10^5$ M^{-1} s^{-1}.

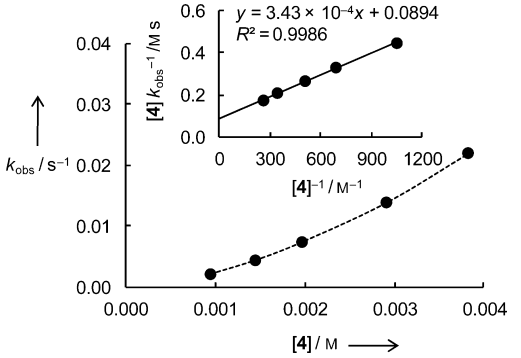
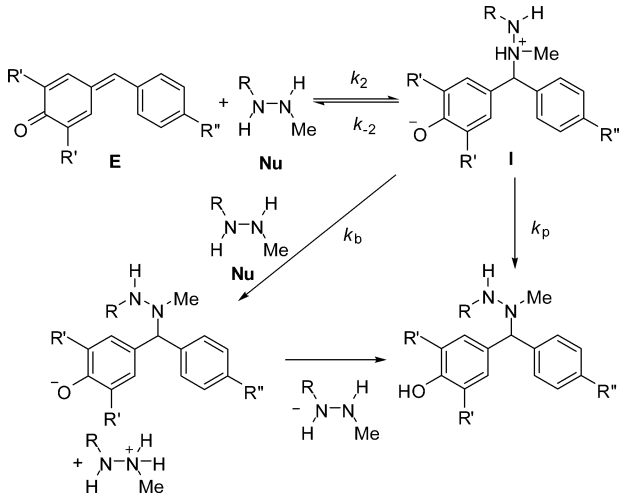


Figure 3. Plot of k_{obs} versus [4] for the reaction of methylhydrazine (**4**) with **16b** in CH_3CN at 20 °C. Inset: Plot of [4]/k_{obs} versus 1/[4] from which the second-order rate constant k_2 (1/0.0894 M s = 11.2 M^{-1} s^{-1}) was obtained as the reciprocal intercept.

Scheme 7. Reaction of Quinone Methides 16b and 16c (E) with the Mono- and 1,2-Dimethylhydrazines 4 and 5 (Nu)



For the reaction of methylamine (**13**) with **16h**, KO*t*Bu was used as an alternative deprotonation agent. The similar rate constants obtained with both bases confirmed the complete deprotonation of methylamine hydrochloride by DBU and proved that the reactivities of the amines were not affected by hydrogen bonding of the amines to the protonated amines or the protonated DBU. Stock solutions of ammonia (**12**) were prepared by gas injection in acetonitrile, and trimethylamine was used as a 33% solution in ethanol. In both cases, the concentrations of the stock solutions were determined by titration with hydrochloric acid.

Tetramethylhydrazine was not used in our kinetic studies, because we could not obtain this compound in sufficient purity, and even small contaminations by trimethylhydrazine (**3**) are problematic since previous work[11] suggested trimethylhydrazine (**3**) to be considerably more nucleophilic than tetramethylhydrazine.

While linear k_{obs} versus [nucleophile] plots were also obtained for the reactions of methylhydrazine (**4**) and 1,2-dimethylhydrazine (**5**) with most electrophiles, the correlations between k_{obs} and the hydrazine concentrations showed upward curvatures for the reactions of **4** with **16b** and **5** with **16c** in acetonitrile (Figure 3).

In these cases, the attack of the hydrazines is followed by a rate-determining proton transfer step, in which a second hydrazine molecule acts as general base catalyst (Scheme 7). An analogous behavior was previously observed for the reactions of secondary amines with quinone methides,[14d] as well as with thiocarbonates, thionobenzoates, and activated esters of indole-3-acetic acid.[22]

The kinetics of the reactions in Scheme 7 follow the rate law of eq 3, which is derived in the Supporting Information; it can be rewritten as eq 4.

$$k_{obs} = \frac{k_2 k_b [\mathbf{Nu}]^2}{k_{-2} + k_b[\mathbf{Nu}]} \quad (3)$$

$$\frac{[\mathbf{Nu}]}{k_{obs}} = \frac{1}{k_2} + \frac{k_{-2}}{k_2 k_b [\mathbf{Nu}]} \quad (4)$$

In line with eqs 3 and 4, plots of [**Nu**]/k_{obs} against 1/[**Nu**] were linear for a wide range of concentrations, as illustrated in the inset of Figure 3 for the reaction of **4** with **16b**. The second-order rate constants k_2 marked with footnote *g* in Table 2 were obtained from the intercepts ($1/k_2$) of these linear correlations.

Since in all other reactions, including those of dimethylamine (**14**) and methylhydrazine (**4**) with quinone methides in acetonitrile, linear correlations of the observed rate constants with the concentrations of the nucleophiles were obtained (see Supporting Information), one can conclude that the initial attack of the nucleophiles is generally irreversible, i.e., $k_{-2} \ll k_b[\mathbf{Nu}]$.

The reactions of hydrazine (**1**) and methylhydrazine (**4**) with the benzhydrylium ions **16** have also been studied in water, where competing reactions with either water or hydroxide ions have to be considered. The observed first-order rate constants k_{obs} are the sum of the rate constants for the reactions of the benzhydrylium ions **16** with the hydrazines (k_2), with hydroxide ($k_{2,OH}$), and with water (k_w) as described previously (eq 5).[14h,i]

$$k_{obs} = k_2[\text{hydrazine}] + k_{2,OH}[OH^-] + k_w \quad (5)$$

The concentrations of the hydrazines and of hydroxide were calculated from the pK_{aH} values as described in the Supporting Information. With these concentrations and the previously published values for $k_{2,OH}$[14k] one can calculate $k_{1,eff}$ as defined by eq 6.

$$k_{1,eff} = k_{obs} - k_{2,OH}[OH^-] = k_2[\text{hydrazine}] + k_w \quad (6)$$

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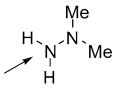
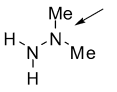
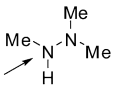
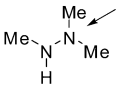
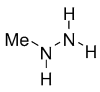
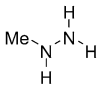
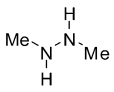
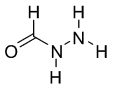
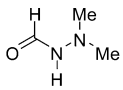
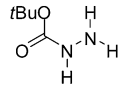
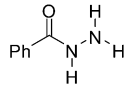
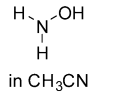
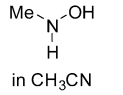
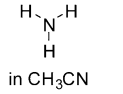
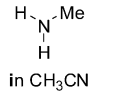
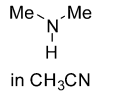
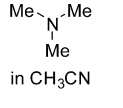
Table 2. Second-Order Rate Constants k_2 for Reactions of Reference Electrophiles 16 with the Amines 1−15 and 26 at 20 °C and Resulting N and s_N Parameters

Nucleophile	N	s_N	Ar_2CH^+	k_2 / M^{-1} s^{-1}
1  in H_2O	13.46	0.57	**16e**	1.97×10^2
			16f	4.31×10^2
			16g	9.25×10^2 [a]
			16h	1.89×10^3
			16i	4.52×10^3 [b]
1  in CH_3CN	16.45	0.56	**16c**	2.23×10^2 [c]
			16d	3.41×10^3 [c]
			16e	8.74×10^3 [c]
			16f	2.09×10^4 [c]
			16h	1.58×10^5 [c]
			16i	2.95×10^5 [c]
			16j	1.22×10^6 [c]
			16k	9.90×10^6 [c]
2  in CH_3CN	11.72[d]	0.73[d]	**16c**	5.69×10^{-1} [c]
			16d	1.18×10^1 [c]
			16f	1.27×10^2 [c]
			16h	1.44×10^3 [c]
			16i	2.46×10^3 [c]
2  in CH_3CN	22.41[e]	0.45[e]	**16h**	3.78×10^6 [c]
			16i	8.06×10^6 [c]
			16j	3.46×10^7 [c]
			16k	2.04×10^8 [c]
3  in CH_3CN	12.43[f]	0.75[f]	**16f**	6.15×10^2 [c]
			16g	1.26×10^3 [c]
			16h	3.74×10^3 [c]
			16i	1.17×10^4 [c]
3  in CH_3CN	17.75[e]	0.53[e]	**16j**	3.00×10^6 [c]
			16k	1.81×10^7 [c]
			16l	4.58×10^8 [c]
4  in H_2O	17.23	0.45	**16d**	1.59×10^3
			16e	3.75×10^3
			16f	5.83×10^3
			16g	1.16×10^4
4  in CH_3CN	17.73	0.58	**16b**	1.12×10^1 [g]
			16c	1.46×10^3
			16d	3.32×10^4
			16f	2.15×10^5
			16j	1.22×10^7
			16k	8.65×10^7
5  in CH_3CN	16.15	0.68	**16c**	4.44×10^2 [g]
			16d	1.64×10^4
			16e	4.46×10^4
			16f	9.24×10^4
			16h	5.24×10^5
6  in CH_3CN	10.35	0.76	**16i**	4.24×10^2
			16j	4.33×10^3
			16k	6.53×10^4
			16l	1.26×10^7
			16n	6.50×10^7
7  in CH_3CN	15.69	0.51	**16l**	2.18×10^7
			16m	4.08×10^7
			16n	1.08×10^8
8  in CH_3CN	11.40	0.70	**16i**	1.31×10^3
			16j	1.06×10^4
			16k	1.37×10^5
			16l	1.42×10^7
			16n	7.12×10^7
9  in CH_3CN	12.49	0.66	**16i**	4.06×10^3
			16j	3.66×10^4
			16k	4.92×10^5
10  in CH_3CN	12.80	0.63	**16c**	2.44 [g]
			16d	5.80×10^1 [h]
			16f	3.01×10^2 [h]
			16i	4.33×10^3 [h]
11  in CH_3CN	14.10	0.76	**16d**	1.09×10^3 [h]
			16f	1.09×10^4 [h]
			16h	9.20×10^4 [h]
			16i	1.78×10^5 [h]
12  in CH_3CN	11.39	0.69	**16c**	2.88×10^{-1}
			16f	4.76×10^1
			16h	4.54×10^2
			16i	1.53×10^3
			16j	9.05×10^3
13  in CH_3CN	15.19[i]	0.68[i]	**16c**	1.37×10^2 [h]
			16d	2.65×10^3 [h]
			16f	2.03×10^4 [h]
			16h	1.68×10^5 [h]
			16h	1.71×10^5 [j]
			16i	4.00×10^5 [j]
14  in CH_3CN	17.96	0.63	**16a**	1.50×10^1 [h]
			16c	4.63×10^3 [h]
			16d	9.77×10^4 [j]
			16e	2.65×10^5 [h]
15  in CH_3CN	23.05	0.45	**16h**	6.54×10^6
			16i	2.00×10^7
			16j	7.27×10^7
			16k	4.05×10^8
26 in CH_3CN			**16i**	4.20×10^3

[a] Cosolvent: 0.75 vol % CH_3CN. [b] Cosolvent: 1.0 vol % CH_3CN. [c] Rate constants for the reactions of **1**−**3** with **16** and resulting nucleophilicity parameters for **1**−**3** in acetonitrile from ref 11. [d] Reaction at the primary center of **4**. [e] Reaction at the tertiary centers of **2** or **3**, respectively. [f] Reaction at the secondary center of **3**. [g] Second-order rate constants k_2 were derived from eq 4 and are less precise. [h] The nucleophiles were generated by deprotonation of the corresponding hydrochloride salts with DBU. [i] For the determination of the nucleophilicity parameters N and s_N, the average of the second-order rate constants obtained from reactions of **16h** with **13** generated from methylamine hydrochloride (**13**·HCl) with KO*t*Bu or DBU was used. [j] The nucleophiles were generated by deprotonation of the corresponding hydrochloride salts with KO*t*Bu.

As a consequence, the second-order rate constants k_2 for the reactions of hydrazines **1** and **4** with **16** in water were obtained from the slopes of the correlations of $k_{1,eff}$ with the hydrazine concentrations (Table 2). It is observed that neither the reactions with hydroxide nor with water contribute more than 1% to the overall observed rate constants. As described above for the reactions in acetonitrile, the linearity of the $k_{1,eff}$ versus [hydrazine] plots indicates a rate law that is first order in

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hydrazine, implying that the C−N-bond formation and not the subsequent deprotonation is the rate-determining step.

As ammonia (**12**) yielded the secondary amine **27** in the reaction with **16i** (see above), we have also determined the kinetics of the reaction of **16i** with the intermediate primary amine **26**, which was synthesized by treatment of $(dma)_2CHOH$ with phthalimide and subsequent hydrolysis with hydrochloric acid according to the literature.[23] As shown in Table 2, **26** reacts 2.7 times faster with **16i** than ammonia (**12**). As more than 70 equiv of ammonia was used for the determination of its nucleophilic reactivity toward **16i**, the measured rate constants refer to the formation of the monosubstituted product **26**, which did not react with further **16i** under the conditions of the kinetic experiments. This interpretation is confirmed by the linear dependence of the observed rate constants on the concentration of NH_3 in the investigated concentration range, which would not be obtained if the subsequent reaction of **26** with **16i** would contribute to the observed rate constant.

The formation of the secondary amine **27** under synthetic conditions must, therefore, be the result of thermodynamic control. Traces of protons may regenerate **16i** from **26** and thus lead to the thermodynamically more favored product **27**. This interpretation is in line with the results by Villiger and Kopetschni, who showed that **26** disproportionates to ammonia (**12**) and **27** under proton catalysis.[24]

When the logarithms of the second-order rate constants k_2 were plotted against the previously reported electrophilicity parameters E of the benzhydrylium ions and quinone methides **16**, linear correlations were obtained (Figure 4), from which the nucleophile-specific parameters N and s_N (Table 2) were determined according to eq 1.

We can now compare the nucleophilic reactivities of the amines and hydrazines **1**−**15**, which cover the reactivity range from $10 < N < 24$, with each other and with those of other amines. The s_N parameters of the nucleophiles studied in this work vary from 0.45 to 0.76, i.e., the relative reactivities of these amines will depend on the reactivities of the reference electrophiles. In order to avoid ambiguity, the following discussion will focus on the rates of the reactions with $(dma)_2CH^+$ (**16i**) (Figures 5 and 6). Whereas the nucleophilicity parameters N in Table 2 refer to the gross reactivities of the molecules, the rate constants for the symmetrical nucleophiles hydrazine (**1**) and 1,2-dimethylhydrazine (**5**) in Figures 5 and 6 were corrected by the statistical factor of 2 to reflect the relative reactivities of the individual nucleophilic centers. Figure 5 shows a comparison of the second-order rate constants for the reactions of **16i** with differently substituted amines, hydrazines, hydrazides, and hydroxylamines in acetonitrile. The rows illustrate the influence of α-substitution as well as branching (β-substitution), while the columns reflect the effect of methylation of the reactive center, i.e., the change from primary over secondary to tertiary centers.

Replacement of the hydrogen atoms in ammonia (**12**) by alkyl groups significantly increases the nucleophilicity. While substitution of one hydrogen by a methyl group results in a 2.6 × 10^2 times higher reactivity, the second and third methyl groups increase the reactivity by factors of 20 (**14**/**13**) and 2.6 (**15**/**14**). The activation by long-chained alkyl groups is considerably smaller: One propyl group activates by a factor of 93 (**31**/**12**). In comparison, diethylamine (**34**) is 5.5 times more reactive than **31**, and the third ethyl group even lowers the reactivity by a factor of 4.5 (**35**/**34**). We thus arrive at the noticeable conclusion that trimethylamine (**15**) is 1.1 × 10^2 times more nucleophilic than triethylamine (**35**).

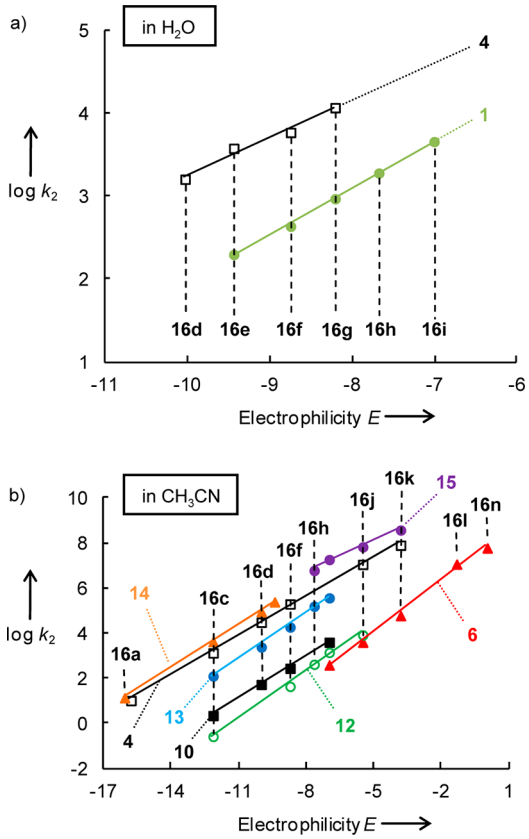

Figure 4. Correlations of the second-order rate constants log k_2 with the E parameters of the reference electrophiles for the reactions of selected representative nucleophiles with benzhydrylium ions and quinone methides **16** at 20 °C in (a) H_2O and (b) acetonitrile.

As shown in the first line of Figure 5, branching of the alkyl groups in primary amines leads to a steady reduction of reactivity, and *tert*-butylamine (**33**) is 58 times less nucleophilic than methylamine (**13**).

The vertical comparison of hydrazine (**1**), methylhydrazine (**4**), and 1,1-dimethylhydrazine (**2**) shows that the methyl groups in hydrazine activate the substituted nitrogen by factors of 11 (**4**/**1**) and 4.9 (**2**/**4**), respectively, i.e., the trend is similar to that in the series methylamine (**13**), dimethylamine (**14**), trimethylamine (**15**).

The retarding effect of methyl groups on the reactivity of the adjacent nitrogen corresponds to the branching effect in the series of the primary amines. This effect is more pronounced in the series of hydrazines, however. While isopropylamine (**32**) is 7.6 times less reactive than methylamine (**13**), the NH_2 group in 1,1-dimethylhydrazine (**2**) is 60 times less reactive than one NH_2 group in the parent hydrazine (**1**). Similar retarding effects of methyl groups at the adjacent nitrogen center can be observed in the series of hydrazines with secondary and tertiary nitrogen reaction centers: the NHMe group of trimethylhydrazine (**3**) is 69 times less reactive than one position in 1,2-dimethylhydrazine (**5**), which in turn reacts 2.0 times slower than the NHMe group of methylhydrazine (**4**); analogously the NMe_2 group of trimethylhydrazine (**3**) is 17 times less reactive than the corresponding group in 1,1-dimethylhydrazine (**2**).

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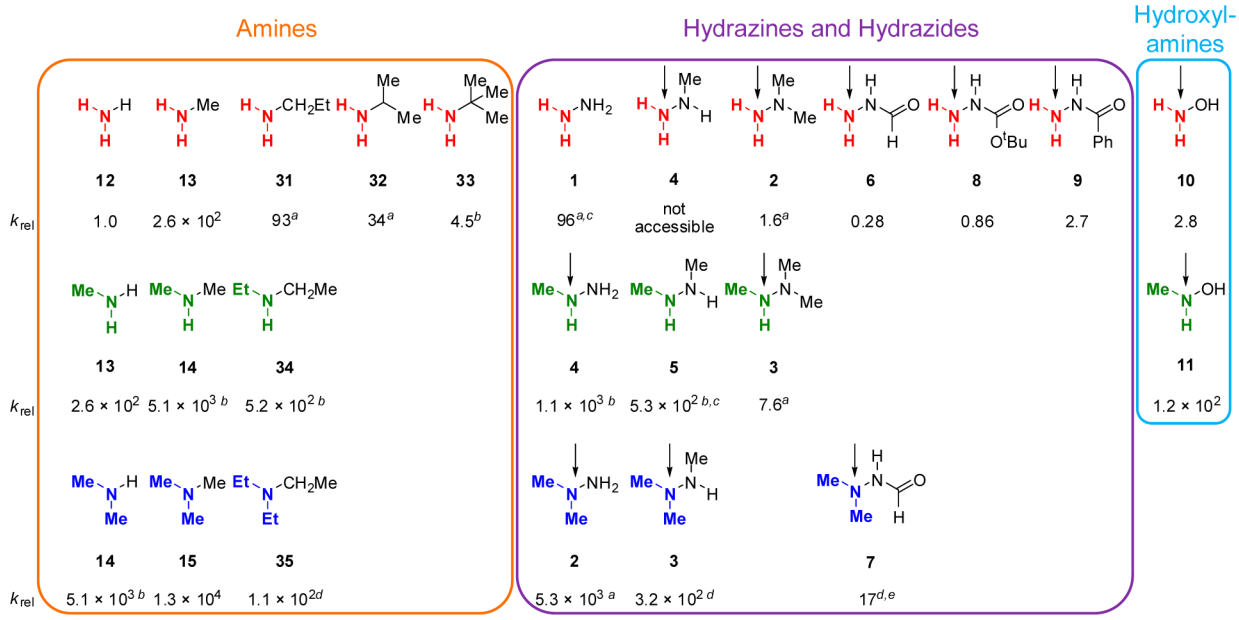

Figure 5. Comparison of relative second-order rate constants for the reactions of $(dma)_2CH^+$ (**16i**) with ammonia, amines, hydrazines, hydrazides, and hydroxylamines in CH_3CN at 20 °C (centers of attack are marked in red for primary nitrogens, in green for secondary nitrogens, in blue for tertiary nitrogens). Notes: [a]The rate constants for the reactions of **16i** with **1**−**3**[11] and **31**−**32**[14d] were reported previously. [b]The rate constants were calculated by eq 1 using the *E*, *N*, and s_N parameters.[11,14a,d] [c]The rate constants for the reactions of **16i** with the symmetrical hydrazines **1** and **5** were statistically corrected by a factor of 2. [d]Nucleophiles **7** and **35** and the NMe_2 group of **3** do not react with $(dma)_2CH^+$ (**16i**), and rate constants for these reactions were calculated by eq 1 using the *E*, *N*, and s_N parameters.[11,14a] [e]The rate constant for the reaction of **7** with **16i** was obtained by extrapolation over a wide range and has to be considered approximate.

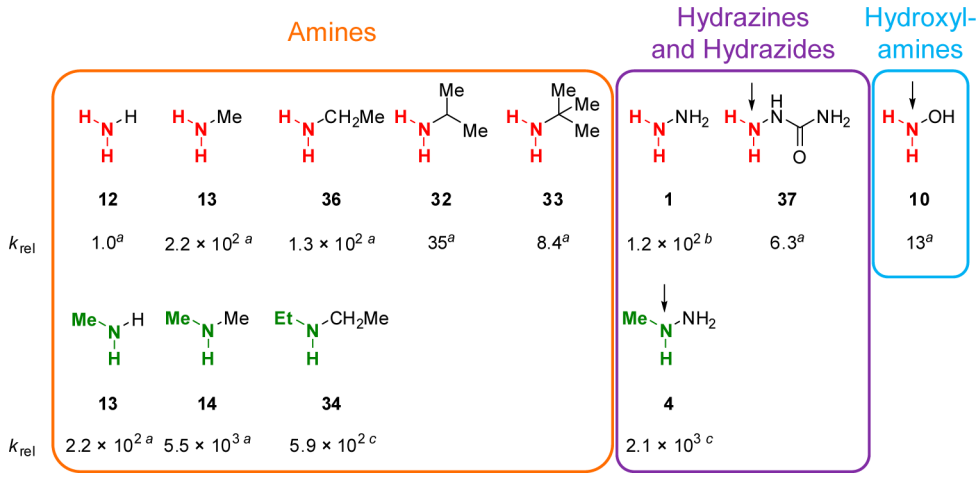

Figure 6. Comparison of relative second-order rate constants for reactions of $(dma)_2CH^+$ (**16i**) with amines, hydrazines, semicarbazide (**37**), and hydroxylamine (**10**) in H_2O at 20 °C (centers of attack are marked in red for primary nitrogens and in green for secondary nitrogens). Notes: [a]Rate constants for the reactions of **16i** with **10**,[14k] **12**−**14**, **32**−**34**, **36**,[14h] and **37**[14k] were reported previously. [b]The rate constant for the reaction of **16i** with hydrazine (**1**) was statistically corrected by a factor of 2. [c]The rate constants were calculated by eq 1 using the *E*, *N*, and s_N parameters.[14h]

1,1-Dimethylation of formohydrazide (**6**→**7**) increases the reactivity by a similar amount (factor 62) as 1,1-dimethylation of hydrazine (**1**→**2**, factor 55).

An increase of reactivity by *N*-methylation was also observed in the series of hydroxylamines. With a factor of 41 (**11**/**10**) the effect is somewhat larger than in the series of amines (**14**/**13** factor of 20) and hydrazines (**4**/**1** factor of 11).

We will now compare the effects of heteroatom substitution. While replacement of one hydrogen in NH_3 by methyl increases the reactivity 2.6 × 10^2 fold, the NH_2 group activates by a factor of 96 (**1**/**12**) and OH by a factor of 2.8 (**10**/**12**). Slight retarding effects are observed for the formamido group (**6**/**12**, factor 0.28) and the *tert*-butoxycarbonylamido group (**8**/**12**, factor 0.86), whereas the benzamido group in **9** induces a 2.7-fold higher reactivity.

A similar trend can be observed in the series of the secondary reaction centers (second row of Figure 5). While methylation of methylamine activates by a factor of 20 (**14**/**13**), amination activates less (**4**/**13** = 4.1) and hydroxylation even deactivates slightly (**11**/**13** = 0.45).

The third row of Figure 5 shows that replacement of H in dimethylamine by methyl activates only 2.6-fold (**15**/**14**) and that replacement of H by NH_2 does not affect the

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nucleophilicity (**2** ≈ **14**), while the formamido group deactivates significantly (**7**/**14** = 1/3.0 × 10^2).

In summary, in all three rows discussed, hydrazines R_2N-NH_2 are generally less nucleophilic than the corresponding amines R_2N-Me, independent of the nature of R.

Though the absolute rate constants for the reactions of amines and hydrazines are approximately 10^2 times smaller in water than in acetonitrile, the relative reactivities of ammonia (**12**), primary and secondary amines, and hydrazines are almost identical in the two solvents (Figure 6). One, therefore, has to conclude that the differences in reactivities of the amines and hydrazines derived from these kinetic data reflect intrinsic properties of these nucleophiles, which are only slightly affected by solvation. Only hydroxylamine (**10**) deviates somewhat, as it reacts 13 times faster than ammonia (**12**) in water, while the reactivity ratio is only 2.8 in acetonitrile. Possibly, in water the electrophilic attack at nitrogen is accompanied by simultaneous deprotonation of the amino group.

Correlation of Kinetic with Thermodynamic Data. As shown in Figure 7, the rate constants of the reactions of amines

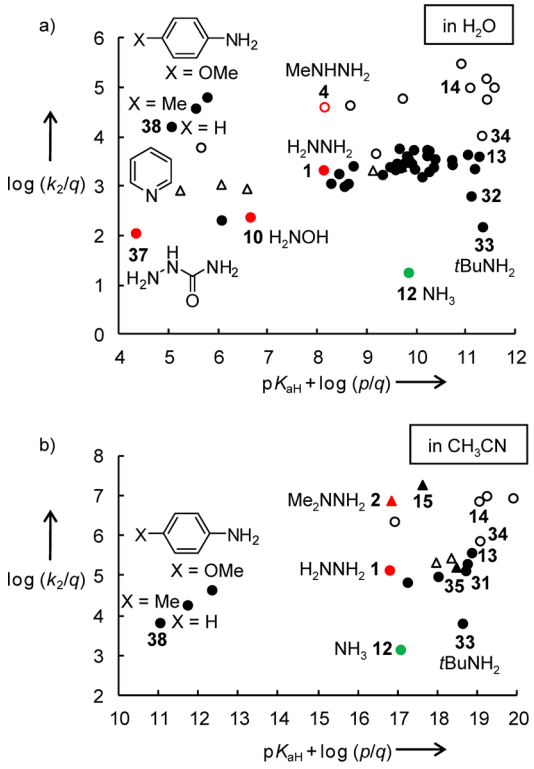

Figure 7. Brønsted plots of the statistically corrected second-order rate constants versus the statistically corrected basicities[14,26] for the reactions of $(dma)_2CH^+$ (**16i**) with amines at 20 °C (a) in H_2O and (b) acetonitrile (p = number of equivalent protons of the conjugated acids;[25c,27] q = number of equivalent nucleophilic centers;[25c,27] filled circles: primary amines, open circles: secondary amines, filled triangles: tertiary amines; open triangles: pyridines; green symbols: ammonia (**12**); red symbols: α-nucleophiles).[11,14]

and hydrazines with $(dma)_2CH^+$ (**16i**) in water (Figure 7a) and acetonitrile (Figure 7b) are not correlated with their basicities, in agreement with earlier reports.[14d,h,25] One can see some general trends, however, which were previously reported for reactions with other electrophiles:[6j,o,v,w] Secondary amines (open circles in Figure 7) generally react faster than primary amines (filled circles in Figure 7) of the same basicities, which are again more reactive than ammonia (**12**, green circles in Figure 7). Among the primary amines, anilines have the lowest basicities but nevertheless are among the strongest nucleophiles in water and react with similar rates as other primary amines in acetonitrile.[14d,h] Increasing size of the alkyl groups reduces the nucleophilic reactivities but not the Brønsted basicities as shown by the low reactivities of isopropylamine (**32**) and *tert*-butylamine (**33**) compared to other primary amines or by the greatly reduced reactivity of triethylamine (**35**) in comparison with the slightly less basic trimethylamine (**15**).

When the Brønsted-type correlation for the reactions in water is restricted to structurally related α-unbranched primary amines, a linear correlation with β_{Nu} = 0.22 is obtained, from which hydrazine (**1**), hydroxylamine (**10**), and semicarbazide (**37**) do not deviate significantly (Figure 8a). This observation

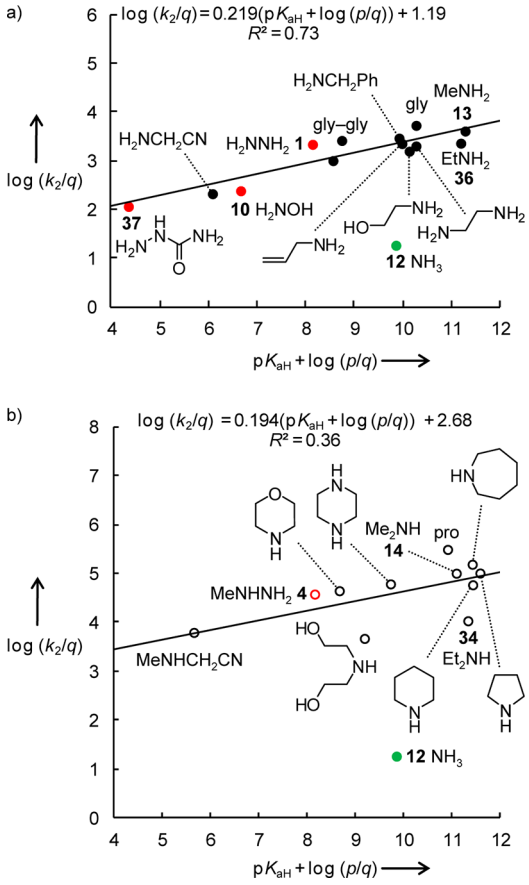

Figure 8. Brønsted plots of the statistically corrected second-order rate constants versus the statistically corrected basicities[14,26] for the reactions of $(dma)_2CH^+$ (**16i**) with (a) unbranched primary and (b) secondary amines in H_2O at 20 °C (p = number of equivalent protons of the conjugated acids;[25c,27] q = number of equivalent nucleophilic centers[25c,27]).[14]

contrasts an earlier report that α-nucleophiles, including hydrazine (**1**), methylhydrazine (**4**), and semicarbazide (**37**), showed an upward deviation of 1.5 orders of magnitude in an analogous Brønsted correlation for the reactions of malachite green with primary amines (β_{nuc} = 0.42).[6s] Though previous analyses indicated that the magnitude of the α-effect increases with β_{nuc},[5,6i,l,o] the large difference in reactions with benzhydrylium ions and malachite green is surprising.

The Brønsted correlation for the reactions of secondary amines with the benzhydrylium ion **16i** shows more scatter

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(Figure 8b) than that of the primary unbranched amines (Figure 8a). Again, no significant deviation for the α-nucleophile methylhydrazine (**4**) is observed.

As previously reported, the reactions of stabilized benzhydrylium ions with tertiary amines proceed incompletely, in contrast to the analogous reactions with primary or secondary amines, where the initially formed ammonium ions are subsequently deprotonated.[14a,f] We were, therefore, able to determine equilibrium constants for the reactions of benzhydrylium ions with 1,4-diazabicyclo[2.2.2]octane (DABCO; **39**) and quinuclidine (**40**) in acetonitrile.[14f]

An analogous determination of equilibrium constants for the attack of benzhydrylium ions at the NMe_2 groups of the hydrazines **2** and **3** was impossible, because the initial formations of the quaternary hydrazinium ions were reversible and the benzhydrylium ions were consumed completely by the subsequent slower reactions with the adjacent NH_2 or NHMe group (Scheme 1). However, when the reactions of the carbocations **16h,i** with high concentrations of **2** were monitored on the μs time scale using the laser-flash photolysis setup, monoexponential decays of the absorbances of **16h,i** were found (Figure 9).[11] After these decays, which correspond

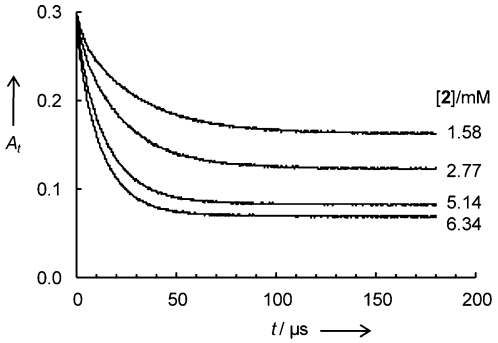


Figure 9. Exponential decays of the absorbance at λ = 605 nm on the μs time scale during the reaction of **16i** generated from **16i**-PBu_3 (1.41×10^{-5} M) with different concentrations of 1,1-dimethylhydrazine (**2**) in acetonitrile at 20 °C.

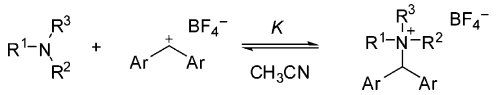
to the fast attack at the NMe_2 group ($k_2' = 3.78 \times 10^6$ M^{-1} s^{-1} for **16h** and 8.05×10^6 M^{-1} s^{-1} for **16i**), the benzhydrylium absorbances reached plateaus because the subsequent reactions at the NH_2 group ($k_2 = 1.44 \times 10^3$ M^{-1} s^{-1} for **16h** and 2.46×10^3 M^{-1} s^{-1} for **16i**) occurred on the seconds time scale.

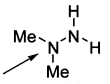
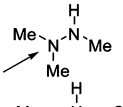
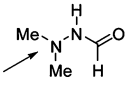
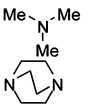
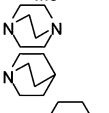
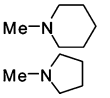
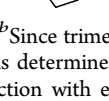
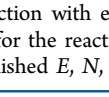
From the initial absorbances (A_0) of the benzhydrylium ions generated by the 7 ns laser pulse and the absorbances at the plateaus on the microsecond time scale (A_{eq}), the equilibrium constants (K) as defined by eq 7 were determined as the slopes of the linear correlations of $(A_0 - A_{eq})/A_{eq}$ with [Nu] (Table 3).

$$K = \frac{[Ar_2CHNu^+]}{[Ar_2CH^+][Nu]} = \frac{A_0 - A_{eq}}{A_{eq}[Nu]} \quad (7)$$

We were not able to determine the equilibrium constants for the reactions of other benzhydrylium ions with **2**. The better stabilized carbocations (**16d–f**) gave such low concentrations of quaternary hydrazinium ions by attack at the NMe_2 group that only the slower reactions at the NH_2 group were observable.[11] With more reactive carbocations (**16j–k**), on the other hand, the formation of the quaternary hydrazinium ions was almost quantitative, even when low concentrations of

Table 3. Equilibrium Constants K for the Reactions of Benzhydrylium Ions Ar_2CH^+ (16) with the Hydrazines Containing Tertiary Nitrogen Centers 2, 3, 7 and the Tertiary Amines 15 and 39–42 in Acetonitrile at 20 °C



	Amine	Ar_2CH^+	K [M^{-1}]	k_2 [M^{-1} s^{-1}]
2		**16h**	3.3×10^1	3.78×10^6 [a]
		16i	4.7×10^2	8.06×10^6 [a]
3		**16j**	1.0×10^3	3.00×10^6 [a]
7		**16l**	1.9×10^1	2.18×10^7
		16m	1.1×10^2	4.08×10^7
		16n	1.2×10^3	1.08×10^8
15 [b]		**16h**	1.3×10^2	6.54×10^6
		16i	1.2×10^3	2.00×10^7
39		**16h**	4.89×10^3 [c]	6.95×10^7 [c]
40		**16h**	4.49×10^4 [c]	5.22×10^7 [c]
41		**16h**	5.9	5.44×10^5 [d]
42		**16h**	3.5×10^2	7.19×10^6 [e]

[a]From ref 11. [b]Since trimethylamine (**15**) was used as a 33% ethanolic solution, K was determined from measurements on the μs time scale, where the reaction with ethanol did not occur. [c]From ref 14f. [d]The rate constant for the reactions of **41** with **16h** was calculated by eq 1 using the published E, N, and s_N parameters.[14a] [e]From ref 14a.

the hydrazine **2** were used, such that the determination of K was again impossible.

For the same reasons, the reaction of the benzhydrylium ion **16j** with trimethylhydrazine (**3**) was the only one for which the equilibrium constant for the attack at the NMe_2 group of **3** could be determined.

Equilibrium constants for the reactions of **16l–n** with the NMe_2 group of *N*′,*N*′-dimethylformohydrazide (**7**) were similarly determined on the microsecond time scale, because the fast initial reactions were followed by unknown subsequent reactions on a slower time scale. As the subsequent reactions were not considerably slower than the initial ones, the equilibrium constants K were determined from the initial absorbances A_0 and the constant C obtained by fitting the monoexponential function $A = A_0\ e^{-k_{obs}t} + C$ to the time-dependent absorbances.

Due to unknown subsequent reactions it was also impossible to determine the equilibrium constants for the formation of quaternary ammonium ions from the benzhydrylium ions **16g–n** with *N*-methylpiperidine (**41**) and *N*-methylpyrrolidine (**42**) using conventional UV–vis spectrometers.[14a] Therefore, the corresponding equilibrium constants were determined by the same procedure described above for the 1,1-dimethylhydrazines.

A correlation of the rate constants for the reactions of the tertiary amines and hydrazines with $(pyr)_2CH^+$ BF_4^- (**16h**) with the corresponding equilibrium constants is linear with a slope of 0.52 (Figure 10) from which 1,1-dimethylhydrazine (**2**) and trimethylhydrazine (**3**)[28] do not deviate.

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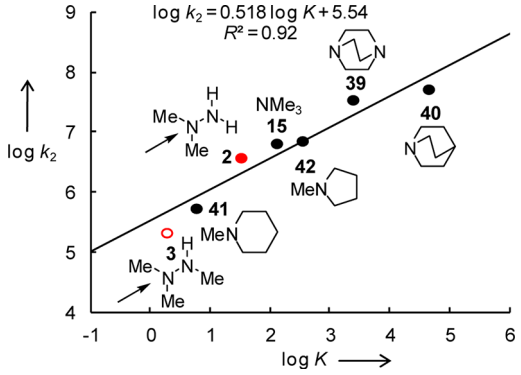

Figure 10. Plot of the rate constants for reactions of tertiary amines with $(pyr)_2CH^+$ BF_4^- (**16h**) in acetonitrile at 20 °C versus the corresponding equilibrium constants (black: tertiary amines; red: 1,1-dimethylhydrazines). Data points for **2** and **3** were not included for the determination of the slope. The rate constant for the reactions of **3** with **16h** was calculated with the published E, N, and s_N parameters.[11] The rate and equilibrium constants for the reaction of **16h** with DABCO (**39**) were statistically corrected by a factor of 2.

CONCLUSION

As previously described for numerous classes of nucleophiles,[10] including amines,[14] the reactions of hydrazines and hydroxylamines with benzhydrylium ions follow the linear free energy relationship eq 1, which provides a quantitative comparison of their nucleophilicities and allows us to include them into our comprehensive nucleophilicity scale.[10] Remarkably, alkyl effects are almost identical in the amine and hydrazine series, i.e., in both series methyl substitution in the α-position causes a significant increase of nucleophilicity, whereas methyl substitution in the β-position causes a significant decrease of nucleophilicity.

If the enhanced nucleophilicity of hydrazine (factor of 10^2) and hydroxylamine (factor of 3) relative to ammonia is assigned to an α-effect, one has to realize that this α-effect is smaller than the activating effect of the α-methyl group in methylamine, whatever its origin is. The problem of the reference system remains, when we follow the current, more generally accepted definition for the α-effect, that α-nucleophiles show positive deviations in Brønsted plots.

Though we feel unable to interpret the contrasting results obtained with malachite green, our investigations clearly show that neither hydrazines nor hydroxylamine deviate from log k_2 versus pK_{aH} correlations for the reactions of primary alkylamines with benzhydrylium ions. If alkylamines are considered as references, the common log k_2 versus pK_{aH} correlation implies that neither hydrazines nor hydroxylamines show an α-effect. However, one might also argue that alkyl groups, like NH_2 and OH, show an α-effect, because NH_3 is considerably below their common correlation line. Whatever definition is employed, as anilines are more reactive than ammonia and are considerably more nucleophilic than isobasic hydrazines and hydroxylamines, they should be considered as α-effect amines par excellence.

In order to elucidate the significance of the α-effect in reactions with other electrophiles we are presently investigating the kinetics of the reactions of amines, hydrazines, and hydroxylamines with acyl derivatives and alkyl halides.

EXPERIMENTAL SECTION

Materials. The benzhydrylium tetrafluoroborates (**16d–n**)-BF_4[10c] and quinone methides **16a–c**[10b,29] were synthesized as described in the literature. Hydrazine monohydrate (**1**·H_2O), hydroxylamine hydrochloride (**10**·HCl), *N*-methylhydroxylamine hydrochloride (**11**·HCl), methylamine hydrochloride (**13**·HCl), dimethylamine hydrochloride (**14**·HCl), and trimethylamine (**15**, 33% ethanolic solution) were purchased and used without further purification. Methylhydrazine (**4**), benzohydrazide (**9**), and 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU) were purchased and purified by distillation or recrystallization prior to use. *N*-Methylpiperidine (**41**) and *N*-methylpyrrolidine (**42**) were distilled over $LiAlH_4$ prior to use. Commercially available 1,2-dimethylhydrazine hydrochloride (**5**·HCl) was deprotonated with NaOH in analogy to a literature procedure.[30] Solutions of ammonia (**12**) in acetonitrile were prepared by gas injection.

Formohydrazide (**6**),[31] *N*′,*N*′-dimethylformohydrazide (**7**),[30] *tert*-butyl hydrazinecarboxylate (**8**),[32] and $(dma)_2CHNH_2$ (**26**)[23] were synthesized according to literature procedures. Trimethylhydrazine (**3**) has been synthesized as described previously.[11]

The phosphonium tetrafluoroborates (**16h–k**)-PBu_3 were prepared by adding equimolar amounts of PBu_3 to solutions of the benzhydrylium tetrafluoroborates (**16h–k**), which gave completely or almost colorless solutions.[33] The phosphonium tetrafluoroborates (**16l–n**)-PPh_3 were obtained by reactions of the benzhydrols (**16l–n**)OH with $HPPh_3^+$ BF_4^-.[34]

Acetonitrile (>99.9%, extra dry) was purchased and used without further purification. Water was distilled and passed through a water purification system (resistivity 18 MΩ/cm).

Analytics. In the ^1H and ^{13}C NMR spectra the chemical shifts in ppm refer to tetramethylsilane (δ_H = 0.00) or the solvent residual signals as internal standard: $CDCl_3$ (δ_H = 7.26, δ_C = 77.0), CD_3CN (δ_H = 1.94, δ_C = 1.32), or d_6-DMSO (δ_H = 2.50, δ_C = 39.5). The following abbreviations were used for signal multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. NMR signal assignments were based on additional 2D-NMR experiments (COSY, HSQC, and HMBC). For reasons of simplicity, the ^1H NMR signals of AA′BB′-spin systems of *p*-substituted aromatic rings were treated as doublets.

HRMS in EI mode (70 eV) were determined with sector field detectors. HRMS-ESI spectra were obtained on an Fourier transform ion cyclotron resonance mass spectrometer (IonMax ion source, 4 kV).

Product Characterization. *2,6-Di-tert-butyl-4-((1-methylhydrazinyl)(p-tolyl)methyl)-phenol (**17**).* Methylhydrazine (**4**, 25 μL, 0.48 mmol) was added to a solution of tol(*t*-Bu)$_2$QM (**16b**, 50 mg, 0.16 mmol) in acetonitrile (10 mL) over 5 min at rt. After 30 min of stirring, the volatile compounds were evaporated under reduced pressure: **17** (54 mg, 0.15 mmol, 94%), colorless crystals; mp 94–96 °C (hexane). ^1H NMR (400 MHz, CD_3CN): δ 1.38 (s, 18 H, $C(CH_3)_3$), 2.27 (s, 3 H, CH_3), 2.31 (s, 3 H, NCH_3), 4.08 (s, 1 H, Ar_2CH), 5.34 (br s, 1 H, OH), 7.10 (d, J = 7.8 Hz, 2 H, H_{ar}), 7.24 (s, 2 H, H_{ar}), 7.32 (d, J = 8.1 Hz, 2 H, H_{ar}). ^{13}C NMR (100 MHz, CD_3CN): δ 21.1 (q), 30.6 (q), 35.2 (s), 47.1 (q), 82.3 (d, Ar_2CH), 124.9 (d), 128.3 (d), 130.1 (d), 135.7 (s), 137.3 (s), 138.3 (s), 142.4 (s), 153.5 (s). HRMS (ESI, positive) m/z calcd for $C_{23}H_{35}N_2O^+$: 355.2744, found 355.2744.

*2,6-Di-tert-butyl-4-((1,2-dimethylhydrazinyl)(p-tolyl)methyl)-phenol (**18**).* 1,2-Dimethylhydrazine (**5**, 60 μL, 0.83 mmol) was added to a solution of tol(*t*-Bu)$_2$QM (**16b**, 100 mg, 0.324 mmol) in acetonitrile (15 mL) over 15 min at rt. After 30 min of stirring, the volatile compounds were evaporated under reduced pressure: **18** (117 mg, 0.317 mmol, 98%), colorless oil. ^1H NMR (400 MHz, CD_3CN): δ 1.40 (s, 18 H, $C(CH_3)_3$), 2.23 (s br, 1 H, NH), 2.27 (s, 3 H, CH_3), 2.30 (s, 3 H, NCH_3), 2.45 (s, 3 H, $NHCH_3$), 4.35 (s, 1 H, Ar_2CH), 5.29 (br s, 1 H, OH), 7.08 (d, J = 8.2 Hz, 2 H, H_{ar}), 7.24 (s, 2 H, H_{ar}), 7.30 (d, J = 8.1 Hz, 2 H, H_{ar}). ^{13}C NMR (100 MHz, CD_3CN): δ 21.1 (q), 30.7 (q), 35.2 (q), 35.5 (s), 42.3 (q), 78.1 (d, Ar_2CH), 124.9 (d), 128.4 (d), 129.8 (d), 136.4 (s), 136.9 (s), 137.9 (s), 142.7 (s), 153.2

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(s). HRMS (ESI, positive) m/z calcd for $C_{24}H_{37}N_2O^+$: 369.2900, found 369.2898.

*N′-(Bis(4-(dimethylamino)phenyl)methyl)-formohydrazide (**19**).* A solution of $(dma)_2CH^+BF_4^-$ (**16i**, 50 mg, 0.15 mmol) in acetonitrile (5 mL) was added to a solution of formohydrazide (**6**, 9.0 mg, 0.15 mmol) in acetonitrile (5 mL) at rt. Then trimethylamine (0.1 mL, 33% in ethanol) was added, and volatile compounds were evaporated under reduced pressure after 5 min stirring at rt. The residue was dissolved in $CDCl_3$ and filtered. According to the ^{1}H NMR, the product **19** was formed exclusively as a 2:1 mixture of the (*Z*)- and (*E*)-isomers.[35] ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.91 (s, 12 H, CH_3 *Z*), 2.92 (s, 12 H, CH_3 *E*), 4.14 (d, J = 5.6 Hz, 1 H, N*H*CH *E*), 4.81 (d, J = 5.0 Hz, 1 H, Ar_2CH *E*), 5.09 (s, 1 H, Ar_2CH *Z*), 6.67−6.69 (m, 9 H, 4 × H_{ar}, *Z*, 4 × H_{ar} *E*, N*H*CHO *E* superimposed), 6.97 (s, 1 H, N*H*CHO *Z*), 7.17 (d, J = 8.8 Hz, 4 H, H_{ar} *E*), 7.28 (d, J = 8.6 Hz, 4 H, H_{ar} *Z*), 8.00 (s, 1 H, CHO *Z*), 8.26 (d, J = 10.9 Hz, 1 H, CHO *E*). ^{13}C NMR (100 MHz, $CDCl_3$): δ 40.7 (q, $N(CH_3)_2$ *E*), 40.8 (q, $N(CH_3)_2$ *Z*), 67.6 (d, Ar_2CH *E*), 69.1 (d, Ar_2CH *Z*), 112.8 (d, ArH *Z* and *E* superimposed), 128.1 (s, q_{Ar} *E*), 128.5 (d, ArH *Z*), 128.5 (d, ArH *Z*), 129.5 (s, q_{Ar} *E*), 150.1 (s, q_{Ar} *Z*), 150.2 (s, q_{Ar} *E*), 160.0 (d, CHO *Z*), 166.9 (d, CHO *E*). HRMS (ESI, negative) m/z calcd for $C_{18}H_{23}N_4O^-$: 311.1877, found 311.1881.

*tert-Butyl 2-(bis(4-(dimethylamino)phenyl)methyl)-hydrazinecarboxylate (**20**).* *tert*-Butyl hydrazinecarboxylate (**8**, 39 mg, 0.30 mmol) was added to a solution of $(dma)_2CH^+BF_4^-$ (**16i**, 100 mg, 0.294 mmol) in acetonitrile (5 mL) and stirred for 5 min at rt. Then 2 M NaOH (10 mL) was added, and the solution was extracted with diethyl ether (15 mL). The ethereal phase was dried (Na_2SO_4) and filtered, and the volatile compounds were evaporated under reduced pressure: **20** (113 mg, 0.294 mmol, quantitative), colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.42 (s, 9 H, $C(CH_3)_3$), 2.88 (s, 12 H, $N(CH_3)_2$), 4.30 (s br, 1 H, NH), 5.11 (s, 1 H, Ar_2CH), 6.09 (s br, 1 H, NH), 6.66 (d, J = 8.9 Hz, 4 H, H_{ar}), 7.25 (d, J = 8.7 Hz, 4 H, H_{ar}). ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.5 (q), 40.8 (q), 67.2 (d, Ar_2CH), 80.2 (s), 112.7 (d), 128.6 (d), 130.2 (s), 149.9 (s), 156.7 (s). HRMS (EI, positive) m/z calcd for $C_{22}H_{32}N_4O_2^+$: 384.2520, found 384.2512.

*N′-(Bis(4-(dimethylamino)phenyl)methyl)-benzohydrazide (**21**).* Benzohydrazide (**9**, 60 mg, 0.44 mmol) was added to a solution of $(dma)_2CH^+BF_4^-$ (**16i**, 150 mg, 0.441 mmol) in acetonitrile (5 mL) over 5 min at rt. Then 2 M NaOH (5 mL) was added, the solution was extracted with diethyl ether (15 mL), and the ethereal phase was dried (Na_2SO_4) and filtered. The solvent was partially evaporated under reduced pressure, and the residue was cooled to −60 °C to crystallize the product: **21** (161 mg, 0.41 mmol, 93%), colorless crystals; mp 143−144 °C (Et_2O). ^{1}H NMR (300 MHz, CD_3CN): δ 2.88 (s, 12 H, CH_3), 5.10 (s br, 2 H, Ar_2CH, NH), 6.71 (d, J = 8.9 Hz, 4 H, H_{ar}), 7.28 (d, J = 8.8 Hz, 4 H, H_{ar}), 7.38−7.42 (m, 2 H, H_{ar}), 7.46−7.53 (m, 1 H, H_{ar}), 7.61−7.66 (m, 2 H, H_{ar}), 8.36 (d br, J = 6.4 Hz, 1 H, NH). ^{13}C NMR (75 MHz, CD_3CN): δ 40.9 (q), 68.3 (d, Ar_2CH), 113.5 (d), 128.0 (d), 129.3 (d), 129.5 (d), 131.6 (s), 132.5 (d), 134.5 (s), 151.2 (s), 167.9 (s). HRMS (ESI, negative) m/z calcd for $C_{24}H_{27}N_4O^-$: 387.2190, found 387.2190.

*N′-(Bis(4-(dimethylamino)phenyl)methyl)-hydroxylamine (**22**) and N,N-(Bis-(bis(4-(dimethylamino)phenyl)methyl))-hydroxylamine (**23**).* Trimethylamine (**15**, 0.5 mL 33% in ethanol, 0.1 mg, 2 mmol) was added to hydroxylamine hydrochloride (**10**·HCl, 85 mg, 1.2 mmol) at rt, and acetonitrile (10 mL) was added. A solution of $(dma)_2CH^+BF_4^-$ (**16i**, 75 mg, 0.22 mmol) in acetonitrile (10 mL) was added dropwise at rt. The solution was concentrated under reduced pressure, diethyl ether (5 mL) was added, the precipitate was filtered off, and volatile compounds were evaporated under reduced pressure. According to the ^{1}H NMR spectrum of the crude product, a 9:1 mixture of **22** and **23** was obtained. **22**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.89 (s, 12 H, CH_3), 5.05 (s, 1 H, Ar_2CH), 5.53 (br s, 2 H, NH and OH superimposed), 6.68 (d, J = 8.7 Hz, 4 H, H_{ar}), 7.22 (d, J = 8.8 Hz, 4 H, H_{ar}). ^{13}C NMR (75 MHz, $CDCl_3$): δ 40.8 (q), 69.6 (d, Ar_2CH), 112.8 (d), 128.6 (d), 129 (s), 150.0 (s). HRMS (EI, positive) m/z calcd ($C_{17}H_{24}N_3O^+$) 286.1914, found 286.1914. **23**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.89 (s, 24 H, CH_3), 4.81 (s, 2 H, Ar_2CH), 5.53 (br s, 1 H, OH superimposed by **22**), 6.68 (d, 8.7, 8 H, H_{ar}), 7.29 (d, J = 8.7 Hz, 8 H, H_{ar}). ^{13}C NMR (75 MHz, $CDCl_3$): δ 40.9 (q), 70.2 (d, Ar_2CH), 112.6 (d), 129.6 (d), 130.6 (s), 149.6 (s).

*N-(Bis(4-(dimethylamino)phenyl)methyl)-N-methylhydroxylamine (**24**).* Trimethylamine (**15**, 0.3 mL 33% in ethanol, 0.08 g, 1 mmol) was added to *N*-methylhydroxylamine hydrochloride (**11**·HCl, 60 mg, 0.72 mmol) at rt. A solution of $(dma)_2CH^+BF_4^-$ (**16i**, 100 mg, 0.294 mmol) in acetonitrile (5 mL) was added dropwise over 5 min. The 2 M NaOH (10 mL) was added, and the solution was extracted with diethyl ether (15 mL). The ethereal phase was dried (Na_2SO_4) and filtered, and the volatile compounds were evaporated under reduced pressure: **24** (67 mg, 0.22 mmol, 76%), colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.56 (s, 3 H, $N(OH)(CH_3)$), 2.87 (s, 12 H, $N(CH_3)_2$), 4.43 (s, 1 H, Ar_2CH), 5.16 (s br, 1 H, OH), 6.65 (d, J = 8.8 Hz, 4 H, H_{ar}), 7.28 (d, J = 8.7 Hz, 4 H, H_{ar}). ^{13}C NMR (100 MHz, $CDCl_3$): δ 40.8 (q), 46.2 (q), 79.0 (d, Ar_2CH), 112.8 (d), 128.5 (d), 130.8 (s), 149.8 (s). HRMS (EI, positive) m/z calcd for $C_{18}H_{25}N_3O^+$: 299.1998, found 299.2006.

*N-(Bis(1,2,3,5,6,7-hexahydropyrido(3,2,1-ij)quinolin-9-yl)methyl)-hydroxylamine (**25**).* Trimethylamine (**15**, 0.5 mL 33% in ethanol, 0.1 mg, 2 mmol) was added to hydroxylamine hydrochloride (**10**·HCl, 7.8 mg, 0.11 mmol) at rt. A solution of $(jul)_2CH^+BF_4^-$ (**16e**, 50 mg, 0.11 mmol) in acetonitrile (5 mL) was added dropwise at rt. The solution was concentrated under reduced pressure, diethyl ether (5 mL) was added, the precipitate was filtered off, and volatile compounds were evaporated under reduced pressure: **25** (41 mg, 0.11 mmol, quant.), colorless oil. ^{1}H NMR (400 MHz, d_6-DMSO): δ 1.24 (s br, 1 H, NH), 1.80−1.86 (m, 8 H, $CH_2CH_2CH_2$), 2.61 (t, J = 6.5 Hz, 8 H, $CH_2CH_2CH_2N$), 3.02 (t, J = 5.5 Hz, 8 H, $CH_2CH_2CH_2N$), 4.57 (s, 1 H, Ar_2CH), 6.64 (s, 4 H, H_{Ar}), 7.15 (s br, OH). ^{13}C NMR (100 MHz, d_6-DMSO): δ 21.8 (t), 27.2 (t), 49.4 (t), 69.4 (d, Ar_2CH), 120.4 (s), 125.8 (d), 130.0 (s), 141.4 (s). HR-MS (ESI, positive) m/z calcd for $C_{25}H_{29}N_2^+$ $[M - NHOH]^+$: 357.2325, found 357.2325.

*Bis(bis(4-(dimethylamino)phenyl)methyl)-amine (**27**).* A solution of $(dma)_2CH^+BF_4^-$ (**16i**, 100 mg, 0.294 mmol) in acetonitrile (10 mL) was added to a solution of ammonia (**12**, 10 mL, 0.54 M, 5.4 mmol) in acetonitrile over 30 min at rt. After diethyl ether (20 mL) was added, the solution was washed with 2 M NaOH (25 mL), dried (Na_2SO_4), and filtered, and the solvent was evaporated under reduced pressure: **27** (75 mg, 0.14 mmol, 98%), colorless crystals; mp 191−192 °C (pentane), lit.[24] mp 188 °C (benzene, ethanol). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.62 (s br, 1 H, NH), 2.91 (s, 24 H, $N(CH_3)_2$), 4.61 (s, 2 H, Ar_2CH), 6.68 (d, J = 8.8 Hz, 8 H, H_{ar}), 7.22 (d, J = 8.7 Hz, 8 H, H_{ar}). ^{13}C NMR (75 MHz, $CDCl_3$): δ 41.0 (q), 62.2 (d, Ar_2CH), 112.8 (d), 128.4 (d), 133.5 (s), 149.6 (s). HRMS (EI, positive) m/z calcd for $C_{34}H_{43}N_5^+$: 521.3518, found 521.3513.

*(Bis(4-(dimethylamino)phenyl)methyl)-methylamine (**28**).* Methylamine (**13**, 1 mL, 33% in ethanol, 0.2 g, 8 mmol) was added to a solution of $(dma)_2CH^+BF_4^-$ (**16i**, 100 mg, 0.294 mmol) in acetonitrile (10 mL) and stirred for 5 min at rt. Then 2 M NaOH (10 mL) was added, and the solution was extracted with diethyl ether (15 mL). The ethereal phase was dried ($MgSO_4$) and filtered, and the volatile compounds were evaporated under reduced pressure: **28** (82 mg, 0.29 mmol, 98%), colorless crystals; mp 125−126 °C (pentane). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.39 (s, 3 H, $NH(CH_3)$), 2.90 (s, 12 H, $N(CH_3)_2$), 4.54 (s, 1 H, Ar_2CH), 6.68 (d, J = 8.8 Hz, 4 H, H_{ar}), 7.23 (d, J = 8.7 Hz, 4 H, H_{ar}). ^{13}C NMR (75 MHz, $CDCl_3$): δ 35.2 (q), 40.9 (q), 68.4 (d, Ar_2CH), 112.9 (d), 128.0 (d), 132.9 (s), 149.7 (s). HRMS (EI, positive) m/z calcd for $C_{18}H_{25}N_3^+$: 283.2048, found 283.2038.

*(Bis(4-(dimethylamino)phenyl)methyl)-dimethylamine (**29**).* Dimethylamine (**14**, 0.5 mL 40% in water, 0.2 g, 4 mmol) was added to a solution of $(dma)_2CH^+BF_4^-$ (**16i**, 100 mg, 0.294 mmol) in acetonitrile (10 mL) and stirred for 5 min at rt. Then 2 M NaOH (10 mL) was added, and the solution was extracted with diethyl ether (15 mL). The ethereal phase was dried (Na_2SO_4) and filtered, and the volatile compounds were evaporated under reduced pressure: **29** (89 mg, 0.30 mmol, quantitative), pale yellow crystals; mp 92−93 °C (hexane), lit.[36] mp 94 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.19 (s, 6 H, $Ar_2CHN(CH_3)_2$), 2.88 (s, 12 H, $N(CH_3)_2$), 3.91 (s, 1 H, Ar_2CH), 6.65 (d, J = 8.8 Hz, 4 H, H_{ar}), 7.25 (d, J = 8.9 Hz, 4 H, H_{ar}). ^{13}C NMR

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(75 MHz, $CDCl_3$): δ 40.9 (q), 44.9 (q), 76.8 (d, Ar_2CH), 112.8 (d); 128.5 (d), 132.2 (s), 149.6 (s). HRMS (EI, positive) m/z calcd for $C_{19}H_{27}N_3^+$: 297.2205, found 297.2201.

(Bis(4-(methoxy)phenyl)methyl)-trimethylammonium chloride (30). A solution of $(ani)_2CHCl$ (**16n**-Cl, 50 mg, 0.19 mmol) in acetonitrile (5 mL) was added to trimethylamine (**15**, 0.2 mL 33% in ethanol, 0.05 g, 0.8 mmol) at rt. Volatile compounds were evaporated under reduced pressure: **30** (60.5 mg, 0.188 mmol, 99%) colorless oil. ^{1}H NMR (400 MHz, CD_3CN): δ 3.16 (s, 9 H, $N(CH_3)_3$), 3.77 (s, 6 H, OCH_3), 6.86 (s, 1 H, Ar_2CH), 6.98 (d, J = 9.0 Hz, 4 H, H_{ar}), 7.91 (d, J = 8.9 Hz, 4 H, H_{ar}). ^{13}C NMR (100 MHz, CD_3CN): δ 52.2 (q), 56.2 (q), 79.5 (d, Ar_2CH), 115.5 (d), 126.3 (s), 133.8 (d), 161.7 (s). HRMS (ESI, negative) m/z calcd for $C_{18}H_{24}Cl_2NO_2^-$: 356.1190, found 356.1196.

Kinetic Experiments. The kinetics of the reactions of **1**−**15** and **26** with the benzhydrylium ions and quinone methides **16** were followed by UV−vis spectroscopy in acetonitrile or water at 20 °C.

For slow reactions ($\tau_{1/2}$ > 10 s), the spectra were collected at different times by using a diode array spectrophotometer that was connected to a quartz immersion probe (5 mm light path) by fiber optic cables with standard SMA connectors. All kinetic measurements in CH_3CN were carried out in Schlenk glassware under exclusion of moisture. The temperature of the solutions during the kinetic studies was maintained at 20 ± 0.1 °C and monitored with a thermocouple probe that was inserted into the reaction mixture.

Stopped-flow spectrophotometer systems were used for the investigation of faster reactions (10 ms < $\tau_{1/2}$ < 10 s). The kinetic runs were initiated by mixing equal volumes of the solutions of the amines and the electrophiles **16**.

Reactions with $\tau_{1/2}$ < 10 ms were analyzed by laser-flash photolytic generation of **16h**−**n** from phosphonium ions in presence of excess nucleophile. Solutions of the carbocation precursors were irradiated with a 7 ns pulse from a quadrupled Nd:YAG laser (266 nm, 40−60 mJ/pulse), and a xenon lamp was used as probe light for UV−vis detection. The system was equipped with a fluorescence flow cell and a synchronized pump system, which allows complete exchange of the sample volume between subsequent laser pulses. For each concentration, ≥ 50 individual measurements were averaged.[37]

The nucleophiles **1**−**15** and **26** were used in large excess (>8 equiv) relative to the electrophiles **16** to ensure first-order conditions with $k_{obs} = k_2[Nu]_0 + k_0$. From the exponential decays of the absorbances at λ_{max} of **16**, the first-order rate constants k_{obs} (s^{-1}) were obtained by least-squares fitting to the single-exponential curve $A_t = A_0\, e^{-k_{obs}t} + C$. The slopes of plots of k_{obs} versus the concentrations of the nucleophiles yielded the second-order rate constants k_2 ($M^{-1}\ s^{-1}$).

Stock solutions of hydroxylamine (**10**), *N*-methylhydroxylamine (**11**), methylamine (**13**), and dimethylamine (**14**) were generated for the kinetic measurements by partial deprotonation of the corresponding hydrochloride salts with 0.50−0.95 equiv of DBU. For the reactions of **13** with **16 h**−**i** and of **14** with **16d**, KO*t*Bu has been used as alternative deprotonation agent. Stock solutions of ammonia (**12**) were prepared by gas injection in acetonitrile, and trimethylamine was used as a 33% solution in ethanol. In both cases, the concentrations of the stock solutions were determined by titration with hydrochloric acid.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Details of kinetic experiments and NMR spectra of all compounds characterized. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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