

Nucleophilic Reactivities of Pyrroles

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The second-order rate constants of the reactions of alkyl-substituted pyrroles with a series of benzhydrylium ions were determined in acetonitrile, and the reaction products were fully characterized by NMR spectroscopy and mass spectrometry. The formation of the σ adducts is the rate-limiting step of these reactions. Because the second-order rate constants correlate linearly with the electrophilicity parameters of the benzhydrylium ions, the determination of the nucleophilicity parameters N and s according to the linear free energy relationship $\log k_2$ (20 °C) = $s(N + E)$ was achieved. With these findings, a direct comparison of the nucleophilic reac-

tivities of these π -excessive heterocycles with other nucleophiles became possible, and the pyrroles were integrated into the comprehensive scale of nucleophilicity, covering a range of 8–9 orders of magnitude from *N*-(triisopropylsilyl)pyrrole ($N = 3.12$), the weakest nucleophile of this series, to kryptopyrrole (3-ethyl-2,4-dimethylpyrrole, $N = 11.63$). Thus, highly reactive pyrroles show similar nucleophilic reactivities as enamines, whereas those of less-reactive pyrroles are comparable to allylsilanes or indoles.

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Introduction

Pyrrole and its derivatives are biochemically important compounds and can be found as substructures in many natural products, for example, heme, chlorophyll, and the pyrrole alkaloids.^[1] Electrophilic substitution of pyrroles, which comprise electron-rich π -systems, have been investigated intensively.^[2] In 1957, Treibs and Fritz derived a qualitative reactivity scale for alkyl-substituted pyrroles from their reactivities towards diazonium salts of variable electrophilicity.^[3] The most comprehensive quantitative comparison of the reactivities of arenes and heteroarenes has been based on the σ^+_{arene} constants, which are defined by the Hammett–Brown relationship [Equation (1)].^[2c,4]

$$\log k/k_0 = \rho\sigma^+_{\text{arene}} \quad (1)$$

The σ^+_{arene} constants (equivalent to σ_p^+ or σ_m in the case of monosubstituted benzenes) are a measure for the relative reactivities of one position of an arene or heteroarene in relation to one position of benzene. They were typically derived by competition experiments, where an electrophile was allowed to select between a pair of arenes or from the rates

of S_N1 reactions of the side chain of the corresponding arenes.^[4]

However, σ^+_{arene} parameters have only been determined for the parent pyrrole and *N*-methylpyrrole. As knowledge of the nucleophilic reactivities of pyrroles is crucial for their well-directed use in synthesis,^[5] particularly as nucleophiles in organocatalysis cycles (iminium catalysis),^[6] we set out to obtain quantitative information on the nucleophilicities of alkyl-substituted pyrroles (Figure 1).

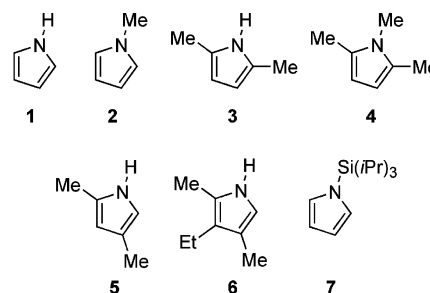


Figure 1. Structures of pyrroles 1–7.

We previously reported that the reactions of carbocations with π systems follow Equation (2) where electrophiles are characterized by one parameter (electrophilicity E) and nucleophiles are characterized by two parameters (nucleophilicity N and slope s).^[7] Recently, it was demonstrated that Equation (2) can also be employed for S_N2 reactions if an additional, electrophile-specific parameter s_E is included.^[8]

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$$\log k_2 (20^\circ\text{C}) = s(N + E)$$

(2)

The reactivity parameters N and s of N -methylpyrrole (**2**, $N = 5.85$, $s = 1.03$)^[7b,9] and N -(triisopropylsilyl)pyrrole (**7**, $N = 3.12$, $s = 0.93$)^[10] were already determined in dichloromethane solution, and the N parameter of the parent pyrrole (**1**, $N = 4.63$) was estimated.^[10] We have now studied the reactions of four alkyl-substituted pyrroles **3–6** with a series of benzhydrylium ions **8** (for structures see Table 1) in acetonitrile solution and used the kinetic data to determine the N and s parameters of these pyrroles.

Table 1. List of benzhydrylium ions Ar_2CH^+ (**8**) used in this study as reference electrophiles.

Reference electrophile ^[a]	E ^[b]
	(lil) ₂ CH ⁺ (8a)
	(jul) ₂ CH ⁺ (8b)
	(ind) ₂ CH ⁺ (8c)
	(pyr) ₂ CH ⁺ (8d)
	(dma) ₂ CH ⁺ (8e)
	(mpa) ₂ CH ⁺ (8f)
	(mor) ₂ CH ⁺ (8g)
	(dpa) ₂ CH ⁺ (8h)
	(mfa) ₂ CH ⁺ (8i)
	(pfa) ₂ CH ⁺ (8j)

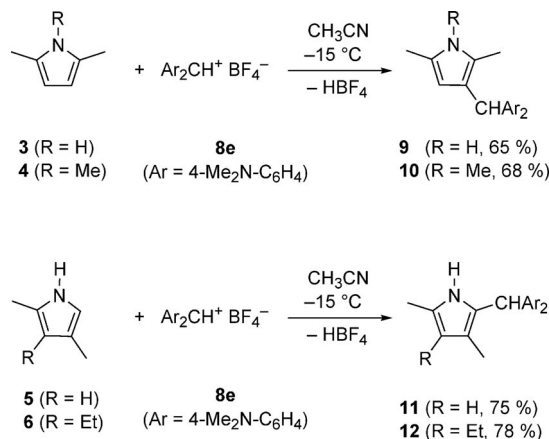
[a] Counterion: BF_4^- . [b] Electrophilicity parameters E are from ref.^[7b]

Results and Discussion

Product Characterization

Product studies were performed with the 4,4'-bis(dimethylamino)benzhydrylium ion $[(\text{dma})_2\text{CH}^+]$, **8e**, $E =$

-7.02] because it is readily available and reacts fast with most of the pyrroles **3–6**. When $(\text{dma})_2\text{CH}^+\text{BF}_4^-$ (**8e-BF₄**) was combined with pyrroles **3–6** in acetonitrile at room temperature, the resulting NMR spectra indicated the formation of complex product mixtures. Reactions proceeded smoothly, however, with selective formation of **9–11**, when solutions of **8e-BF₄** in acetonitrile were added dropwise to vigorously stirred solutions of the corresponding pyrroles (2 equiv.) in acetonitrile at -15°C . Compound **12** was synthesized by dropping a solution of kryptopyrrole (**6**) into a cooled solution (-15°C) of **8e-BF₄** until the blue color of carbocation **8e** vanished (Scheme 1).



Scheme 1. Products of the reactions of pyrroles **3–6** with **8e-BF₄** in CH_3CN at -15°C .

Reaction products **9–12** are highly sensitive towards oxidants, light, and heating; they usually turned into pink oils within several minutes. The NMR spectra of these oils, however, only show trace amounts of impurities and indicate the structures of **9–12** (for details see the Supporting Information). The products of the reactions of pyrroles **1**, **2**, and **7** with benzhydrylium ions **8** were characterized previously.^[9,10]

Whereas pyrroles **3**, **4**, and **6** have only one site for electrophilic attack, pyrrole **5** may, in principle, be attacked at C-3 and C-5. From the NMR spectra we can derive that regioselective substitution of 5-H took place. The proton of the $-\text{CHAr}_2$ moiety absorbs as a singlet at $\delta = 5.13$ – 5.16 ppm when it is attached to the 3-position of pyrrole (in compounds **9** and **10**) and at $\delta = 5.33$ – 5.36 ppm when it is located in the 2-position of the pyrrole ring (in compounds **11** and **12**). In the ^{13}C NMR spectra, the benzhydryl $-\text{CHAr}_2$ carbon atom of **9–12** absorbs at $\delta = 45.1$ – 46.5 ppm (Table 2).

Table 2. NMR chemical shifts of the CHAr_2 group of **9–12** (in CDCl_3).

Compound	δ_{H} / ppm	δ_{C} / ppm
9	5.13	45.1
10	5.16	45.3
11	5.33	46.5
12	5.36	45.2

Kinetics of the Reactions of Pyrroles with Benzhydrylium Ions

The kinetics of the reactions of pyrroles **3–6** with benzhydrylium ions **8** were monitored by UV/Vis spectroscopy at 20 °C by using the previously described methods.^[11] Pyrroles **3–6** were used in high excess (usually >10 equiv.) to keep their concentrations almost constant throughout the reactions. Exponential decay of the absorbances of benzhydrylium ions **8** was observed for all reactions and linear correlations between the observed first-order rate constants and the pyrrole concentrations were obtained as demonstrated in Figure 2 for the combination of 1,2,5-trimethylpyrrole (**4**) with **8c**.

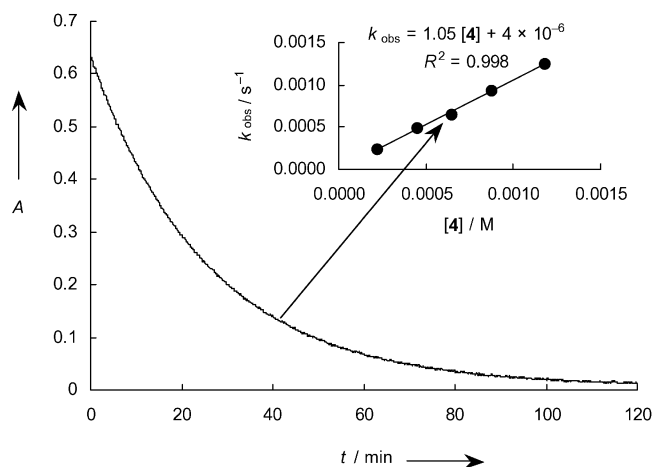


Figure 2. Exponential decay of the absorbance at 625 nm during the reaction of **4** (6.48×10^{-4} M) with **8c** (1.05×10^{-5} M). The correlation of the first-order rate constants k_{obs} with the concentrations of **4** (in the insert) is linear with a slope corresponding to the second-order rate constant k_2 .

The second-order rate constants of the reactions of pyrroles **3–6** with benzhydrylium ions **8** in CH_3CN are listed in Table 3.

When the reaction of 2,4-dimethylpyrrole (**5**) with $(\text{lil})_2\text{CH}^+$ (**8a**) was carried out in the presence of variable concentrations of 1,4-diazabicyclooctane (DABCO), the consumption of **8a** remained almost unaffected, which indicates that the formation of the σ complex is rate limiting. It was previously shown that the equilibrium constant for adduct formation from DABCO and $(\text{lil})_2\text{CH}^+$ (**8a**) is so small that at low concentrations coordination of these two substrates does not occur.^[12]

For the reaction of 2,5-dimethylpyrrole (**3**) with $(\text{dpa})_2\text{CH}^+$ (**8h**), a pseudo-first-order rate law was observed when more than 80 equiv. of **3** was employed. With less than 80 equiv. of **3**, a pseudo-first-order behavior was only obeyed during the first half life of the reaction with **8h**. Similar deviations from an ideal first-order rate law were observed when less than 40 equiv. of 1,2,5-trimethylpyrrole (**4**) was combined with $(\text{pyr})\text{CH}^+$ (**8d**).

When 1,2,5-trimethylpyrrole (**4**) was treated with $(\text{mpa})_2\text{CH}^+$ (**8f**) in dichloromethane, we obtained complex kinetics, and even after the addition of an equimolar amount of

Table 3. Second-order rate constants k_2 for the reactions of pyrroles **3–6** with benzhydrylium ions **8** in CH_3CN at 20 °C and resulting N and s parameters.

Pyrrole	N	s	Ar_2CH^+	$k_2 / \text{M}^{-1} \text{s}^{-1}$
3	8.01	0.96	$(\text{pyr})_2\text{CH}^+$ (8d)	1.40
			$(\text{mpa})_2\text{CH}^+$ (8f)	2.19×10^2
			$(\text{mor})_2\text{CH}^+$ (8g)	2.52×10^2
			$(\text{dpa})_2\text{CH}^+$ (8h)	$3.87 \times 10^{4[\text{a}]}$
			$(\text{mfa})_2\text{CH}^+$ (8i)	7.32×10^3
4	8.69	1.07	$(\text{ind})_2\text{CH}^+$ (8c)	1.05
			$(\text{pyr})_2\text{CH}^+$ (8d)	7.74
			$(\text{mpa})_2\text{CH}^+$ (8f)	1.59×10^3
			$(\text{mor})_2\text{CH}^+$ (8g)	1.72×10^3
			$(\text{dpa})_2\text{CH}^+$ (8h)	$1.15 \times 10^{5[\text{a}]}$
5	10.67	0.91	$(\text{lil})_2\text{CH}^+$ (8a)	4.29
			$(\text{jul})_2\text{CH}^+$ (8b)	1.26×10^1
			$(\text{ind})_2\text{CH}^+$ (8c)	4.97×10^1
			$(\text{pyr})_2\text{CH}^+$ (8d)	4.45×10^2
			$(\text{mpa})_2\text{CH}^+$ (8f)	2.47×10^4
6	11.63	0.95	$(\text{mor})_2\text{CH}^+$ (8g)	4.65×10^4
			$(\text{lil})_2\text{CH}^+$ (8a)	4.00×10^1
			$(\text{ind})_2\text{CH}^+$ (8c)	4.51×10^2
			$(\text{pyr})_2\text{CH}^+$ (8d)	3.83×10^3
			$(\text{mpa})_2\text{CH}^+$ (8f)	4.74×10^5
			$(\text{mor})_2\text{CH}^+$ (8g)	4.48×10^5

[a] The k_2 values for **8h** deviates significantly from the linear correlations of $\log k_2$ with E and were not used for the determination of N and s .

the weak base *N*-methylmorpholine,^[13] kinetics were observed that deviated from a first-order behavior. The evaluation of the first half life of these reactions resulted in $k_2 = 1 \times 10^2 \text{ M}^{-1} \text{ s}^{-1}$. When the same reactions were performed in acetonitrile solution, perfect first-order kinetics were obtained and the resulting k_2 value is approximately 20 times larger than that in dichloromethane (see Table 3). For the analogous reactions of indoles with benzhydrylium ions, the reactivity increases only by a factor of 3 to 5 when changing from dichloromethane to acetonitrile solution.^[14]

When the logarithms of the second-order rate constants k_2 (as listed in Table 3) and the previously reported rate constants for the analogous reactions of *N*-methylpyrrole (**2**) are plotted against the electrophilicity parameters E of benzhydrylium ions **8**, linear correlations are obtained (Figure 3) that allow us to evaluate the N and s parameters according to Equation (2).

All correlation lines have slopes close to 1, that is, the relative reactivities of the pyrroles are almost independent of the nature of the reaction partners. If a slope of 1.0 is also assumed for the parent pyrrole (**1**), one can calculate $N = 4.63$ for the unsubstituted pyrrole (**1**) from the previously published rate constant ($k_2 = 31.2 \text{ M}^{-1} \text{ s}^{-1}$) for its reaction with $(\text{pfa})_2\text{CH}^+$ (**8j**) in dichloromethane.^[10] With $s = 1.0$, the range from $N = 4.63$ (**1**) to $N = 11.63$ (**6**) corresponds to an increase in reactivity by a factor of 10 million by the three alkyl groups in **6**, which corresponds to relative reaction times of 1 min to 20 years!

When we plot the N values of pyrroles **3–6** against the corresponding $\text{p}K_{\text{aH}}$ values, a linear correlation is observed (Figure 4).

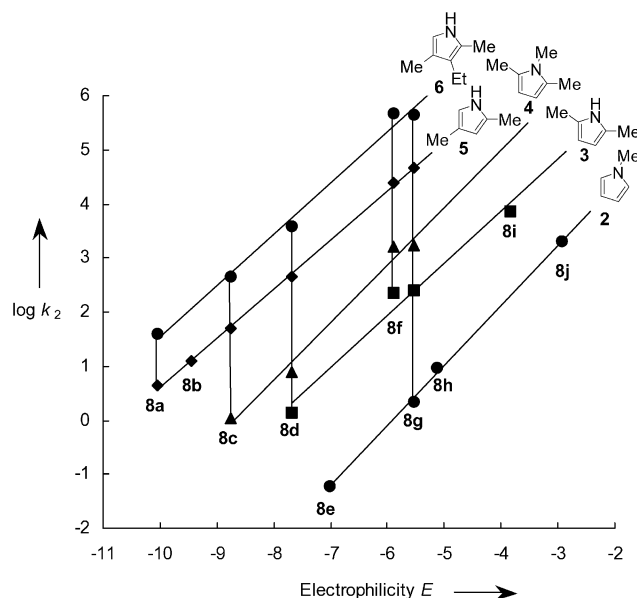


Figure 3. Correlation of the rate constants [$\log k_2$ (20 °C)] in CH_3CN] for the reactions of **2–6** with benzhydrylium ions **8** in relation to their electrophilicity parameters E ; for *N*-methylpyrrole (**2**), the k_2 values refer to reactions in CH_2Cl_2 from ref.^[17b]

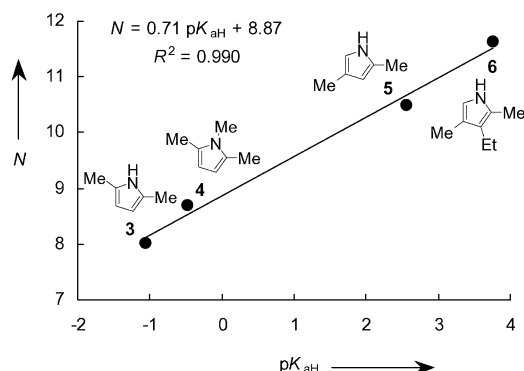
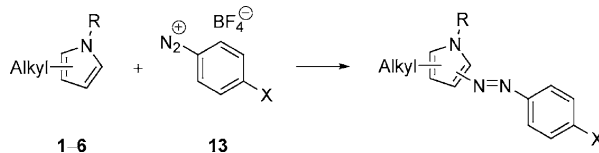


Figure 4. Correlation of the nucleophilicity parameters N of pyrroles **3–6** with the corresponding $\text{p}K_{\text{aH}}$ values in water (taken from ref.^[115]).

The slope of the line in Figure 4 is equivalent to the Brønsted parameter as the average s parameter of pyrroles equals 1. We can thus conclude that 71% of the changes of basicities of pyrroles are found as changes of nucleophilicity.

Reactions of Pyrroles with Other Electrophiles

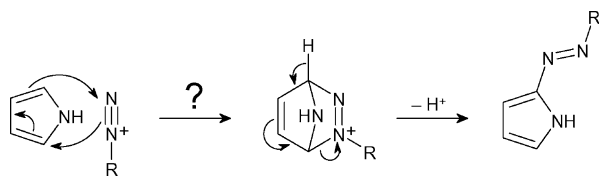
In 1977, Butler, Pogorzelec, and Shepherd reported rate constants for the reactions of pyrroles **1–6** with a variety of *p*-substituted arenediazonium ions **13** in acidic aqueous solution (Scheme 2).^[2g]



Scheme 2. Reactions of pyrroles **1–6** with differently substituted arenediazonium salts **13**.

We previously derived electrophilicity parameters E of arenediazonium ions from the rates of their reactions with various nucleophiles in acetonitrile.^[16] Because Zollinger^[17] and Matsui^[18] found azo couplings to be only 2–3 times faster in water than in acetonitrile, Equation (2) allows us to calculate rate constants for the reactions of pyrroles with **13a** ($\text{X} = \text{OMe}$), **13b** ($\text{X} = \text{H}$), and **13c** ($\text{X} = \text{NO}_2$), which are directly comparable to the rate constants reported by Butler (Table 4).

Although calculated and experimental data for the azo couplings with pyrroles **3–6** agree remarkably well (within a factor of 2–60), the reported rate constants for the reactions with pyrrole (**1**) and *N*-methylpyrrole (**2**) are 170–16000 times larger than the calculated values. In view of the approximate nature of Equation (2) we do not want to draw definite conclusions from these deviations. However, it is at least surprising that the decrease in basicity (Table 4) from **3** and **4** to **1** and **2**, which results in a reduced reactivity towards benzhydrylium ions, is not accompanied by a lower reactivity towards diazonium salts. One may speculate whether in these cases an initial Diels–Alder reaction with subsequent ring-opening (Scheme 3) is responsible for the unexpected high reactivity.^[19,20]



Scheme 3. Possible Diels–Alder reaction between diazonium ions and pyrrole.

Table 4. Comparison of the rate constants for the reactions of pyrroles **1–6** with arenediazonium salts **13a–c** determined by Butler^[2g] and calculated by $\log k = s(N + E)$ [Equation (2)].

Pyrrole	N (s)	$\text{p}K_{\text{aH}}^{[a]}$	13a ($\text{X} = \text{OMe}$, $E = -8.4$) ^[b]		13b ($\text{X} = \text{H}$, $E = -7.2$) ^[b]		13c ($\text{X} = \text{NO}_2$, $E = -5.1$) ^[b]	
			$k / \text{M}^{-1} \text{s}^{-1[c]}$	$k_{\text{calcd.}} / \text{M}^{-1} \text{s}^{-1[d]}$	$k / \text{M}^{-1} \text{s}^{-1[c]}$	$k_{\text{calcd.}} / \text{M}^{-1} \text{s}^{-1[d]}$	$k / \text{M}^{-1} \text{s}^{-1[c]}$	$k_{\text{calcd.}} / \text{M}^{-1} \text{s}^{-1[d]}$
1	4.63 (1.00)	−3.80	2.8	1.7×10^{-4}	6.8	2.7×10^{-3}	220	3.4×10^{-1}
2	5.85 (1.03)	−2.90	10.9	2.4×10^{-3}	25.2	4.1×10^{-2}	1.00×10^3	5.9
3	8.01 (0.96)	−1.07	9.8	4.2×10^{-1}	32.5	6.0	— ^[e]	6.2×10^2
4	8.69 (1.07)	−0.49	11.8	2.0	24.4	3.9×10^1	1.60×10^3	6.9×10^3
5	10.67 (0.91)	2.55	6.80×10^3	1.2×10^2	1.34×10^4	1.4×10^3	— ^[e]	1.2×10^5
6	11.63 (0.95)	3.75	3.05×10^4	1.2×10^3	1.77×10^5	1.6×10^4	— ^[e]	1.6×10^6

[a] $\text{p}K_{\text{aH}}$ values in water from ref.^[115] [b] Electrophilicity parameters E from ref.^[16] [c] Second-order rate constants at 25 °C from ref.^[2g] [d] Calculated rate constants by using Equation (2) refer to 20 °C. [e] Not determined.

Conclusions

Alkyl groups were found to have an enormous activating effect on the nucleophilicities of pyrroles. Whereas parent compound **1** has a nucleophilicity comparable to that of silylated enol ethers, allylsilanes, and indoles, 2,3,4-trialkylated pyrrole **6** is 10^7 times more reactive and possesses a nucleophilicity comparable to enamines, ketene acetals, and pyridines (Figure 5). With the N and s parameters determined in this work, it becomes possible to make predictions of absolute rate constants for reactions of pyrroles with electrophiles of known E parameters. Strong deviations between observed and calculated rate constants are discussed as indicators for a change in mechanism.

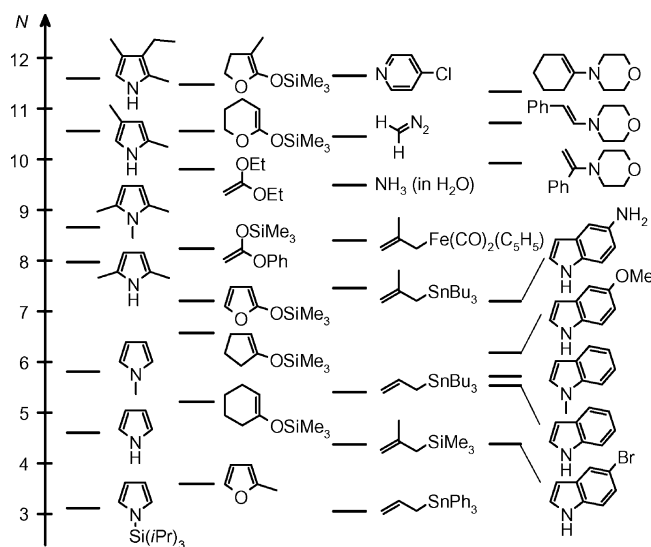


Figure 5. Comparison of the nucleophilicities of pyrroles with those of other types of nucleophiles.

Experimental Section

General Section: Benzhydrylium tetrafluoroborates **8-BF₄** (see Table 1) were synthesized by literature procedures.^[7b] 2,5-Dimethylpyrrole (**3**), 1,2,5-trimethylpyrrole (**4**), 2,4-dimethylpyrrole (**5**), 3-ethyl-2,4-dimethylpyrrole (**6**), 1,4-diazabicyclo[2.2.2]octane (DABCO), and *N*-methylmorpholine were purchased and purified by distillation or recrystallization prior to use. ¹H (300 MHz) and ¹³C NMR (75.5 MHz) spectra were measured with a Bruker ARX 300 instrument. Mass spectra were recorded with a MAT 95 Q instrument.

Reactions of Pyrroles 3–5 with Benzhydrylium Salt 8e-BF₄: A solution of the benzhydrylium salt (0.14 g, 0.40 mmol) in acetonitrile (100 mL) was added dropwise to a stirred solution of the appropriate freshly distilled pyrrole (0.80 mmol) in acetonitrile (20 mL) at –15 °C. The solution was washed with ice water, dried, filtered, and the solvents evaporated in vacuo.

Substituted pyrrole **12** was obtained by adding an acetonitrile solution (20 mL) of **6** (0.10 mL, 0.74 mmol) to a stirred solution of **8e-BF₄** (0.14 g, 0.40 mmol) in acetonitrile (50 mL) at –15 °C. After fading of the blue color, the solution was washed with ice water, dried, filtered, and the solvents evaporated in vacuo.

For details and characterization of the products see the Supporting Information.

Kinetics: The kinetics of the reactions of the benzhydrylium ions with the pyrroles were followed by UV/Vis spectroscopy by using work stations similar to that described previously.^[11]

For slow reactions ($\tau_{1/2} > 10$ s), the UV/Vis spectra were collected at different times by a J&M TIDAS diode array spectrophotometer that was connected to a Hellma 661.060-UV quartz Suprasil immersion probe (5 mm light path) through fiber optic cables with standard SMA connectors. All kinetic measurements were made in Schlenk glassware under exclusion of moisture. The temperature of the solutions during the kinetic studies was maintained to within ± 0.2 °C by using circulating bath cryostats and monitored with thermocouple probes that were inserted into the reaction mixture.

A stopped-flow spectrophotometer system (Applied Photophysics SX.18MV-R) was used for the investigation of rapid reactions of benzhydrylium ions with nucleophiles ($\tau_{1/2} < 10$ s). The kinetic runs were initiated by mixing equal volumes of acetonitrile solutions of the pyrroles and the benzhydrylium salts. Concentrations and rate constants for the individual kinetic experiments for the reactions of pyrroles with benzhydryl cations are given in the Supporting Information.

Supporting Information (see footnote on the first page of this article): Preparative procedures, product characterization, and details of the individual runs of the kinetic experiments are available.

Acknowledgments

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