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Nucleophilic Reactivities of Azulene and Fulvenes

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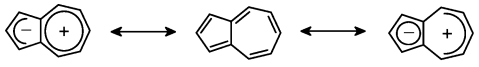
Dedicated to Professor Heinz Langhals on the occasion of his 60th birthday

Keywords: Carbocations / Aromaticity / Kinetics / Linear free energy relationships / UV/Vis spectroscopy / Nucleophilic addition

The kinetics of the reactions of azulene (**1**), 6,6-dimethylfulvene (**2**), 6-[4-(dimethylamino)phenyl]fulvene (**3**) and 6-(julolidin-9-yl)fulvene (**4**) with a set of benzhydrylium ions (reference electrophiles) have been investigated in MeCN. The second-order rate constants for these reactions correlate linearly with the electrophilicity parameters (*E*) of the benzhydrylium ions. According to the linear free-enthalpy relationship $\log k_2(20\ °C) = s(N + E)$, the nucleophilicity parameters *N* and *s* of the π-nucleophiles **1**–**4** were determined and compared with those of other types of nucleophiles. Azulene (**1**, *N* = 6.66) is about 10 times more nucleophilic than *N*-methylpyrrole and comparable to 2-methylindole.

Introduction

Azulene is a 10-π-electron nonbenzenoid, nonalternant, catacondensed, aromatic system with unique properties: a deep blue color, a dipole moment of 1.08 ± 0.02 D (in benzene) and high reactivity towards electrophiles and nucleophiles.[1] As depicted in Scheme 1, these properties can be explained by the polar resonance structures with a fused tropylium cation and cyclopentadienyl anion. Being readily available through Hafner's elegant synthetic approach,[2] azulene (**1**) and its derivatives became key compounds for the study of nonbenzenoid aromaticity.[3–5]



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Scheme 1.

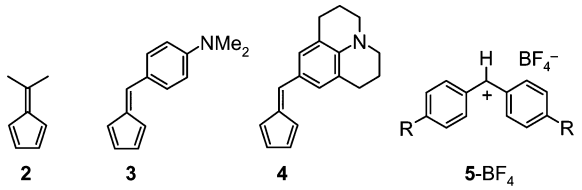
With pK_{BH+} = –1.66[6] and σ^+_{arene} = –1.60,[7] azulene can be expected to be comparable to *N*-methylpyrrole (pK_{BH+} = –2.90,[8] σ^+_{arene} = –1.90[9]) and *N*-methylindole (pK_{BH+} = –2.32,[10] σ^+_{arene} = –1.58[7]) in Brønsted basicity and reactivity towards electrophiles.

In order to include azulene in our comprehensive nucleophilicity scale, which allows for the direct comparison of the reactivities of a large variety of π-, n- and σ-nucleophiles, we have studied the kinetics of their reactions with benzhydrylium ions (Ar_2CH^+), which we employ as reference electrophiles, following the previously established methodology.[11] Because azulene incorporates the cross-conjugated π-system of fulvenes, we have also studied the nucleophilic properties of the 6-donor-substituted fulvenes **2**–**4**.

We have previously reported that the reactions of carbocations with π-systems follow the linear free-energy relationship [Equation (1)], where electrophiles are characterized by one parameter [electrophilicity (*E*)], and nucleophiles are characterized by two parameters [nucleophilicity (*N*) and slope (*s*)].[11–14]

$$\log k_2(20\ °C) = s(N + E) \quad (1)$$

In this paper, we will show that the second-order rate constants of the reactions of azulene (**1**) and the fulvenes **2**–**4** with benzhydrylium ions **5** (see Scheme 2 and Table 1) can be described by Equation (1), which allows for the determination of the *N* and *s* values of **1**–**4**.



2 **3** **4** **5**-BF_4

Scheme 2.

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Table 1. Benzhydrylium ions Ar_2CH^+ (**5**) used as reference electrophiles in this study.

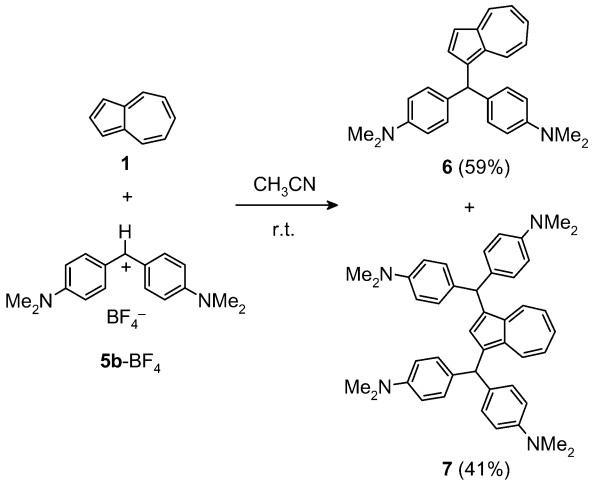
Entry	Ar_2CH^+ (**5**)[a]	R	E[b]
1	$(pyr)_2CH^+$ (**5a**)	$-N(CH_2)_4$	–7.69
2	$(dma)_2CH^+$ (**5b**)	$-NMe_2$	–7.02
3	$(mpa)_2CH^+$ (**5c**)	–NMePh	–5.89
4	$(mor)_2CH^+$ (**5d**)	$-N(CH_2CH_2)_2O$	–5.53
5	$(dpa)_2CH^+$ (**5e**)	$-NPh_2$	–4.72
6	$(mfa)_2CH^+$ (**5f**)	$-N(Me)CH_2CF_3$	–3.85
7	$(pfa)_2CH^+$ (**5g**)	$-N(Ph)CH_2CF_3$	–3.14

[a] Counterion: BF_4^-. [b] E values are from ref.[11]

Results

Product Characterization

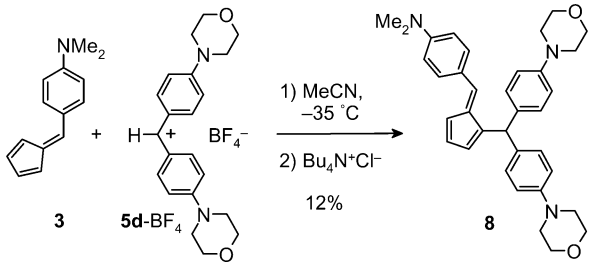
The treatment of azulene (**1**, 4.3 equiv.) with 4,4′-bis(dimethylamino)benzhydrylium tetrafluoroborate (**5b**-BF_4) in MeCN at r.t. yielded the monosubstitution product **6** in 59% and the bis-substitution product **7** in 41% yield (Scheme 3).



Scheme 3.

Compounds **6** and **7** have previously been obtained from **1** and the corresponding benzhydryl alcohol **5b**-OH in the presence of acetic acid.[15]

Fulvene **3** and 4,4′-bis(morpholino)benzhydrylium tetrafluoroborate (**5d**-BF_4) reacted in MeCN at –35 °C to give 12% of **8** (Scheme 4), the structure of which was confirmed by single-crystal X-ray analysis.

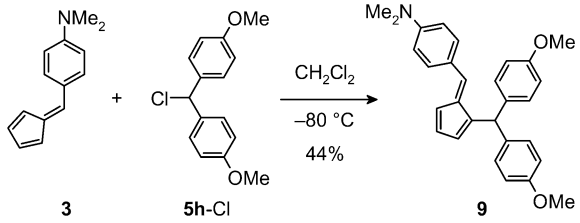


Scheme 4.

The low yield of **8** can be explained by its high sensitivity towards acids. Because it decomposed on silica gel, we used column chromatography on neutral Al_2O_3 for its purification.

When fulvene **3** was combined with the less reactive benzhydrylium salt $(dma)_2CH^+BF_4^-$ (**5b**-BF_4) in MeCN at r.t., the resulting NMR spectra indicated a fast consumption of **3** with formation of a complex product mixture, probably oligomers of **3**. The cationic polymerization of fulvenes induced by Brønsted acids has previously been reported in the literature.[16–18]

The monosubstitution product **9** was obtained in 44% yield by combining 2 equiv. of **3** and benzhydryl chloride **5h**-Cl in CH_2Cl_2 at –80 °C (Scheme 5).



Scheme 5.

Kinetic Investigations

The kinetic studies were conducted in MeCN at 20 ± 0.1 °C under first-order conditions with a large excess (>10 equiv.) of the nucleophiles **1**–**4** over the benzhydrylium ions **5**. We followed the progress of the reactions by UV/Vis spectroscopy with diode array spectrometers equipped with fiber optics and a submersible probe; the evaluation was performed at λ_{max} of **5**. We obtained the first-order rate constants (k_{obs}) from the exponential decays of the UV/Vis absorbances of the electrophiles **5**. Plots of k_{obs} versus the concentrations of the nucleophiles **1**–**4** were linear with negligible intercepts (Figure 1), and their slopes yielded the second-order rate constants (k_2, Table 2). Slower subsequent reactions of the initially formed adducts with the excess of fulvenes caused an increase of the absorptions

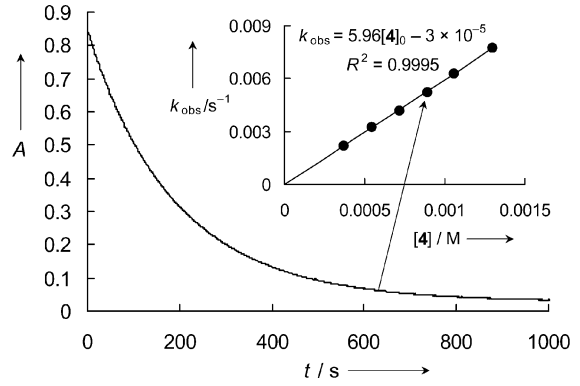


Figure 1. Determination of the second-order rate constant for the reaction of **5b** (1.44×10^{-5} M) with **4** in MeCN at 20 °C (k_2 = 5.96 $M^{-1} s^{-1}$, the decay of the absorbance at 605 nm is shown for [**4**] = 8.89×10^{-4} M).

at the monitored wavelengths. Because these processes occurred after the reactions under consideration, they did not affect the kinetics reported in Table 2. We observed complex kinetics in CH_2Cl_2 but did not evaluate further.

Table 2. Second-order rate constants (k_2) for the reactions of the electrophiles **5** with the nucleophiles **1**–**4** in MeCN at 20 °C and resulting N and s parameters for **1**–**4**.

Entry	Nucleophile; N, s	Electrophile[a]	k_2 [$M^{-1}s^{-1}$]
1	**1**; 6.66, 1.02	$(dma)_2CH^+$ (**5b**)	4.29×10^{-1}
2		$(mor)_2CH^+$ (**5d**)	1.38×10^{1}
3		$(mfa)_2CH^+$ (**5f**)	7.36×10^{2}
4	**2**; 3.93, 0.88	$(mor)_2CH^+$ (**5d**)	4.43×10^{-2}
5		$(dpa)_2CH^+$ (**5e**)	2.37[b]
6		$(mfa)_2CH^+$ (**5f**)	7.92×10^{-1}
7		$(pfa)_2CH^+$ (**5g**)	6.66
8	**3**; 6.72, 0.87	$(dma)_2CH^+$ (**5b**)	4.88×10^{-1}
9		$(mpa)_2CH^+$ (**5c**)	1.35×10^{1} [b]
10		$(mor)_2CH^+$ (**5d**)	1.38×10^{1}
11		$(mfa)_2CH^+$ (**5f**)	2.77×10^{2}
12	**4**; 7.79, 1.06	$(pyr)_2CH^+$ (**5a**)	1.34
13		$(dma)_2CH^+$ (**5b**)	5.96
14		$(mpa)_2CH^+$ (**5c**)	1.93×10^{2} [b]
15		$(mor)_2CH^+$ (**5d**)	2.49×10^{2}

[a] Counterion: BF_4^-. [b] Data not used for the calculation of N and s values (see text).

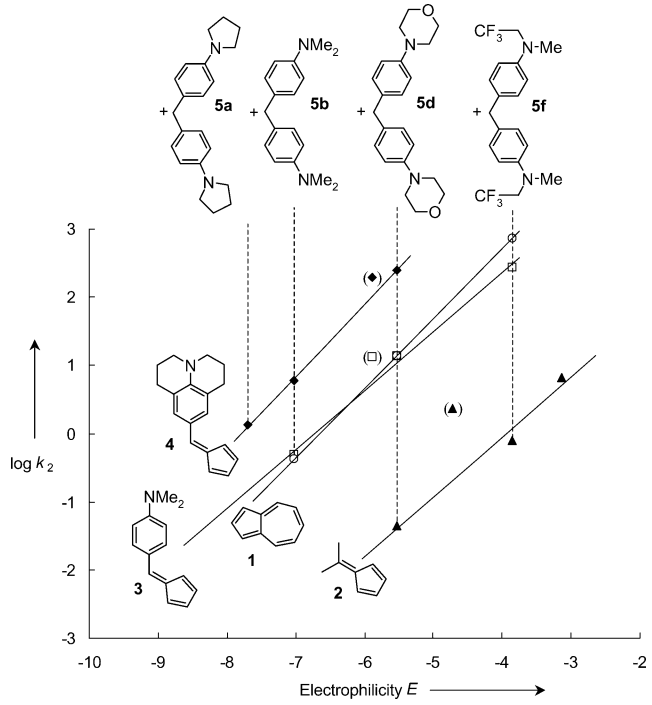


Figure 2. Correlation of log k_2 (20 °C, MeCN) for the reactions of **1**–**4** with the benzhydrylium ions **5** in relation to their electrophilicity parameters E. – Points in parentheses were not used for the correlations (see text).

Discussion

In order to determine the nucleophilicity parameters N and s of the nucleophiles **1**–**4** according to Equation (1), we plotted the logarithms of the second-order rate constants (log k_2) versus the E parameters of the corresponding electrophiles. The plots for the reactions of azulene (**1**) and fulvenes **2**–**4** with the reference electrophiles **5** were linear, though the benzhydrylium ions **5c** and **5e** showed systematic deviations (Figure 2).

Analogous deviations have previously been reported when the reactions of these two carbocations with other nucleophiles have been studied in MeCN.[19] Therefore, we did not take into consideration the rate constants for **5c** and **5e** for calculations of the N and s parameters.

All correlation lines had slopes close to 1 as previously reported for other π-nucleophiles (e.g. pyrroles,[19a] indoles[20] and alkenes[11]), which implies that the relative reactivities of these compounds are almost independent of the nature of the electrophiles. As a consequence, structure-reactivity relationships can be based on the nucleophilicity values, which are summarized in Figure 3.

According to Figure 3, azulene (**1**, N = 6.66) is considerably more nucleophilic than 6,6-dimethylfulvene (**2**, N = 3.93) and is comparable to the [4-(dimethylamino)phenyl]-substituted fulvene **3** (N = 6.72) and 2-methylindole (N = 6.91).[20] Azulene largely exceeds the nucleophilicity of 1,3-dimethoxybenzene (N = 2.48) and 2-methylfuran (N = 3.61).[11]

Figure 3 furthermore shows that 6,6-dimethylfulvene (**2**), which yields a 1,1,2,5-tetraalkylpentadienyl cation by reaction with an electrophile, is approximately 1 to 1.5 orders of magnitude more nucleophilic than 2-methyl- or 4-methyl-1,3-pentadiene, which yield trialkylsubstituted allyl cations.

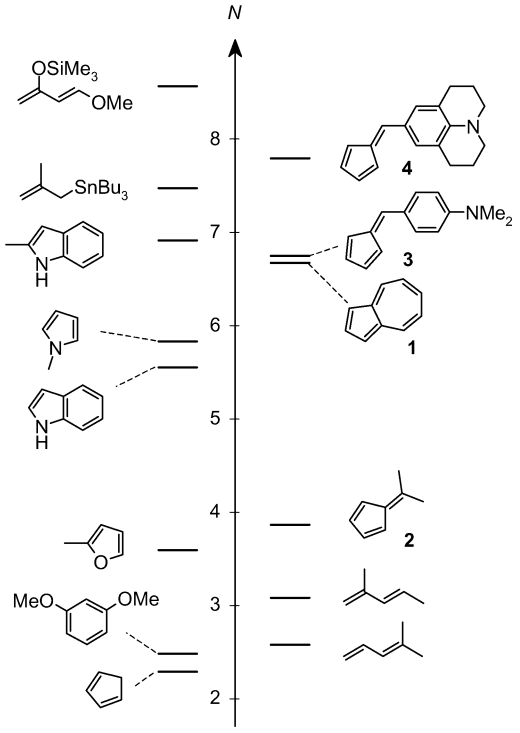


Figure 3. Comparison of the nucleophilicities of azulene (**1**) and fulvenes **2**–**4** (in MeCN) with those of other types of nucleophiles (in CH_2Cl_2).

A comparison of **2** with cyclopentadiene (N = 2.30)[13] reveals that the extra isopropylidene group of **2** activates by a factor of about 40.

We obtained the N and s values for **1**–**4** given in Table 2 from their reactions with benzhydrylium ions. The question arises whether these numbers are also useful for predicting their reactivities toward other types of electrophiles. To the best of our knowledge, so far only one system has been reported that addresses this question. Terrier and coworkers determined[21] a second-order rate constant of 5.88 $M^{-1} s^{-1}$ (MeCN, 25 °C) for the reaction of 4,6-dinitrobenzofuroxane with azulene (**1**). From the electrophilicity parameter of this electrophile (E = –5.06)[20] and the N and s values of **1** given in Table 2, we calculated k_2 as 42.9 $M^{-1} s^{-1}$ at 20 °C. Though the difference between calculated and experimental values will increase slightly when the difference in reaction temperature is taken into account, it is obvious that the deviation is considerably less than a factor of 10^2, which we consider satisfactory for a 3-parameter correlation covering 40 orders of magnitude in reactivity.[22,23]

Conclusions

Azulene (**1**) is the most nucleophilic neutral hydrocarbon characterized so far in our nucleophilicity scales. Its high nucleophilic reactivity, which has been explained by its polarized structure (Scheme 1) has thus been quantified. The directly determined nucleophilicity parameter for azulene (**1**, N = 6.66) is in between N = 7.7 (estimated from pK_{BH+} = –1.66[6] and the correlation $N = 0.71pK_{BH+} + 8.87$)[19a] and N = 4.7 (estimated from σ^+_{arene} = –1.58[7] and the correlation $N = -6.8\sigma^+ - 6.2$).[24] With the N and s values determined in this work, it now becomes possible to predict absolute rate constants for the reaction of azulene (**1**) and fulvenes **2**–**4** with the large variety of electrophiles with known E values.[14,25]

Experimental Section

General Section: Benzhydrylium tetrafluoroborates **5**-BF_4 (see Table 1) were synthesized as described previously.[11] Benzhydryl chloride **5h**-Cl[26] and nucleophiles **1**,[2] **2**,[27] **3**[28] and **4**[28] were synthesized according to literature procedures.

Kinetics: The kinetics of the reactions of the benzhydrylium ions with the nucleophiles **1**–**4** were followed by UV/Vis spectroscopy using a J&M TIDAS diode array spectrophotometer 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 performed in Schlenk glassware under nitrogen. The temperature of the solutions during the kinetic studies was maintained at 20 ± 0.1 °C with circulating bath cryostats.

X-ray Crystal Structure Analysis of 8: The data collection was performed on a Nonius KappaCCD diffractometer equipped with a rotating anode generator. The structure was solved by direct methods with SIR97[29] and refined with SHELXL-97.[30] CCDC-706951 contains the supplementary crystallographic data for compound **8**. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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

Acknowledgments

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