

Nucleophilic reactivity of the azide ion in various solvents[†]

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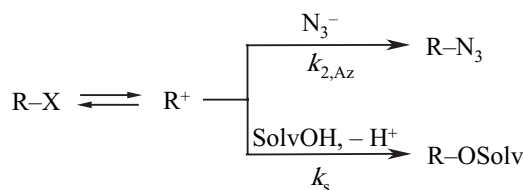
ABSTRACT: The kinetics of the reactions of the azide ion with benzhydrylium ions were investigated photometrically in different alcohol/acetonitrile mixtures and in DMSO at 20 °C. Since the competing reactions of the benzhydrylium ions with the solvents are generally slower, the second-order rate constants of the reactions of the benzhydrylium ions with the azide ion can unambiguously be determined to yield nucleophilicity parameters N and s for the azide ion in different alcohols. Several reactions of the benzhydrylium ions with the azide ion are reversible, which allowed the determination of the equilibrium constants and the rate constants of the reverse reactions. It is found that benzhydrylium ions with annelated six-membered rings are better electrophiles and better electrofuges than the five-membered ring analogs due to the lower intrinsic barriers of the former reactions. Copyright © 2007 John Wiley & Sons, Ltd. *Supplementary electronic material for this paper is available in Wiley InterScience at <http://www.interscience.wiley.com/jpages/0894-3230/suppmat/>*

KEYWORDS: kinetics; linear free energy relationship; nucleophilicity; nucleofugality; intrinsic barriers; equilibrium constants

INTRODUCTION

Organic azides are important substrates for heterocyclic synthesis,¹ particularly Huisgen reactions (1,3-dipolar cycloadditions, click chemistry).^{2–4} They are employed as precursors of primary amines⁵ for Staudinger ligations,⁶ and many other synthetic applications.^{5,7,8} Alkyl azides are usually synthesized via S_N2 reactions from alkyl halides and alkali azides,⁵ and the kinetics of these reactions have been studied.⁹

In mechanistic chemistry, the azide-clock method developed by Richard and Jencks¹⁰ found wide application for determining the rates of the reactions of carbocations with solvents.¹¹ When S_N1 reactions are performed in nucleophilic solvents containing azide ions, as shown in Scheme 1, the rate constants k_S can be



Scheme 1.

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derived from the product ratio $[\text{R-OSolv}]/[\text{R-N}_3]$ if the reactions of the carbocations with azide ions are diffusion controlled, that is, $k_{2,\text{Az}} = 5 \times 10^9 \text{ M}^{-1} \text{ sec}^{-1}$.

McClelland *et al.*^{12a} determined rate constants of $(4\text{--}6) \times 10^9 \text{ M}^{-1} \text{ sec}^{-1}$ for the reactions of the parent and of acceptor-substituted tritylium ions with N_3^- from the rates of decay of the absorbances of laser-flash photolytically generated tritylium ions in solutions of NaN_3 in 67/33 (v/v) water–acetonitrile mixtures. Analogous experiments have been reported for other types of carbocations.^{12b,c} In order to define the range, in which the azide-clock method is applicable, we have now determined the nucleophilicity parameters N and s for the azide ion in different solvents using the procedure described previously.^{13,14}

$$\log k(20^\circ\text{C}) = s(E + N) \quad (1)$$

Equation (1), which calculates the rate constants of electrophile–nucleophile combinations from the electrophilicity parameters E , the nucleophilicity parameters N , and the nucleophile specific slope parameters s , has been reported to hold for the reactions of carbocations¹³ and neutral electron deficient π -systems (Michael acceptors,¹⁵ electron-deficient arenes^{16,17}) with a large variety of n -nucleophiles (amines,¹⁸ alcohols,¹⁹ alkoxides,²⁰ phosphanes,²¹ inorganic anions²²), σ -nucleophiles (C–H,²³ Si–H, Sn–H hydride donors²⁴), and π -nucleophiles (heteroarenes,²⁵ enol ethers,²⁶ ketene acetals,²⁷ enamines,²⁸ allyl element compounds,²⁹ transition metal π -complexes,³⁰ diazoalkanes,³¹ and delocalized carbanions^{32–34}). A comprehensive collection of nucleophilicity

Table 1. Benzhydrylium ions employed as reference electrophiles in this work

	Electrophile	E^a
(lil) ₂ CH ⁺		-10.04
(jul) ₂ CH ⁺		-9.45
(ind) ₂ CH ⁺		-8.76
(thq) ₂ CH ⁺		-8.22

^aFrom Ref. 13.

parameters can be found at www.cup.uni-muenchen.de/oc/mayr/DBintro.html. For the determination of N and s parameters of the azide ion, we measured the rates of the reactions of the azide ion with the benzhydrylium ions listed in Table 1 in various solvents.

RESULTS

The azide ion reacts reversibly with amino-substituted benzhydrylium ions [Eqn (2)].

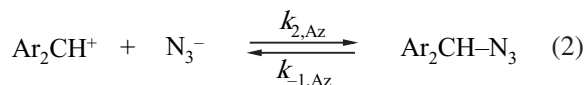


Figure 1 shows the consumption of (lil)₂CH⁺BF₄⁻ in MeOH/MeCN 91/9 (v/v) due to the reactions with N₃⁻. A large excess of N₃⁻ is required to convert a large portion of (lil)₂CH⁺BF₄⁻ into the covalent adduct (lil)₂CH—N₃. The absorbance A of the blue solution decreased during the reaction and finally remained constant at A_{end} . Increasing concentration of the azide anion resulted in a reduction of the A_{end} values.

Rate constants

Except for some reactions which were carried out in DMSO, most reactions of the azide ion with the benzhydrylium cations studied in this work were performed in alcohol/acetonitrile mixtures. Since most benzhydrylium ions react readily with alcohols, the kinetic studies were performed with a stopped-flow instrument by mixing one part of the solutions of the benzhydrylium tetrafluoroborates in acetonitrile with 10 parts of a solution of sodium azide in a pure alcohol or in a

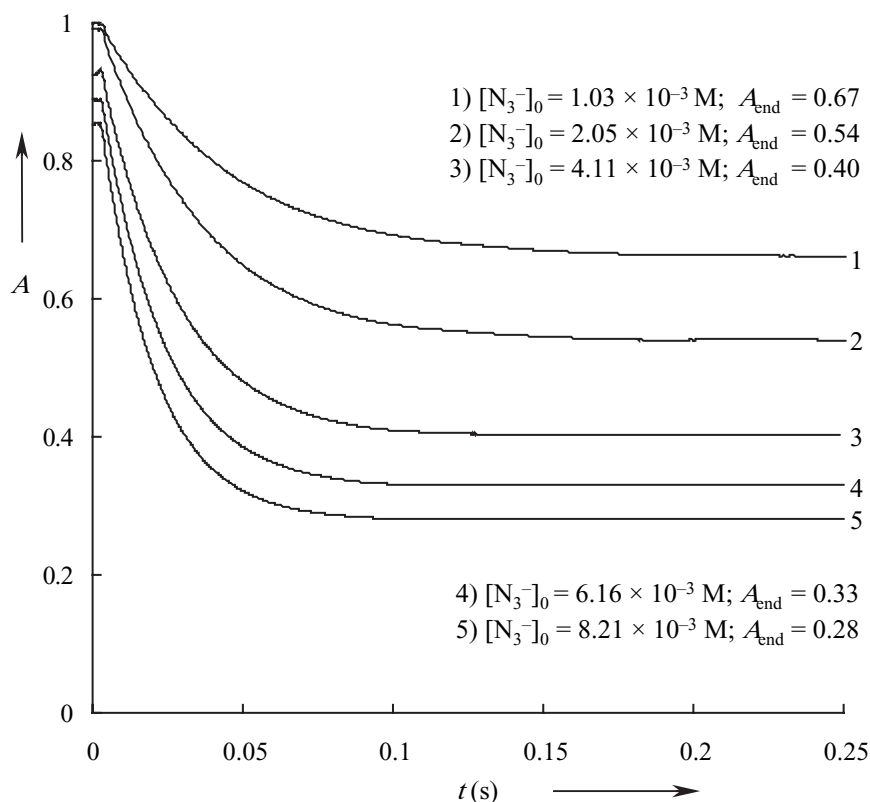


Figure 1. Reversible reactions of the azide ion with (lil)₂CH⁺BF₄⁻ in MeOH/MeCN 91/9 (v/v) at 20 °C, followed at 629 nm, [(lil)₂CH⁺BF₄⁻] = 1.03×10^{-5} M

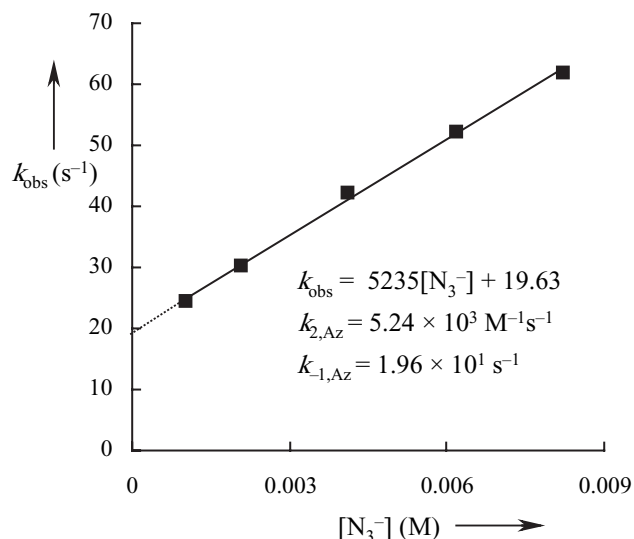


Figure 2. Plot of the pseudo-first-order rate constants k_{obs} (sec^{-1} , at 20°C) for the decay of the $(\text{lil})_2\text{CH}^+\text{BF}_4^-$ concentration in MeOH/MeCN 91/9 (v/v) versus the concentrations of the azide ion

50/50 (v/v) mixture of alcohol and acetonitrile to yield solutions in 91% alcohol/9% acetonitrile (v/v) or 45.45% alcohol/54.55% acetonitrile (v/v), respectively.

Rate constants for the reactions of the benzhydrylium ions (Table 1) with various alcohols have previously been reported.¹⁹ From the results of this paper, one can see that the reactions of benzhydrylium cations with N_3^- are generally much faster than the reactions with alcohols. In several cases (reactions in methanol/acetonitrile mixtures), high concentrations of N_3^- were used, and the determination of the reactivity of the azide ion was not disturbed by the competing reactions of the benzhydrylium ions with the alcohols.

Figure 2 shows that the pseudo-first-order rate constants k_{obs} for the decay of $(\text{lil})_2\text{CH}^+$ increase linearly with $[\text{N}_3^-]$ in MeOH/MeCN 91/9 (v/v). The slope of the correlation corresponds to the second-order rate constants of the forward reaction, $k_{2,\text{Az}}$ ($\text{M}^{-1}\text{sec}^{-1}$), whereas the

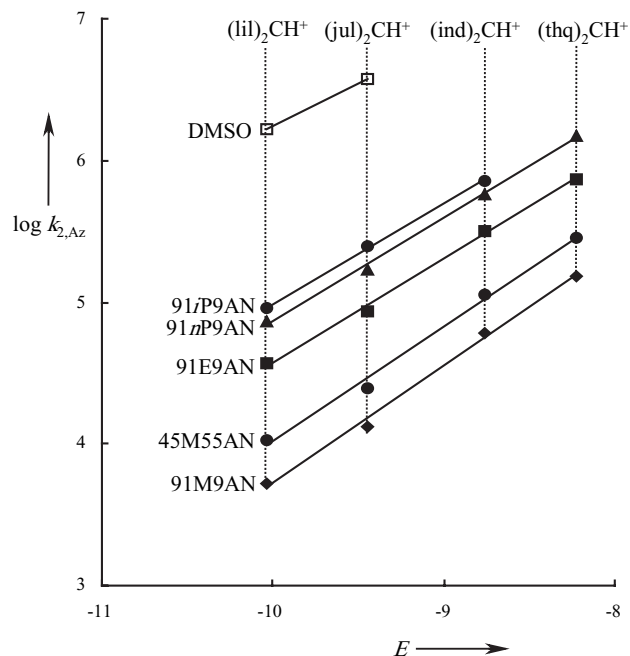


Figure 3. Correlation of $\log k_{2,\text{Az}}$ for the reactions of the azide anion with benzhydrylium ions (at 20°C , in different solvents) versus their electrophilicity parameters E . Solvent mixtures are given as (v/v); solvents: AN = acetonitrile, E = ethanol, M = methanol, nP = propan-1-ol, iP = propan-2-ol

intercept reflects the first-order rate constant of the backward reaction $k_{-1,\text{Az}}$ (sec^{-1}).^{35,36}

Analogous plots of pseudo-first-order rate constants versus the concentrations of the azide ion (Supplementary Material) gave the rate constants for the reversible reactions of the azide anion with benzhydrylium ions in various solvents (Table 2).

The linear plots of $\log k_{2,\text{Az}}$ versus the electrophilicity parameters E (Table 1) of the benzhydrylium ions (Fig. 3) yield the nucleophilicity parameters N and s of the azide anion in various solvents according to Eqn (1) (Table 3).

For the reactions of the azide anion with tritylium ions (T^+) in water/acetonitrile 67/33 (v/v), McClelland^{12a} observed diffusion control when $E > 0$. From the linear

Table 2. Rate constants $k_{2,\text{Az}}$ for the reactions of the azide anion with benzhydrylium ions in different solvents (20°C)

Solvent ^a	$k_{2,\text{Az}}$ ($\text{M}^{-1}\text{sec}^{-1}$) ^b			
	$(\text{lil})_2\text{CH}^+$	$(\text{jul})_2\text{CH}^+$	$(\text{ind})_2\text{CH}^+$	$(\text{thq})_2\text{CH}^+$
91M9AN	5.24×10^3	1.34×10^4	6.09×10^4	1.51×10^5
45M55AN	1.08×10^4	2.44×10^4	1.12×10^5	2.84×10^5
91E9AN	3.71×10^4	8.72×10^4	3.20×10^5	7.40×10^5
91nP9AN	7.23×10^4	1.70×10^5	5.79×10^5	1.48×10^6
91iP9AN	8.97×10^4	2.49×10^5	7.21×10^5	—
DMSO	1.68×10^{6c}	3.77×10^6	—	—

^a Solvent mixtures are given as (v/v); solvents: AN = acetonitrile, E = ethanol, M = methanol, nP = propan-1-ol, iP = propan-2-ol.

^b Estimated errors $\pm 5\%$.

^c From Ref. 18.

Table 3. Nucleophilicity parameters N and s of the azide anion in different solvents

Nucleophile	N	s
N_3^- in 91M9AN	14.54	0.822
N_3^- in 45M55AN	15.01	0.803
N_3^- in 91E9AN	16.30	0.727
N_3^- in 91 <i>n</i> P9AN	16.70	0.726
N_3^- in 91 <i>i</i> P9AN	17.07	0.706
N_3^- in DMSO	20.50 ^a	0.594 ^a

^aThe N and s values are based on only two experimental points.

correlation in the left part of Fig. 4 ($\log k_{2,Az}$ for the methoxy substituted tritylium ions *versus* E^{18}), one can derive $N = 15.03$ and $s = 0.67$ for N_3^- in water/acetonitrile 67/33 (v/v).

When the rate constants for the reverse reaction, that is, $k_{-1,Az}$ for the ionization of Ar_2CH-N_3 (Table 4) are compared, one finds the reactivity order $(ind)_2CH^+ < (thq)_2CH^+ \approx (lil)_2CH^+ < (jul)_2CH^+$ (Fig. 5), which differs from the reverse of the electrophilicity order shown in Fig. 3 and the electrophilicity order found for countless other electrophile nucleophile combinations.^{13,14,18–23}

Since the $k_{-1,Az}$ values listed in Table 4 and plotted in Fig. 5 are the intercepts of correlations as shown in Fig. 2, some of them are not very accurate. We have, therefore, derived them independently from the forward rate constants and the corresponding equilibrium constants.

Equilibrium constants

In order to determine the equilibrium constants, the molar absorptivities (molar extinction coefficients) ϵ of the benzhydrylium tetrafluoroborates were determined in

Table 4. Rate constants $k_{-1,Az}$ for the ionizations of benzhydrylium azides in different solvent systems (20 °C)

Solvent ^a	$k_{-1,Az}$ (sec ⁻¹) ^b			
	(lil) ₂ CHN ₃	(jul) ₂ CHN ₃	(ind) ₂ CHN ₃	(thq) ₂ CHN ₃
91M9AN	19.6	75.2	6.40	20.8
45M55AN	23.6	90.0	7.88	17.4
91E9AN	7.99	24.2	1.83	4.50 ^c
91 <i>n</i> P9AN	6.88	19.6	—	—
91 <i>i</i> P9AN	4.20	11.5	—	—

^aSolvent mixtures are given as (v/v); solvents: AN = acetonitrile, E = ethanol, M = methanol, *n*P = propan-1-ol, *i*P = propan-2-ol.

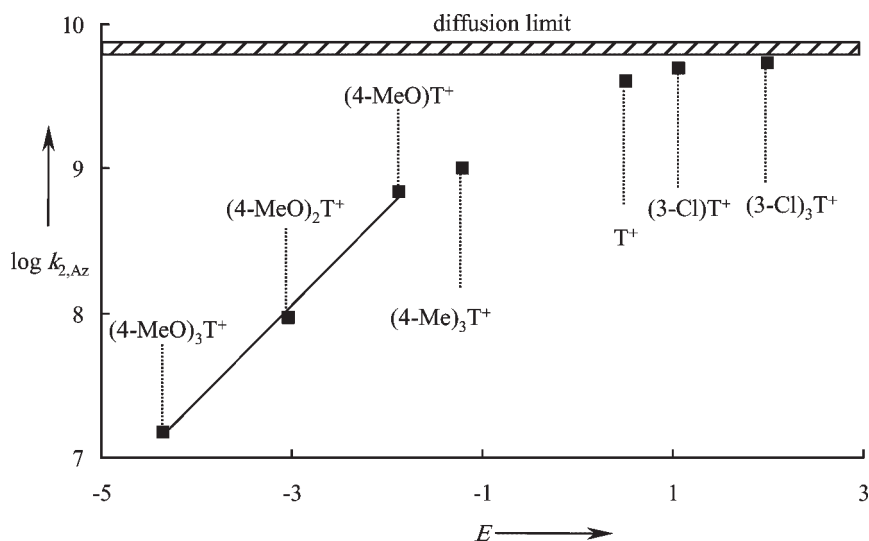
^bEstimated errors $\pm 15\%$.

^cThis value should be considered as approximate.

various solvents (Table 5) assuming the validity of Lambert–Beer's law.

With the ϵ values (Table 5) and the end absorbances A_{end} (Fig. 1) of the benzhydrylium ions after reaching the equilibria, the equilibrium concentrations of Ar_2CH^+ were calculated. Their combination with the initial concentrations of the benzhydrylium ions and of the azide anion yields the equilibrium constants for the reactions of the azide anion with the benzhydrylium ions (Table 6).

Comparison of the equilibrium constants determined at different sodium azide concentrations (Supplementary Material) shows that K somewhat decreases at higher salt concentrations, probably due to increasing solvent polarity. Although the equilibrium constants obtained in this way are generally larger than those calculated as the ratios of the forward and backward rate constants (Table 6, in parentheses), they are in the same order of magnitude and can thus be considered as confirmation of the rate constants $k_{-1,Az}$.

**Figure 4.** Correlation of $\log k_{2,Az}$ for the reactions of the azide anion with tritylium ions (20 °C) in water/acetonitrile 67/33 (v/v) *versus* their electrophilicity parameters E

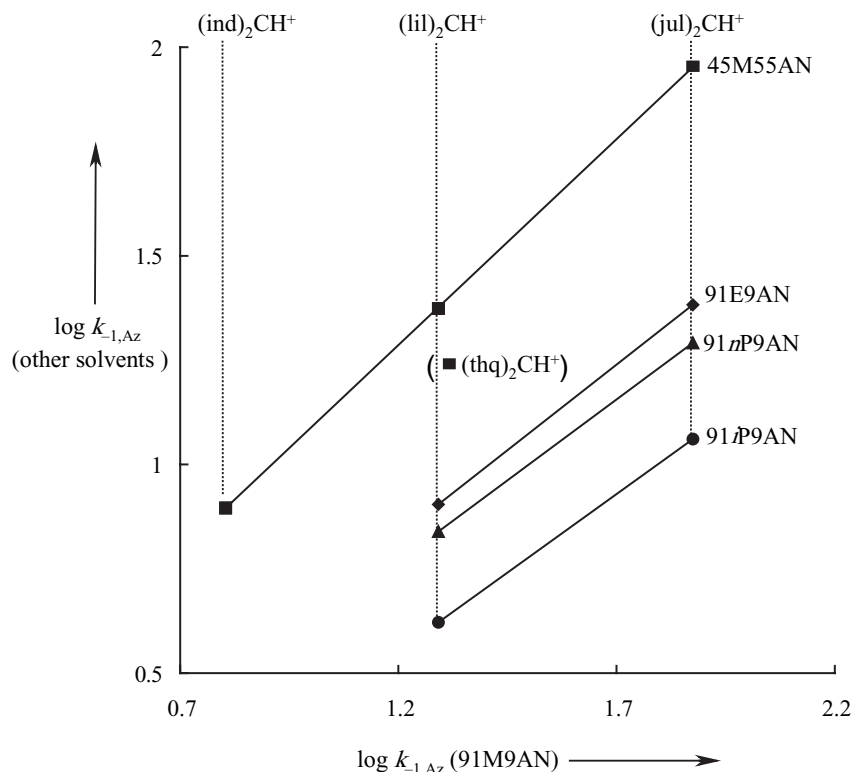


Figure 5. Plot of $\log k_{-1,Az}$ for the ionizations of benzhydrylium azides (at 20 °C, in different solvents) versus $\log k_{-1,Az}$ for the reactions in 91% MeOH/9% MeCN (v/v). Solvent mixtures are given as (v/v); solvents: AN = acetonitrile, E = ethanol, M = methanol, nP = propan-1-ol, iP = propan-2-ol

Table 5. Molar absorptivities ε ($M^{-1} \text{ cm}^{-1}$) of the benzhydrylium ions in different solvents

Solvent ^a	(lil) ₂ CH ⁺	(jul) ₂ CH ⁺	(ind) ₂ CH ⁺	(thq) ₂ CH ⁺
	(629 nm)	(632 nm)	(615 nm)	(618 nm)
91M9AN	9.26×10^4	9.50×10^4	8.64×10^4	6.63×10^4
45M55AN	9.62×10^4	8.53×10^4	8.63×10^4	5.10×10^4
91E9AN	9.68×10^4	1.04×10^5	1.10×10^5	—
91nP9AN	9.07×10^4	1.00×10^5	—	—
91iP9AN	9.35×10^4	9.92×10^4	—	—

^a Solvent mixtures are given as (v/v); solvents: AN = acetonitrile, E = ethanol, M = methanol, nP = propan-1-ol, iP = propan-2-ol.

DISCUSSION

As expected, Fig. 3 and Table 3 show that the nucleophilicity of the azide anion is largest in DMSO and decreases with increasing hydrogen-bonding ability of the alcohols. Vice versa, the ionization rate constants are smallest in the least polar solvent isopropanol and increase slightly in the series *i*-PrOH < *n*-PrOH < EtOH < MeOH.

The unexpected electrofugality order of the benzhydrylium ions, (ind)₂CH⁺ < (thq)₂CH⁺ ≈ (lil)₂CH⁺ < (jul)₂CH⁺, derived from entries 1 and 2 of Table 4 has been confirmed by the equilibrium measurements (Table 6).

Table 6. Equilibrium constants K^a (M^{-1} , Eqn (2)) of the reactions of the azide anion with benzhydrylium ions in different solvent systems (20 °C)

Solvent ^b	(lil) ₂ CH ⁺	(jul) ₂ CH ⁺	(ind) ₂ CH ⁺	(thq) ₂ CH ⁺
91M9AN	3.55×10^2 (2.67×10^2)	1.67×10^2 (1.78×10^2)	1.15×10^4 (9.52×10^3)	9.61×10^3 (7.29×10^3)
45M55AN	5.74×10^2 (4.56×10^2)	2.75×10^2 (2.72×10^2)	1.91×10^4 (1.42×10^4)	2.08×10^4 (1.63×10^4)
91E9AN	5.40×10^3 (4.65×10^3)	3.96×10^3 (3.61×10^3)	2.37×10^{5c} (1.75×10^5)	$(1.64 \times 10^5)^c$
91nP9AN	1.58×10^4 (1.05×10^4)	1.13×10^4 (8.66×10^3)	—	—
91iP9AN	3.91×10^{4c} (2.13×10^4)	3.04×10^4 (2.16×10^4)	—	—

^a Estimated errors ±15%; the values in parentheses are obtained from the ratios of $k_{2,Az}$ and $k_{-1,Az}$.

^b Solvent mixtures are given as (v/v); solvents: AN = acetonitrile, E = ethanol, M = methanol, nP = propan-1-ol, iP = propan-2-ol.

^c These values should be considered as approximate.

Table 7. Intrinsic barriers $\Delta_r G^0$ (kJ mol⁻¹) for the reactions of the azide anion with benzhydrylium ions in different solvent systems (20 °C)

Solvent ^a	(lil) ₂ CH ⁺	(jul) ₂ CH ⁺	(ind) ₂ CH ⁺	(thq) ₂ CH ⁺
91M9AN	57.8	54.6	55.7	53.2
45M55AN	56.6	53.7	54.7	52.5
91E9AN	56.1	53.6	54.9 ^b	—
91 <i>n</i> P9AN	55.6	53.1	—	—
91 <i>i</i> P9AN	56.1 ^b	53.3	—	—

^aSolvent mixtures are given as (v/v); solvents: AN = acetonitrile, E = ethanol, M = methanol, *n*P = propan-1-ol, *i*P = propan-2-ol.

^bThese values should be treated with caution because of the low accuracy of the determination of the equilibrium constants.

At first glance, it appears contradictory that (jul)₂CH⁺ reacts approximately two times faster with the azide anion than (lil)₂CH⁺, and at the same time the ionization of (jul)₂CH—N₃ is 2–3 times faster than the ionization of (lil)₂CH—N₃. Analogously, (thq)₂CH⁺ is a better electrophile and at the same time a better electrofuge than (ind)₂CH⁺. If these results stood by themselves, one might think of an experimental error. However, a similar behavior has been reported for the reactions of these benzhydrylium ions with phosphanes.²¹ Furthermore, reversible reactions of these benzhydrylium ions with other nucleophiles show the same trends (Mayr, Tishkov, unpublished results).

When the concept of intrinsic barriers ΔG_0^\ddagger by Marcus³⁷ is also applied for this type of reaction, one can calculate formal values of ΔG_0^\ddagger by substituting ΔG^\ddagger (from the rate constants in Table 2) and $\Delta_r G^0$ (from the equilibrium constants in Table 6) into the Marcus Eqn (3),

where the work term has been omitted. Table 7 shows that ΔG_0^\ddagger for (jul)₂CH⁺ is generally smaller than for (lil)₂CH⁺. Analogously, the intrinsic barrier is smaller for the reactions of (thq)₂CH⁺ than of (ind)₂CH⁺.

$$\Delta G^\ddagger = \Delta G_0^\ddagger + 0.5\Delta_r G^0 + (\Delta_r G^0)^2/16\Delta G_0^\ddagger \quad (3)$$

Figure 6 illustrates the corresponding Gibbs free energy profiles for the reactions of azide with the four benzhydrylium ions in 91% MeOH/9% MeCN (v/v) which is representative for the situation in other solvents. One can see, that $\Delta_r G^0$ for the reactions of N₃⁻ with the benzhydrylium ions incorporating a five-membered ring, (lil)₂CH⁺ and (ind)₂CH⁺, are the same or slightly more negative than the corresponding values for the six-membered ring analogs (jul)₂CH⁺ and (thq)₂CH⁺, respectively. It is the lower intrinsic barrier for the reactions of (jul)₂CH⁺ and (thq)₂CH⁺ (Table 7), which makes the compounds with the six-membered rings better electrophiles as well as better electrofuges than the five-membered ring analogs.

Let us now consider linear extrapolations of the correlations shown in Fig. 3 towards more reactive carbenium ions. With the *N* and *s* parameters listed in Table 3, one can calculate [Eqn (1)] that log $k_{2,Az} = 10$ is reached for carbocations with electrophilicity parameters between $-3.7 < E < -2.4$ (Table 8). Though a flattening of the correlation lines is known to occur as the diffusion limit is approached, these are the carbenium ions where the reactions with azide become diffusion controlled. In other words, in DMSO, carbocations with $E > -3$, and in simple alcohols, carbocations with $E > -2$ can be expected to undergo diffusion controlled reactions with

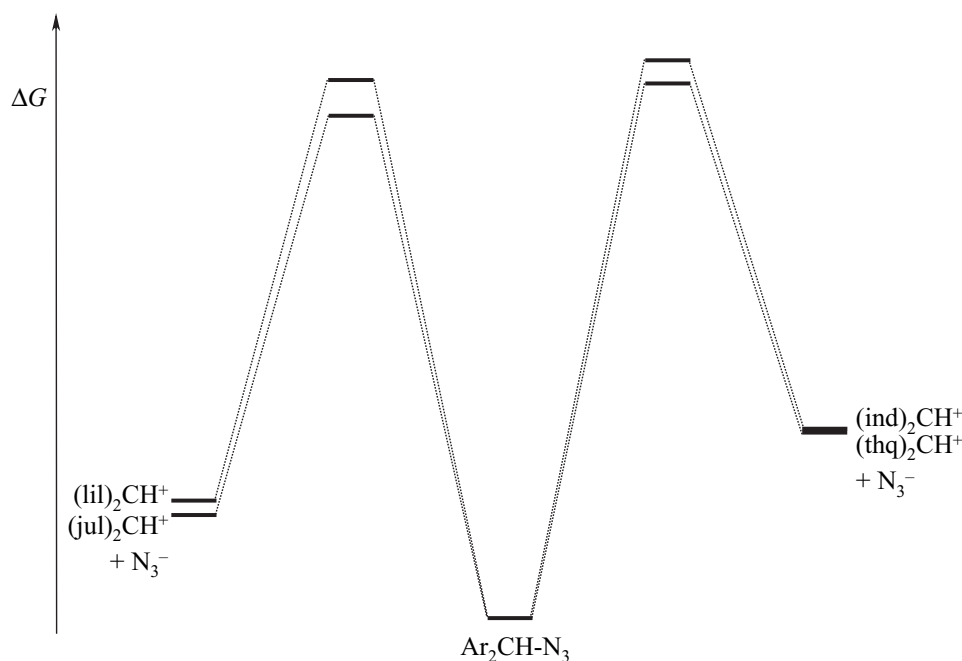
**Figure 6.** Gibbs free energy profiles (20 °C) for the reactions of the azide anion with benzhydrylium ions in MeOH/MeCN 91/9 (v/v)

Table 8. Electrophilicities E of electrophiles at the border of activation and diffusion controlled reactions with the azide anion in different solvents^a

Nucleophile ^a	E^b
N_3^- in 91M9AN	-2.4
N_3^- in 45M55AN	-2.5
N_3^- in 91E9AN	-2.5
N_3^- in 91 <i>n</i> P9AN	-2.9
N_3^- in 91 <i>i</i> P9AN	-2.9
N_3^- in DMSO	-3.7

^aSolvent mixtures are given as (v/v); solvents: AN=acetonitrile, E=ethanol, M=methanol, *n*P=propan-1-ol, *i*P=propan-2-ol.

^bCalculated [Eqn (1)] E values for $\log k_{2,Az} = 10$ based on N and s from Table 3.

the azide ion. Furthermore, Table 4 indicates that carbocations of lower electrophilicity will react reversibly with the azide ion. Thus, for kinetic as well as for thermodynamic reasons the azide-clock method cannot be applied to characterize carbocations with an electrophilicity of $E < -2$.

EXPERIMENTAL

Materials

Reagent grade methanol (99.8%, Acros), anhydrous isopropanol (99.5%, Aldrich), anhydrous acetonitrile (99.5%, Merck), extra dry DMSO ($H_2O < 0.005\%$, Acros), and sodium azide (>99%, Merck) were purchased. Absolute ethanol and propan-1-ol were distilled from iodine-activated magnesium. The benzhydrylium tetrafluoroborates were synthesized as described previously.¹³

Kinetics

The kinetic measurements were performed by following the decay of the absorbances of the colored reference electrophiles using UV-Vis spectroscopy.^{18,28a,38,39}

While the reactions in DMSO were carried out by mixing equal volumes of solutions of sodium azide and benzhydrylium tetrafluoroborate in pure DMSO, the reactions in alcohol/acetonitrile mixtures were performed by mixing 10 volume parts of the solutions of NaN_3 in alcohols or in 50% alcohol/50% acetonitrile (v/v) with 1 volume part of the solutions of the benzhydrylium salts in acetonitrile to yield 91/9 or 45.45/54.55 (v/v) mixtures of alcohols and acetonitrile, respectively.

The fast reaction of the azide anion with $(jul)_2CH^+$ in DMSO was studied by using an Applied Photophysics SX.18MV-R stopped-flow spectrophotometer system. All reactions in alcohol/acetonitrile mixtures were followed by using a Hi-Tech SF-61DX2 stopped-flow spectro-

photometer system (controlled by Hi-Tech KinetAsyst2 software) with syringes set up for a 10/1 mixing ratio.

The temperature of the solutions during all kinetic studies was kept constant (20 ± 0.1 °C) by using a circulating bath thermostat.

Azide concentrations were at least ten times as high as those of the electrophiles, resulting in pseudo-first-order kinetics with an exponential decay of the electrophile concentrations. The pseudo-first-order rate constants k_{obs} (sec^{-1}) were obtained by least squares fitting of the absorbance A of the electrophiles to the single-exponential $A_t = A_0 \exp(-k_{obs}t) + C$.

The slopes of the linear plots of k_{obs} (sec^{-1}) versus the concentrations of the azide ion correspond to the second-order rate constants $k_{2,Az}$ ($M^{-1}sec^{-1}$) of the forward reactions of the azide ion with the electrophiles, and the intercepts reflect the first-order rate constants $k_{-1,Az}$ (sec^{-1}) of the backward reactions.

Equilibrium constants

The molar absorptivities ϵ ($M^{-1}cm^{-1}$) of the benzhydrylium ions in different solvents were determined by UV-Vis spectroscopy based on their concentrations $[Ar_2CH^+]_0$ (M) and the corresponding absorbances A_0 assuming the validity of Lambert–Beer's law. From the end absorbances A_{end} of the benzhydrylium ions (determined at the moment, when the reactions reached equilibria, Fig. 1) and the initial concentrations of the benzhydrylium ions and of the azide anion, the equilibrium concentrations of all the components in the reaction mixtures were calculated.

Acknowledgments

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