

How to predict changes in solvolysis mechanisms*,**

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Abstract: Stopped-flow and laser flash techniques have been employed to investigate the individual steps of the solvolysis reactions of benzhydryl (diarylmethyl) halides and carboxylates. In this way, absolute rate constants for the ionization (k_1), recombination of the carbocation with the leaving group (k_{-1}), and subsequent reaction with the solvent (k_{SolvOH}) have been determined. As the stabilization of the carbocations increases, the mechanism changes from (a) S_N1 reactions with irreversible ionization through (b) S_N1 reactions with common-ion return and (c) S_N2C^+ reactions, where the intermediate carbocations accumulate, to (d) the formation of persistent carbocations which do not undergo subsequent reactions under the selected solvolysis conditions. The correlation equation $\log k = s(N + E)$, where the carbocations are characterized by the electrophilicity parameter E , and leaving groups and solvents are characterized by the nucleophile-specific parameters s and N can be employed to predict the changes of mechanism.

Keywords: kinetics; nucleophilicity; carbocations; linear free energy relationships; nucleofugality.

INTRODUCTION

Ingold's differentiation between S_N2 and S_N1 mechanisms (Fig. 1) was a breakthrough in the understanding of organic reactivity [1,2]. Subsequent studies of the rates and products of solvolysis reactions led Winstein to the suggestion that S_N1 reactions do not proceed through a single intermediate, but that different types of ion pairs as well as free ions are involved [3].

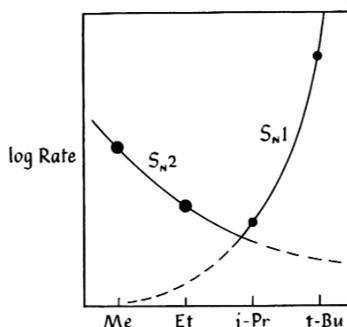


Fig. 1 Changes from S_N2 to S_N1 mechanism according to Ingold [1a].

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The situation described in Fig. 2 is so complicated that it is seldom possible to differentiate the contributions of the different types of ion pairs [4–7].

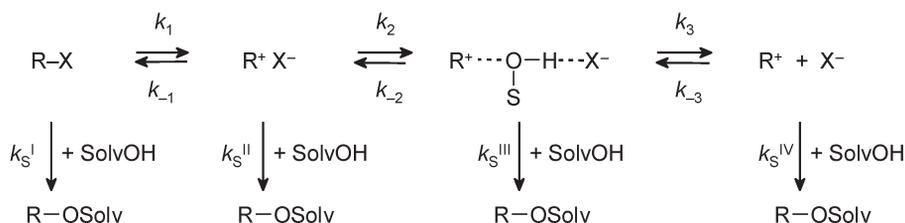


Fig. 2 Solvolysis scheme including different types of ion pairs according to Winstein [3].

Even when free and paired ions are not discriminated, the situation remains ambiguous. Many general organic chemistry texts formulate the $\text{S}_{\text{N}}1$ mechanism with a reversible ionization step as described in Fig. 3, and at the same time claim that the overall reaction rate depends only on the rate of the ionization step and is independent of the rate of the subsequent reaction—a contradiction in terms.

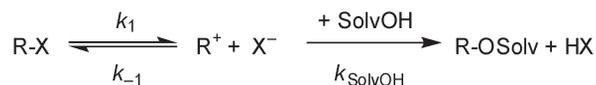


Fig. 3 Simplified solvolysis scheme.

In order to elucidate the changes in solvolysis mechanisms we set out to investigate the individual steps of the simplified solvolysis scheme in Fig. 3 separately, i.e., the rate of ionization (k_1), the rate of common ion return (k_{-1}), and the rate of the subsequent reaction with the solvent (k_{SolvOH}). By using para- and meta-substituted benzhydrylium ions as model substrates (Fig. 4), we kept the steric shielding at the reaction center constant while modifying the stabilization of the carbocations.

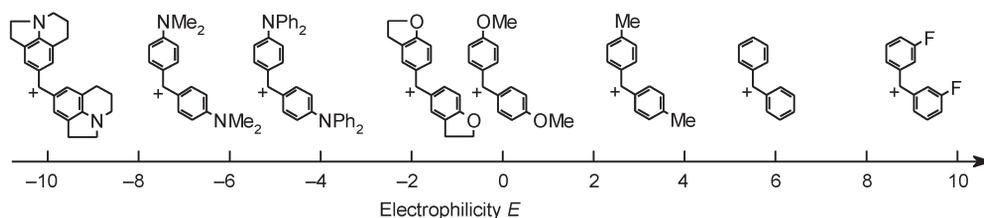


Fig. 4 Flexible tools: A series of benzhydrylium ions as R^+ .

Previous kinetic investigations have shown that the rates of the reactions of benzhydrylium ions with nucleophiles can be described by eq. 1 [8,9], where E is the electrophilicity parameter of the benzhydrylium ions, whereas N and s are nucleophile-specific parameters.

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

REACTIONS OF BENZHYDRILIUM IONS WITH THE SOLVENT

For the determination of k_{SolVOH} (Fig. 3), solutions of the colored benzhydrylium tetrafluoroborates in inert solvents (e.g., acetonitrile or acetone) were mixed with water or an alcohol in a stopped-flow instrument, and the decrease of the absorbance of the carbocation was monitored photometrically (Fig. 5) [10].

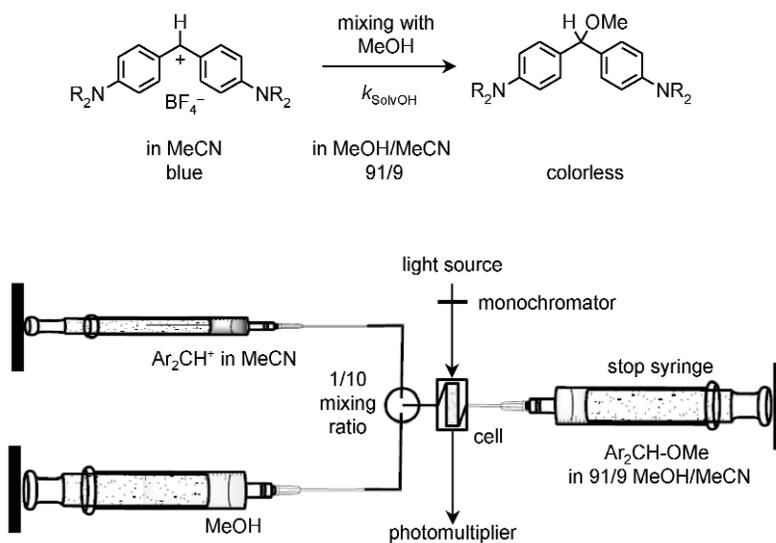


Fig. 5 Determination of solvent nucleophilicity (k_{SolVOH}) by stopped-flow techniques.

Faster reactions or reactions in 100 % alcohols were investigated by the laser flash method [11]. For that purpose, suitable precursors (benzhydryl 4-cyanophenolates or benzhydryl acetates [12]) were irradiated with 10 ns laser pulses (fourth harmonics of a Q-switched Nd:YAG-Laser at $\lambda = 266 \text{ nm}$, power/pulse ca. 50 mJ), and the decays of the colored transients were followed photometrically (Fig. 6) [10].

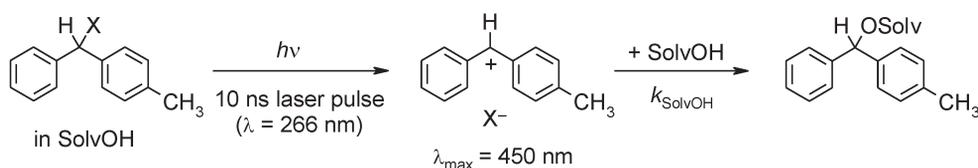


Fig. 6 Determination of solvent nucleophilicity (k_{SolVOH}) by laser flash photolytic generation of a carbocation ($\text{X}^- = 4\text{-cyanophenolate}$ or acetate).

Plots of the first-order rate constants ($\log k$) derived from the exponential decays vs. the empirical electrophilicity parameters E of the benzhydrylium ions turned out to be linear, as required by eq. 1 (Fig. 7). It should be emphasized that the rate constants for the reactions with 2,2,2-trifluoroethanol, which beautifully correlate with E , have been measured by McClelland [13]. The slopes of these correlations corresponded to the nucleophile-specific parameters s , and the negative intercepts on the abscissa gave the nucleophilicity parameters which are termed N_1 in this case in order to indicate that they refer to first-order rate constants.

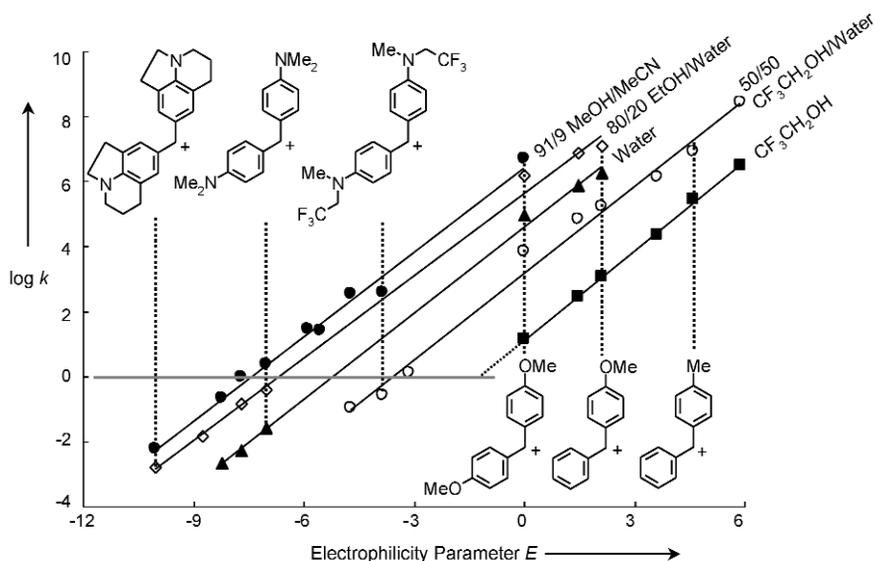


Fig. 7 Rate constants $\log k_{\text{SolvOH}}$ (20 °C) [10,12,13] for the decay of benzhydrylium ions in several solvents plotted against the electrophilicity parameter E [9]; solvent mixtures are given as (v/v).

Figure 8 summarizes the thus obtained N_1 parameters of several solvents and solvent mixtures [10,14] and shows a good correlation of N_1 with Kevill's N_T values [15], which correspond to the solvolysis rates of the *S*-methylbenzothiophenium ion in these solvents. The slope of this correlation (Fig. 8, right) indicates that variation of the nucleophilicity of the solvent affects the reactivities toward carbocations approximately twice as much as toward C_{sp^3} electrophiles (S_N2 reactions).

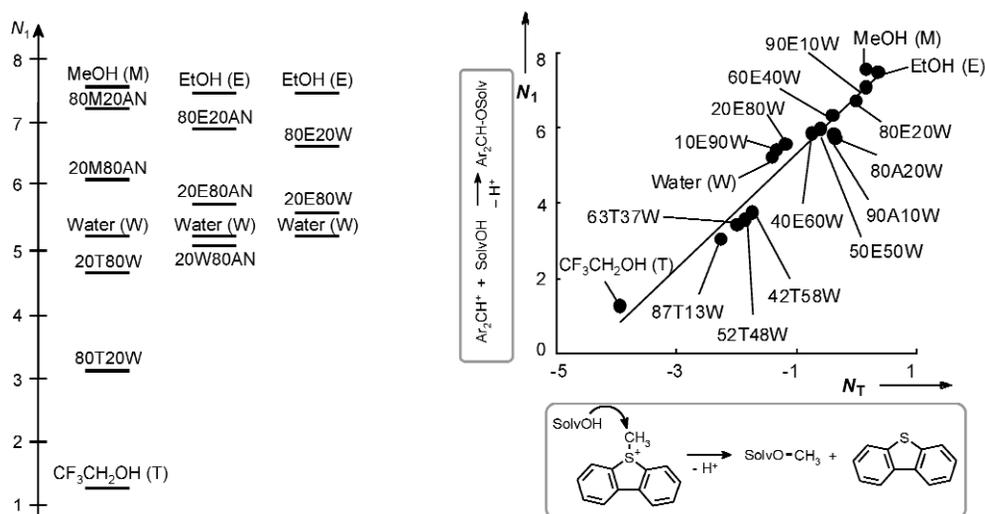


Fig. 8 Solvent nucleophilicities N_1 and their correlation with Kevill's N_T parameters [10].

Because N_1 and the corresponding s parameters have been determined for numerous solvents [10,14], and E parameters have been determined for a variety of carbocations [9], k_{SolVOH} , the rate constant for the second step of Fig. 3, can now be calculated for numerous systems by eq. 1.

COMMON ION RETURN

Analogous techniques have been used to determine the rate constants of the reverse reactions (k_{-1}). Stopped-flow techniques allowed us to determine the rates of the reactions of benzhydrylium tetrafluoroborates with carboxylate anions (Fig. 9). Whereas such combination rates can easily be measured in solvents of low nucleophilicity, e.g., 100 % acetonitrile, the determination of ion combination rates in alcoholic or aqueous solvent mixtures is often problematic because of the competing reactions of the benzhydrylium ions with the solvent. In several cases it was possible, however, also to determine rate constants for the reactions of carboxylate anions with benzhydrylium ions in aqueous solution, and from the plots of $\log k$ vs. the empirical electrophilicity parameters E , the nucleophile-specific parameters N and s for carboxylate anions could be determined [16]. Figure 9 shows that carboxylate nucleophilicities depend strongly on solvent and are smaller in protic solvents.

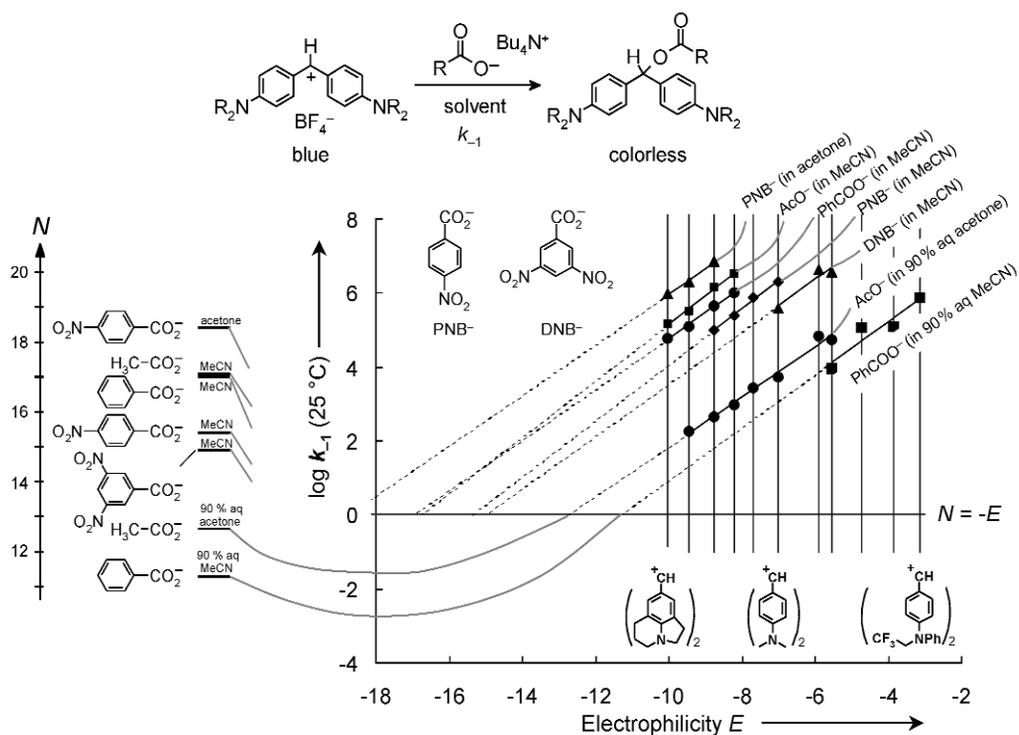


Fig. 9 Determination of the nucleophilicity parameters for carboxylate ions [16].

Because of the high nucleofugalities of chloride and bromide anions, combinations of amino-substituted benzhydrylium ions with Cl⁻ and Br⁻ are often thermodynamically unfavorable, and less stabilized benzhydrylium ions had to be employed for studying the rates of the reactions of benzhydrylium ions with Br⁻ and Cl⁻ [17]. These reactions are so fast, however, that laser flash techniques are needed to measure their rates. As previously described by Pham and McClelland, benzhydrylium *p*-cyanophenolates were irradiated to give benzhydrylium ions [12], the concentrations of which were

measured photometrically. When the benzhydrylium ions were generated in solutions containing variable concentrations of halide ions (usually $\text{Bu}_4\text{N}^+\text{Hal}^-$) the first-order rate constants k_{obs} , which were derived from the exponential decays of the carbocation absorbances, increased linearly with the concentration of the halide ions as illustrated in the left diagram of Fig. 10. While the slopes of the k_{obs} vs. $[\text{Hal}^-]$ plots give the second-order rate constants of the reactions of the benzhydrylium ions with the halide anions, the intercepts of these plots correspond to the reactions of the carbocations with the solvent (k_{SolvOH}) [17]. In analogy to Figs. 7 and 9, nucleophilicity parameters N for halide ions were derived from $\log k_{-1}$ vs. E plots. According to eq. 1, the nucleophilicity parameter N equals $-E$ at $\log k_{-1} = 0$, i.e., N is obtained as the negative intercept on the x -axis in $\log k_{-1}$ vs. E plots (right diagram of Fig. 10).

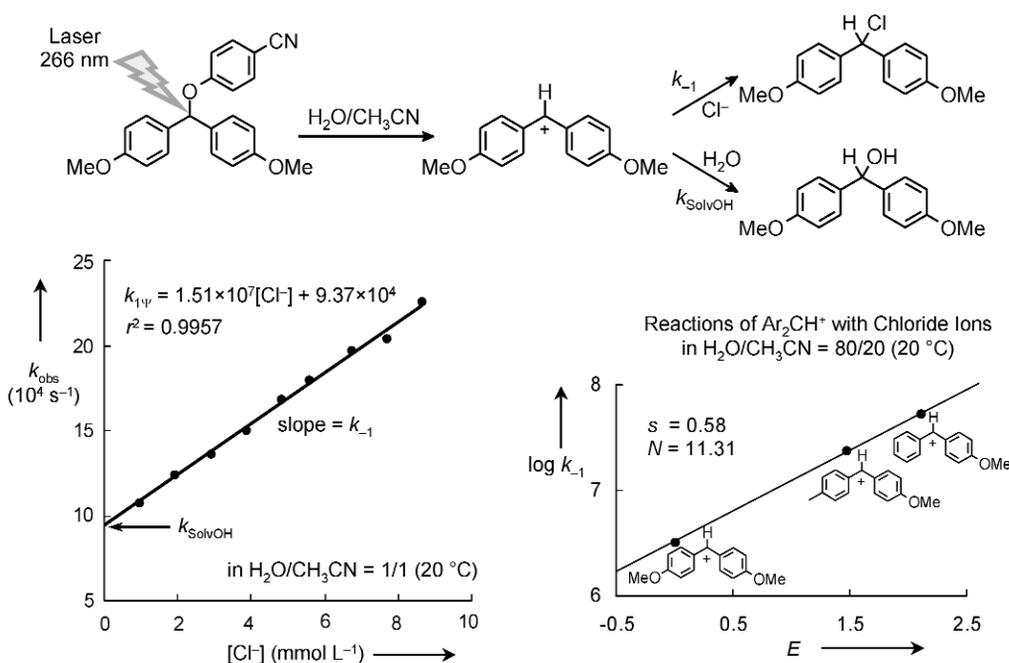


Fig. 10 Determination of halide nucleophilicities (k_{-1}) [17].

As summarized in the left part of Fig. 11, Br^- is a stronger nucleophile than Cl^- in all solvents investigated. The nucleophilicities of both anions decrease as the content of water in acetonitrile is increased. The inverse relationship between $N(\text{Cl}^-)$ in different solvents and the solvent ionizing power Y_{Cl} reveals that hydrogen bonding reduces chloride nucleophilicities as it increases the solvent ionizing power Y_{Cl} in adamantyl chloride solvolysis [18].

When the second-order rate constants k_{-1} for the reactions of benzhydrylium ions with chloride ions and the first-order rate constants for the reactions of benzhydrylium ions with the solvent are plotted against the electrophilicity parameters of the benzhydrylium ions, the mass law constant α is shown to decrease with increasing reactivity of the carbenium ions (Fig. 12) [17,19]. For the sake of simplicity, the diffusion limits for the reactions with Cl^- and with H_2O are drawn at the same level though this is not precisely correct.

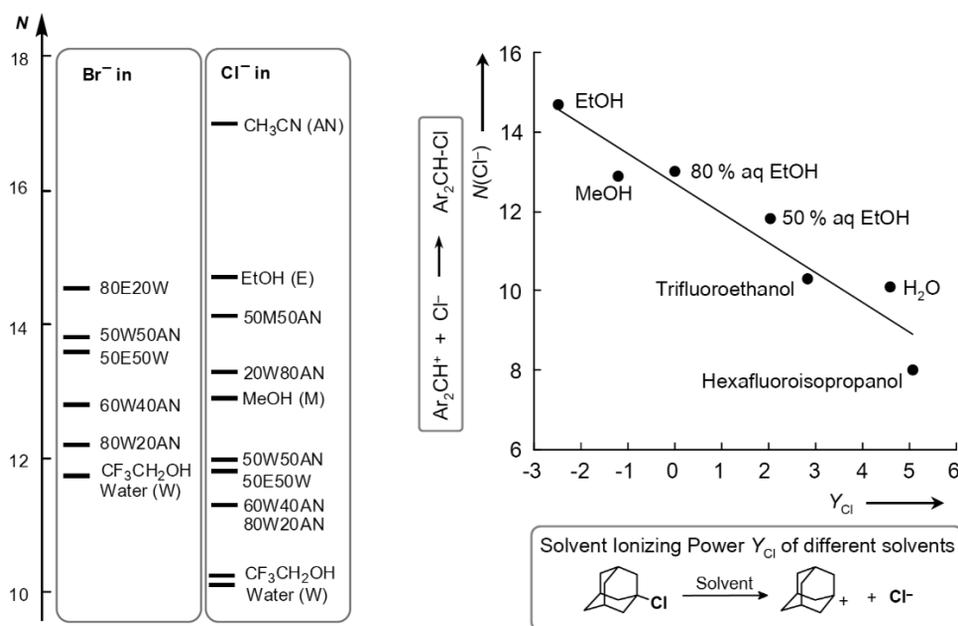


Fig. 11 Bromide and chloride nucleophilicities in different solvents [17] and dependence of the chloride nucleophilicities on the solvent ionizing power Y_{Cl} (from [18]).

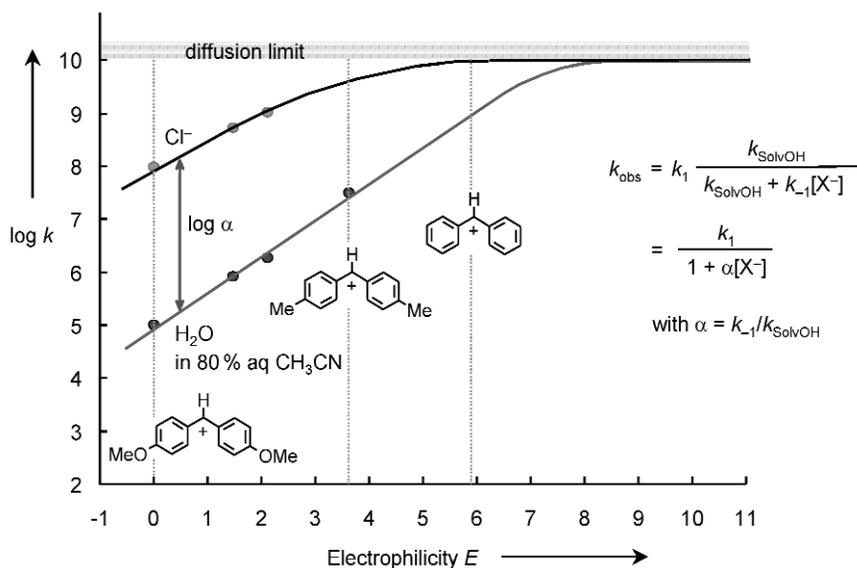


Fig. 12 Mass law constant ($\log \alpha$) as the difference between second-order rate constants of the reactions of the carbocations with Cl^- ($\log k_{-1}$) and the first-order rate constants of their reactions with the solvent ($\log k_{\text{SolvOH}}$).

The importance of common ion return [19] is more easily seen in Fig. 13, where the second-order rate constants for the reactions of benzhydrylium ions are replaced by the corresponding first-order rate constants $k_{-1}[\text{Cl}^-]$ at variable chloride concentrations. One can see that at $[\text{Cl}^-] = 0.1 \text{ M}$, in 80 % aqueous CH_3CN the unsubstituted benzhydrylium ion Ph_2CH^+ reacts with Cl^- and with H_2O with similar rates. More reactive carbocations react faster with water, while less reactive carbocations react faster with Cl^- . For $[\text{Cl}^-] = 0.001 \text{ M}$, it is the 4,4'-dimethoxybenzhydrylium ion which has equal chances to react with water and Cl^- , i.e., at $[\text{Cl}^-] = 0.001 \text{ M}$ in 80 % aqueous acetonitrile, reversibility of the ionization becomes only important for more stabilized carbocations. In 80 and 90 % aqueous acetone, common ion return is also observed for less stabilized carbenium ions [20].

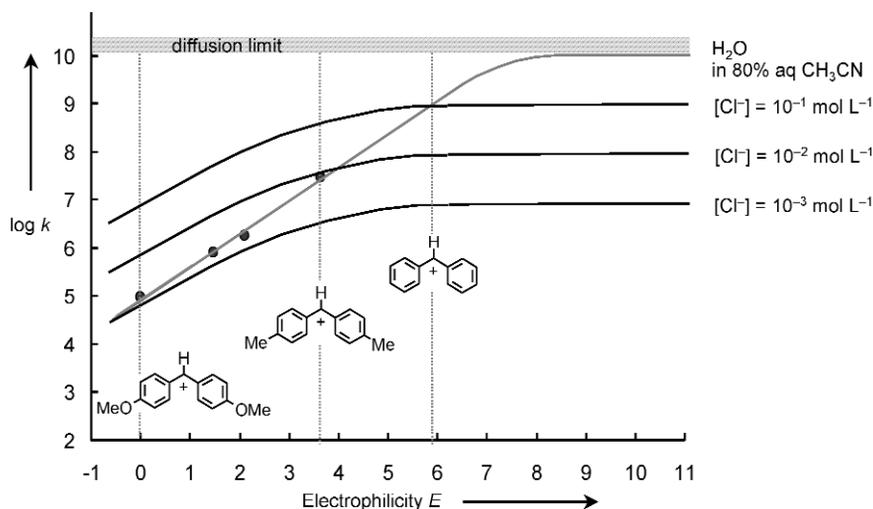


Fig. 13 First-order ($\log k_{\text{SolvoH}}$), and pseudo-first-order rate constants [$\log (k_{-1}[\text{Cl}^-])$] for the reactions of carbocations with the solvent and the nucleofuge, respectively.

IONIZATION RATES

When carbocations are formed as short-lived intermediates and $k_{\text{SolvoH}} > k_{-1}[\text{X}^-]$, the overall rates of solvolysis reactions (Fig. 3) equal the rates of the ionization step. In collaboration with Olga Kronja's group in Zagreb (Croatia) we have collected solvolysis rate constants of benzhydryl derivatives from the literature and complemented them by our own experimental data [21]. The solvolysis rate constants of benzhydryl tosylates, bromides, chlorides, trifluoroacetates, 3,5-dinitrobenzoates, and *p*-nitrobenzoates were then subjected to a least-squares minimization according to

$$\log k_{25^\circ\text{C}} = s_f(N_f + E_f) \quad (2)$$

where the benzhydrylium ions were characterized by the electrofugality parameter E_f [def. $E_f = 0$ for $(p\text{-MeOC}_6\text{H}_4)_2\text{CH}^+$] and combinations of leaving groups and solvents were characterized by the nucleofugality parameters N_f and s_f (def. $s_f = 1.0$ for Cl^- in 100 % EtOH).

While the predictive power of eq. 2 is quite good for benzhydryl derivatives, deviations up to 10^2 have been encountered for other types of substrates [22].

Despite this shortcoming, eq. 2 is a valuable tool for semiquantitatively ordering solvolytic reactivities. In Fig. 14, substrates are ordered with increasing electrofugality (less precise: carbocation stabilization) from bottom to top, and leaving group/solvent combinations are ordered with increasing nucleofugality N_f from right to left. Because $s_f \approx 1$ for all nucleofuges studied so far, differences in s_f are neglected in Fig. 14, which allows one to differentiate substrates which undergo easily measurable

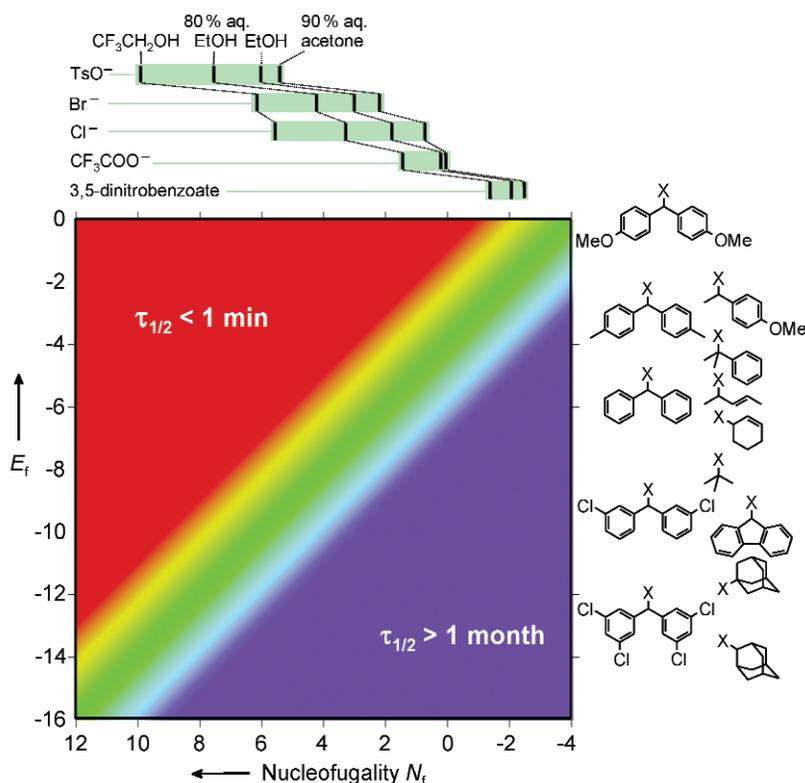


Fig. 14 Semiquantitative prediction of ionization rates by eq. 2 with $s_f = 1$ [22].

solvolysis reactions (green zone) from those which solvolyze very rapidly (red zone) and those which solvolyze very slowly (blue–violet zone).

Bentley has correctly criticized that some of the rate constants used for the calculation of E_f , N_f , and s_f in our original work were incorrect because of common ion return [23]. However, recent work by Denegri and Kronja [24] confirmed the necessity to leave s_f variable for the correlation analysis and not to employ only two parameters for describing the whole set of data as suggested by Bentley [23]. The reason for the choice of eq. 2, an unconventional form of a linear free energy relationship where N_f equals the negative intercept on the abscissa of a $\log k$ vs. E_f correlation, has been explained on page 1649 of ref. [21].

SOLVOLYSES VIA LONG-LIVED CARBOCATIONS

While Fig. 7 predicts that the combination of $(p\text{-MeOC}_6\text{H}_4)_2\text{CH}^+$ (electrophilicity $E = 0$) with $\text{CF}_3\text{CH}_2\text{OH}$ (nucleophilicity $N_1 = 1.23$, $s = 0.92$ [10]) should occur in the 0.1 s time range (eq. 1), Fig. 14 reveals that the ionization of $(p\text{-MeOC}_6\text{H}_4)_2\text{CH-Cl}$ in $\text{CF}_3\text{CH}_2\text{OH}$ should occur in less than a millisecond. Consequently, mixing of a solution of $(p\text{-MeOC}_6\text{H}_4)_2\text{CH-Cl}$ in CH_3CN with 10 volume parts of $\text{CF}_3\text{CH}_2\text{OH}$ in a stopped-flow instrument led to the immediate formation of $(p\text{-MeOC}_6\text{H}_4)_2\text{CH}^+$ which was detected photometrically (Fig. 15) [25]. The observed first-order rate constant for its reaction with $\text{CF}_3\text{CH}_2\text{OH}$ ($k = 11.4 \text{ s}^{-1}$) differed by less than 20 % from that predicted [$\log k = 0.92(1.23 + 0) = 1.13$; $k = 13.6 \text{ s}^{-1}$] by eq. 1.

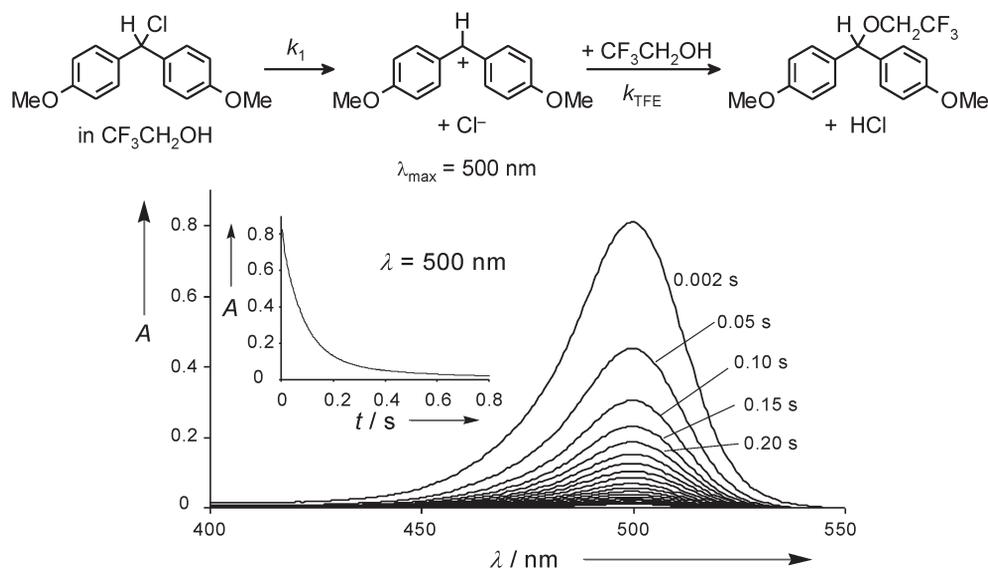


Fig. 15 Solvolysis of $(p\text{-MeOC}_6\text{H}_4)_2\text{CH-Cl}$ (20 °C) in a 91/9-mixture of 2,2,2-trifluoroethanol and acetonitrile (v/v) followed with a stopped-flow diode array UV-vis spectrometer [25].

Rates of ionization and of the subsequent combination of the resulting carbocations with the solvent could be determined when *p*-amino-substituted benzhydryl carboxylates were solvolyzed in aqueous acetone (Fig. 16) [26]. A real-time video showing the appearance and disappearance of the blue carbocations when water was added to a colorless solution of 4,4'-bis(morpholino)benzhydryl acetate in acetonitrile is provided in the supporting information of ref. [26]. $\text{S}_{\text{N}}2\text{C}^+$ reactions, postulated more than 50 years ago by Ingold [1], have thus been realized experimentally.

Further stabilization of the benzhydrylium ions has been achieved by incorporation of the 4-amino group in a bicyclic ring. When 20 vol % of water were added to a colorless acetonitrile solution of the covalent benzhydryl acetate depicted in Fig. 17, a blue solution was obtained within less than a second, which did not fade at prolonged times, i.e., the benzhydrylium ion did not react with water [16]. From the fact that the carbocation absorbance as well as k_{obs} for the ionization process did not depend on the concentration of the acetate ions, one can conclude that ion-combination ($\text{Ar}_2\text{CH}^+ + ^-\text{OAc}$) also does not occur under these conditions.

The upper line of Fig. 18 repeats the message of Fig. 9: The rates ($\log k$) of the combinations of benzoate anions with benzhydrylium ions [16], like the rate constants for hundreds of other nucleophile-electrophile combinations, correlate linearly with the electrophilicity parameters E of the benzhydrylium ions which we have published in 2001 [9a]. Surprisingly, the ionization rate constants of the corresponding benzhydryl benzoates follow a completely different trend (Fig. 18, lower line). In contrast to our expectation, it is not the benzhydrylium ion with lowest electrophilicity ($E = -10.04$) which is formed most rapidly, and the rates of ionization of the benzhydryl benzoates do not decrease steadily as the electrophilicities of the benzhydrylium ions increase [16].

It should be noted, however, that the reactivity pattern shown in the lower graph of Fig. 18 is not a singular case, but is analogously found in a series of other ionization rate constants of benzhydryl carboxylates with different carboxylate leaving groups in different solvents [16]. While we do not yet know the origin for the zig-zag pattern of the lower graph of Fig. 18, a reason for the absence of a linear correlation can be derived from Fig. 19.

From the diffusion-controlled reaction of the ditolylcarbenium ion with bromide in 80 % aqueous acetone (Fig. 19, left) it is evident that the transition state of the ionization of $(p\text{-MeC}_6\text{H}_4)_2\text{CH-Br}$ cor-

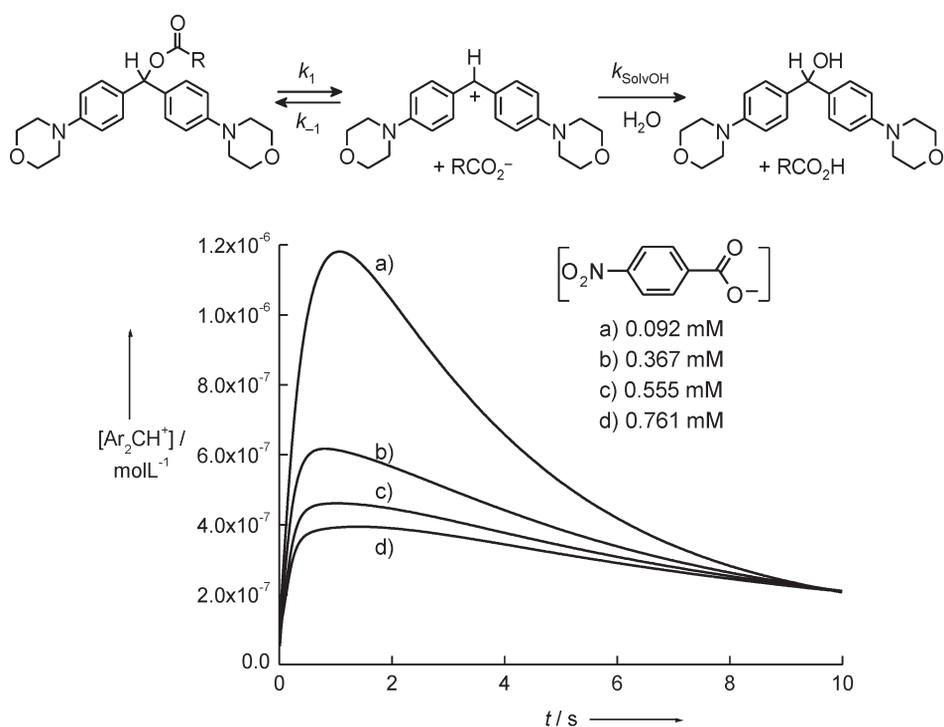


Fig. 16 Carbocation watching in hydrolysis reactions: Formation and consumption of the blue 4,4'-bis(morpholino)benzylidinium ion (monitored photometrically at 612 nm and converted to absolute concentrations) during the solvolysis of 4,4'-bis(morpholino)benzylidinium *p*-nitrobenzoate (0.01 mmol L^{-1}) in 80 % aqueous acetone in the presence of different amounts of tetra-*n*-butylammonium *p*-nitrobenzoate at 25 °C [26].

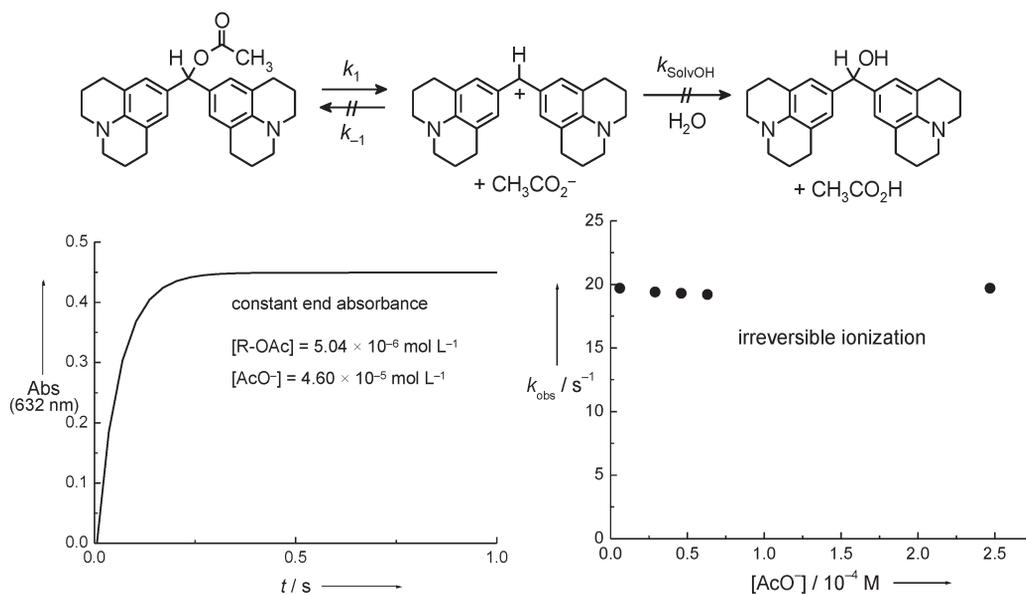


Fig. 17 Direct measurement of the ionization step (in 20 % water/80 % CH_3CN , 25 °C) [16].

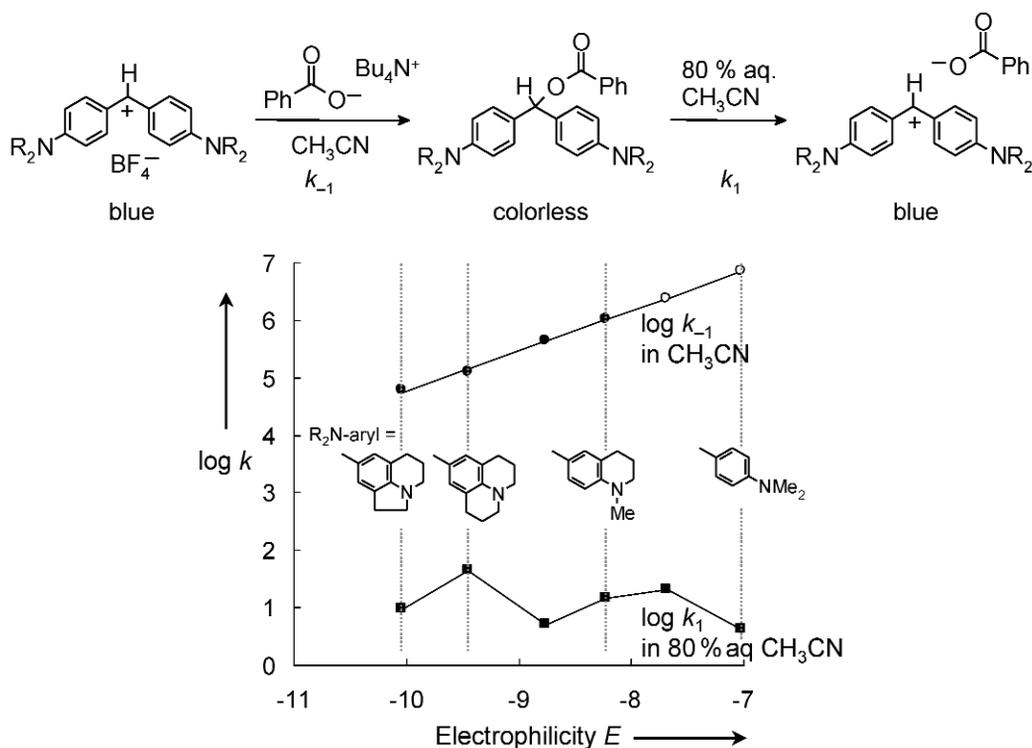


Fig. 18 Comparison of electrophilicities (k_{-1}) and electrofugalities (k_1) of benzhydrylium ions (at 25 °C; open circles for $\log k_{-1}$ were extrapolated by eq. 1) [16].

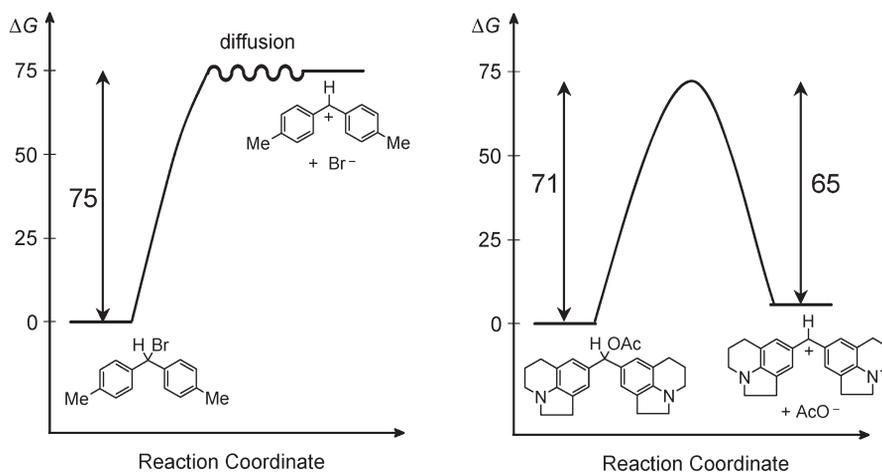


Fig. 19 Ionizations of benzhydryl bromides and acetates in 80 % aqueous acetone (at 25 °C, ΔG in kJ mol^{-1}) [16].

responds to the carbenium ion [27]. In contrast, the ionization of the amino-substituted benzhydryl acetate depicted on the right side of Fig. 19, which occurs with a similar rate in the same solvent, does not proceed through a carbocation-like transition state. Now, the activation energies are not exclusively controlled by the thermodynamic differences between covalent benzhydryl derivatives and benz-

hydrylium ions, and variable intrinsic barriers [28] must be responsible for the breakdown of the correlations [16]. Different transition states for the two types of substrates are also indicated by the slopes of the Winstein–Grunwald correlations depicted in Fig. 20 [29].

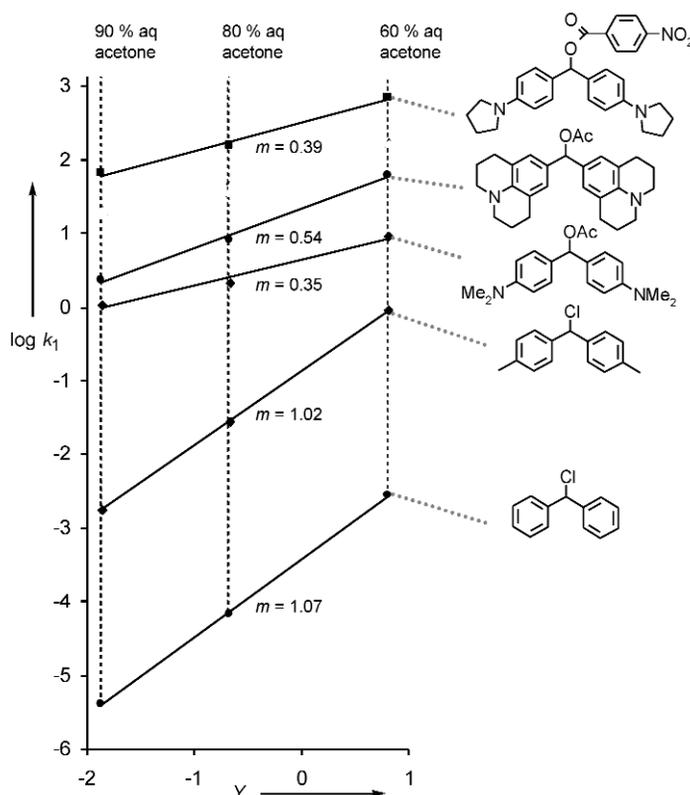


Fig. 20 Correlation between the ionization rate constants k_1 and Winstein–Grunwald's solvent ionizing power γ [16].

While the benzhydryl chlorides with carbocation-like transition states give correlations with $m \approx 1$ as expected for typical S_N1 reactions [29], the ionization reactions of the amino-substituted benzhydryl carboxylates have m values from 0.3 to 0.5 [16] which have previously been considered indicative for S_N2 type reactions. Ionization processes with comparably small values of m have previously been observed for the solvolyses of adamantyl picrates [30] and vinyl derivatives [19b].

CONCLUSION

Figure 21 illustrates that the usual assumption of carbocation-like transition states in common S_N1 solvolysis reactions [31] has found unequivocal support by directly measured diffusion-controlled reactions of carbocations with Cl^- and Br^- and fast subsequent reactions of the carbocations with the solvent [17]. Despite a small barrier for the reaction with the solvent, also the solvolysis of $(4\text{-MeC}_6\text{H}_4)_2\text{CH-Cl}$ in 80 % aqueous ethanol (Fig. 21, right) proceeds with rate-determining formation of the carbocations, because the chloride concentration is usually so small that common ion return cannot compete with the reactions of the carbocations with the solvent (cf. Fig. 13).

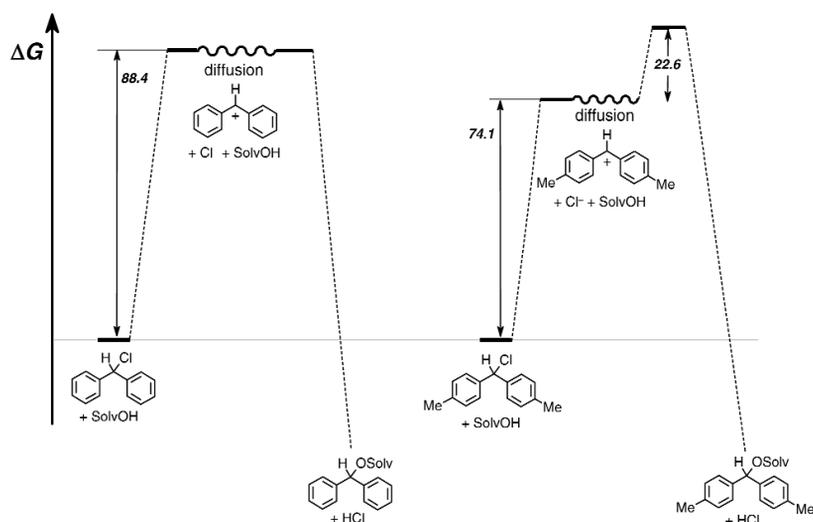


Fig. 21 Free energy profiles of S_N1 solvolysis reactions of benzhydryl chlorides in 80 % aqueous ethanol (at 25 °C, ΔG in kJ mol^{-1}) [17].

As shown in Fig. 22, the benzhydrylium ions generated in the initial step of the solvolyses of dimethoxy-substituted benzhydryl chlorides [21] and of amino-substituted benzhydryl carboxylates [16], do not undergo activationless recombinations with Cl^- [17] and carboxylate anions [16]. The principle of microscopic reversibility implies non-carbocation like transition states of the ionization processes.

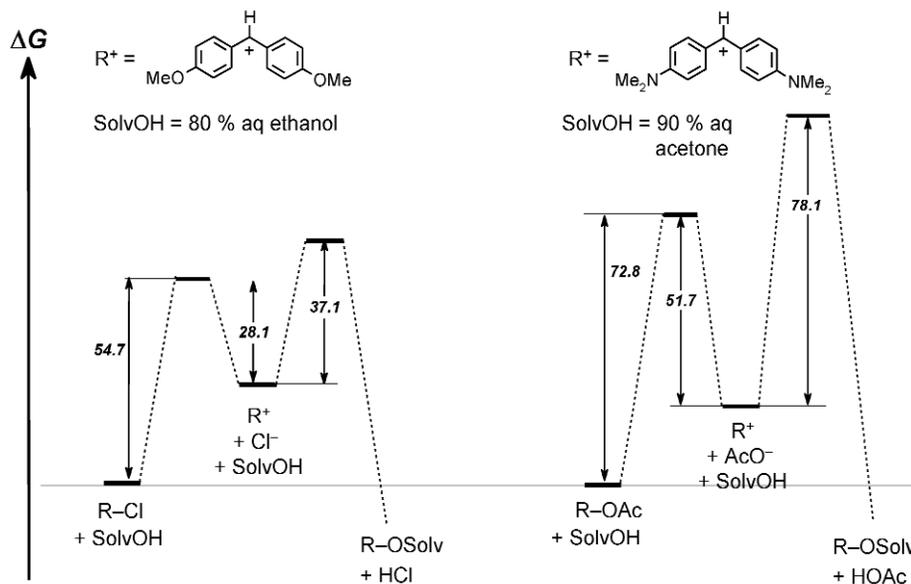


Fig. 22 Free energy profiles for the solvolysis reactions of $(4\text{-MeOC}_6\text{H}_4)_2\text{CH-Cl}$ in 80 % aqueous ethanol [17] and $(4\text{-Me}_2\text{NC}_6\text{H}_4)_2\text{CH-OAc}$ in 90 % aqueous acetone [16] (at 25 °C, ΔG in kJ mol^{-1}).

As summarized in Fig. 23, direct rate measurements and the correlation eqs. 1 and 2 allow us to predict the changes in S_N1 solvolysis mechanisms as the stabilization of the carbocations is varied. We have observed the change from conventional S_N1 reactions with irreversible ionization, through S_N1 reactions with common ion return, over S_N2C^+ mechanisms where carbocations become directly observable intermediates to “stable ion conditions”, where the rates of ionizations became directly measurable as the stabilization of the carbocations was continuously increased. We are now focusing on the mechanistic changes caused by destabilization of the carbocations which involves the change to S_N2 mechanisms according to the Jencks–Richard criterion of carbocation lifetimes [1b,32].

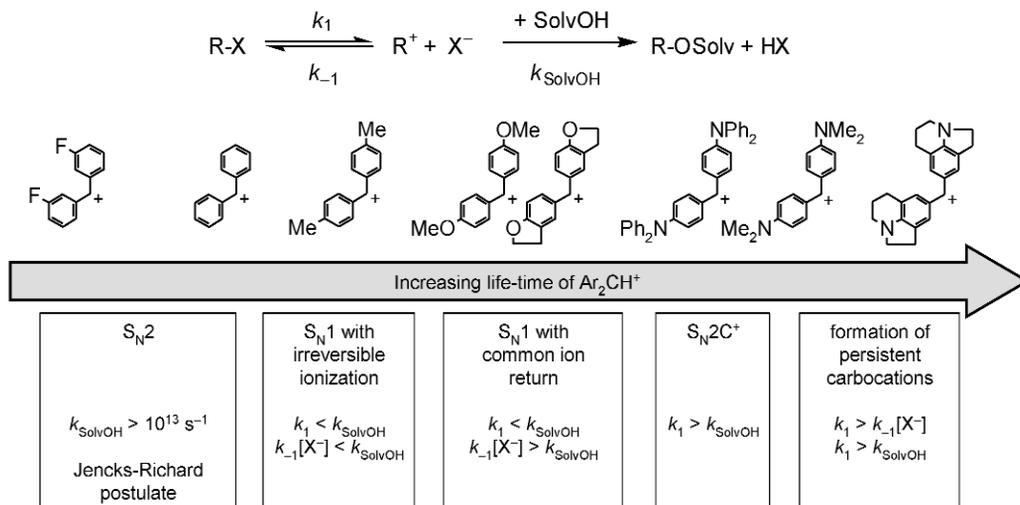


Fig. 23 Variation of the carbocation stabilization changes the mechanism of solvolysis reactions.

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