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Nucleophilicities and Nucleofugalities of Organic Carbonates

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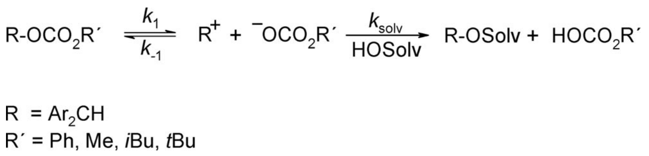
Dedicated to Professor Dieter Lenoir on the occasion of his 75th birthday

Keywords: Kinetics / Linear free energy relationships / Solvolysis / Correlation analysis / Leaving groups

The kinetics of the reactions of the methyl carbonate ion with benzhydrylium ions in acetonitrile have been studied by UV/Vis spectrophotometry. Substitution of the resulting second-order rate constants and the electrophilicity parameters E of the benzhydrylium ions into the linear free energy relationship $\log k = s(N + E)$ yielded the nucleophilicity parameters $N_{25} = 16.03$ and $s_{25} = 0.64$ for methyl carbonate in acetonitrile. The kinetics of the reverse reactions, i.e., of the solvolyses of ring-substituted benzhydryl alkyl carbonates in different aqueous solvents were followed by conductimetry. The obtained first-order rate constants and the known electrofugality parameters E_f of benzhydrylium ions were used to determine the nucleofugality parameters N_f and s_f of the $ROCO_2^-$ groups by using the linear free energy relationship $\log k = s_f(N_f + E_f)$. The leaving group abilities of carbonates decrease by a factor of about 300 from $PhOCO_2^-$ over $MeOCO_2^-$ and iBuOCO$_2^-$ to tBuOCO$_2^-$ in various alcoholic and aqueous solvents. *tert*-Butyl carbonates (tBocO-R) are, thus, considerably more stable with respect to heterolytic cleavage of the O–R bond than other organic carbonates.

Introduction

Alkoxycarbonyl groups are widely used as protecting groups of alcohols and phenols, because they can easily be introduced and removed.[1] Under basic conditions organic carbonates, i.e., the diesters of carbonic acid, are typically more stable than the corresponding esters of carboxylic acids and they have found wide use in organic synthesis.[2,3] Recently, Denegri and Kronja have studied the nucleofugality (leaving group ability) of phenyl and methyl carbonate (k_1 in Scheme 1) in different solvents.[4] *tert*-Butyl carbonates (tBocO–R), the most prominent carbonates, were not included in this study. As these data are of particular interest for synthetically working chemists, we now report on the nucleofugality of the tBocO group. In order to characterize the electrofugalities of benzhydrylium ions which are better stabilized than the 4,4′-dimethoxybenzhydrylium ion, we have furthermore studied the nucleofugality of isobutyl carbonate and extended the work of Denegri and Kronja on the leaving group abilities of methyl carbonate; these data are needed for the construction of comprehensive nucleofugality and electrofugality scales.[5]



Scheme 1. Simplified solvolysis scheme.

In previous work we compared the nucleophilic reactivities of halide[6] and carboxylate[7] ions toward benzhydrylium ions and demonstrated that the relative nucleophilicities are not the inverse of the relative nucleofugalities.[7] In order to extend this comparison to organic carbonates, we have now investigated the nucleophilic reactivity of the methyl carbonate ion by studying the rates of its reactions with benzhydrylium ions, which allows us to include the methyl carbonate ion in the comprehensive reactivity scales based on Equation (1),[8]

$$\log k = s(N + E) \qquad (1)$$

where k is a second-order rate constant, E is an electrophilicity parameter, and N and s are nucleophile-specific parameters.

Results and Discussion

Determination of the Rates of the Combinations of Benzhydrylium Ions with the Methyl Carbonate Ion (k_{-1} in Scheme 2): The reactions of tetra-*n*-butylammonium methyl carbonate with the colored benzhydrylium ions gave color-

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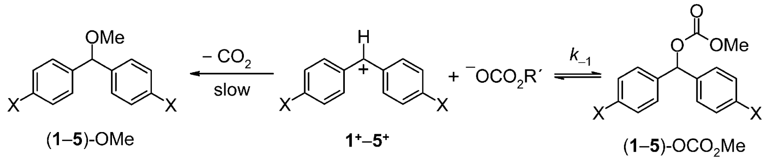
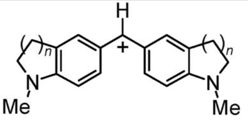
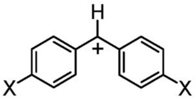


Scheme 2. Combination reaction of benzhydrylium ions with methyl carbonate and subsequent decarboxylation.

less products in acetonitrile. 4-Methoxybenzhydryl methyl carbonate (**6**-OCO$_2$Me) was formed in quantitative yield and isolated as a stable compound. However, we were not able to isolate the corresponding products when using highly stabilized benzhydrylium ions (Table 1), as the products rapidly decarboxylate with formation of the corresponding benzhydryl methyl ethers (**1**–**5**)-OMe (Scheme 2). The mechanism of this decarboxylation reaction is not clear, because a solution of tetra-*n*-butylammonium methyl carbonate in acetonitrile did not decompose noticeably at 25 °C during the time of the kinetic investigations. Possibly ionization of (**1**–**5**)-OCO$_2$Me and recombination of the initially generated ion-pair does not exclusively regenerate the carbonates Ar$_2$CH-OCO$_2$Me; occasionally electrophilic attack at the methoxy oxygen of H$_3$CO-CO$_2$$^-$ yields a zwitterion which decomposes with formation of CO$_2$ and the observed benzhydryl methyl ethers.

Table 1. Benzhydrylium ions Ar$_2$CH$^+$ and their electrophilicity parameters *E*.

No	Ar$_2$CH$^+$		$E^{[a]}$
			
1$^+$	(ind)$_2$CH$^+$	$n = 1$	–8.76
2$^+$	(thq)$_2$CH$^+$	$n = 2$	–8.22
			
3$^+$	(pyr)$_2$CH$^+$	X = N(CH$_2$)$_4$	–7.69
4$^+$	(mor)$_2$CH$^+$	X = N(CH$_2$CH$_2$)$_2$O	–5.53
5$^+$	(mfa)$_2$CH$^+$	X = N(CH$_3$)CH$_2$CF$_3$	–3.85

[a] Electrophilicity parameter as defined by Equation (1) (from ref.[8]).

Most reactions were followed photometrically at the absorption maxima of Ar$_2$CH$^+$ by using a stopped-flow instrument. For studying reactions on the microsecond timescale, the benzhydrylium ions were generated by laser pulse irradiation of benzhydryl tri-*n*-butylphosphonium tetrafluoroborates[9] in acetonitrile solution in the presence of tetra-*n*-butylammonium methyl carbonate. All reactions were performed under pseudo-first-order conditions (high excess of *n*-Bu$_4$N$^+$MeOCO$_2$$^-$) at 25 °C in acetonitrile. The first-order rate constants k_{obs} were obtained from the exponential decays of the absorbances of the electrophiles (Figure 1). Details are given in the Supporting Information.

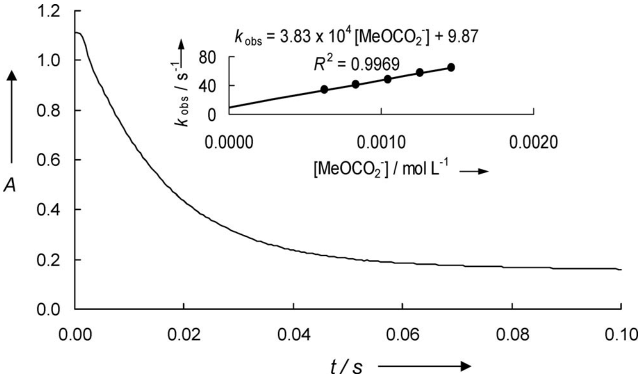


Figure 1. Exponential decay of the absorbance at 616 nm during the reaction of (ind)$_2$CH$^+$ (**1**$^+$) with MeOCO$_2$$^-$ in CH$_3$CN at 25 °C ([(ind)$_2$CH$^+$] = 2.13×10^{-5} M; [MeOCO$_2$$^-$] = 1.25×10^{-3} M; k_{obs} = 57.1 s^{-1}). Insert: determination of the second-order rate constant k_{-1} (3.83×10^4 M^{-1} s^{-1}) as the slope of the correlation of the first-order rate constants k_{obs} vs. [MeOCO$_2$$^-$].

As depicted in Figure 1 the absorbance of the electrophile does not fade completely during the monitored reaction time (0.1 s), indicating an equilibrium between covalent carbonates and ionic starting materials. However, when the reaction shown in Figure 1 was monitored for 2 seconds, complete disappearance of the absorbance of the benzhydrylium ion was observed, which is explained by the subsequent irreversible formation of the benzhydryl methyl ether (Scheme 2).

As illustrated in the insert of Figure 1, k_{obs} increases linearly with the concentration of MeOCO$_2$$^-$. The second-order rate constants k_{-1} listed in Table 2 were obtained as the slopes of these plots [Equation (2)].

$$k_{obs} = k_{-1}[\mathrm{MeOCO_2^-}] \qquad (2)$$

Table 2. Second-order rate constants k_{-1} for the reactions of benzhydrylium ions with Bu$_4$N$^+$MeOCO$_2$$^-$ in acetonitrile at 25 °C.

No	Ar$_2$CH$^+$	$E^{[a]}$	k_{-1} [M^{-1} s^{-1}]
1$^+$	(ind)$_2$CH$^+$	–8.76	3.83×10^4
2$^+$	(thq)$_2$CH$^+$	–8.22	9.69×10^4
3$^+$	(pyr)$_2$CH$^+$	–7.69	2.57×10^5
4$^+$	(mor)$_2$CH$^+$	–5.53	5.21×10^6
5$^+$	(mfa)$_2$CH$^+$	–3.85	5.77×10^7

[a] Electrophilicity parameter as defined by Equation (1) (from ref.[8]).

When the logarithms of the second-order rate constants k_{-1} are plotted against the previously reported electrophilicity parameters *E* of the benzhydrylium ions (Figure 2), a linear correlation is obtained, which yields the nucleophilicity parameter[10] $N_{25} = 16.03$ as the negative intercept on the abscissa (E axis) and the nucleophile-specific slope parameter[10] $s_{25} = 0.64$.

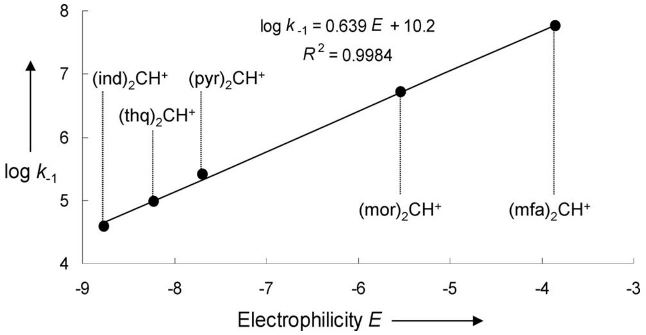


Figure 2. Plot of the second-order rate constants $\log k_{-1}$ (25 °C, acetonitrile) against the electrophilicity parameters E[8] of the reference electrophiles for the reactions of $Bu_4N^+MeOCO_2^-$ with benzhydrylium ions.

As depicted in Figure 3, the nucleophilicity parameter[10] N_{25} for methyl carbonate is in between those of benzoate and 4-nitrobenzoate (PNB).

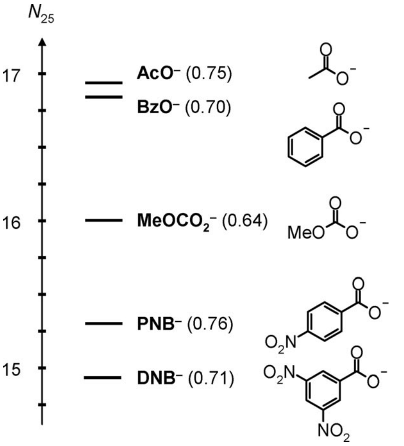


Figure 3. Comparison of the nucleophilicity parameters[7,10] N_{25} of common leaving groups in acetonitrile at 25 °C, s_{25} parameters in parentheses.

The nucleophilicity parameters N as defined by Equation (1) reflect the relative reactivities of anions towards such electrophiles, which react with $\log k = 0$. As the reactions of methyl carbonate and of carboxylates ($N \geq 15$) with such weak electrophiles ($E < -15$) are thermodynamically unfavorable and do not give rise to detectable equilibrium concentrations of covalent esters, it seems to be more appropriate to compare the relative nucleophilic reactivities of these anions towards stronger electrophiles. When $(thq)_2CH^+$ (2^+, $E = -8.22$) is used as reference electrophile, the nucleophilicity order in acetonitrile is:

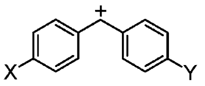
$AcO^- > BzO^- > PNB > MeOCO_2^- > DNB$

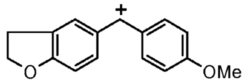
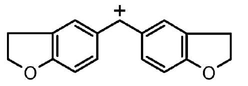
This sequence corresponds to the inverse order of the nucleofugalities of these compounds. However, nucleofugality is not generally the reverse of nucleophilicity, as exemplified by consideration of Cl^-, which is a far better nucleofuge than carboxylate ions but has a similar nucleophilicity as PNB.[6]

Determination of the Nucleofugalities of Organic Carbonates

Synthesis of Precursors: The benzhydryl methyl carbonates **10**-OCO_2Me and **11**-OCO_2Me were prepared by combining the corresponding benzhydrols (see structures of benzhydryl moieties in Table 3) with methyl chloroformate in the presence of pyridine as described previously for (**6–9**)-OCO_2Me.[4] The same method has been used for the synthesis of the benzhydryl isobutyl carbonates (**6–11**)-OCO_2iBu from the corresponding benzhydrols and isobutyl chloroformate. The crude products were obtained as yellow oils which sometimes contained starting material (benzhydrol) and (particularly in case of the donor substituted benzhydryl systems **10$^+$** and **11$^+$**) the aforementioned decarboxylation products (benzhydryl methyl or isobutyl ether). Attempts to purify the crude carbonates by crystallization or column chromatography resulted in decomposition. Therefore, the crude products have been used for the kinetic studies without further purification. As the side products are stable in aqueous organic solution and do not react with the benzhydryl carbonates, they do not interfere with the conductimetric measurements of the solvolysis reactions.

Table 3. Electrofugality parameters E_f of benzhydrylium ions.



	X	Y	E_f
6$^+$	OMe	H	–2.09[a]
7$^+$	OMe	Me	–1.32[a]
8$^+$	OMe	OPh	–0.86[a]
9$^+$	OMe	OMe	0.00
10$^+$			0.61[b]
11$^+$			1.07[b]

[a] These parameters revise previously published values from ref.[5]
[b] Previously unpublished electrofugality parameters, based on this work and additional unpublished data.

The benzhydryl *tert*-butyl carbonates (**8–11**)-OCO_2tBu were prepared by deprotonation of the corresponding benzhydrols with BuLi, followed by treatment with Boc_2O at –78 °C. Pure compounds were obtained by crystallization [in case of (**9–11**)-OCO_2tBu] or column chromatography (in case of **8**-OCO_2tBu).

Determination of Ionization Rates: The solvolysis rates of the benzhydryl carbonates were monitored by following the increase of the conductivity of the reaction mixtures. Because calibration experiments, i.e., portionwise addition of the rapidly solvolyzing benzhydryl methyl carbonate (**10**–OCO_2Me) into 50A50W and 60E40W and determination of the conductivity after completion of the solvolysis, showed a proportionality between conductivity (G) and the concentration of the substrates in the concentration range investigated (see Supporting Information), we were able to obtain first-order rate constants k_1 by fitting the time dependent conductivities G to the monoexponentional function (3).

$$G = G_{\max}\,[1 - \exp(-k_1 t)] + const. \tag{3}$$

Because all solvolyses studied in this work follow first-order rate laws, common ion return[11] (k_{-1} in Scheme 1) obviously does not occur. This is in line with previous work[7] where we have shown that acetate and benzoate ions, which are stronger nucleophiles than methyl carbonate ions, also do not show common ion return in solvolysis reactions under similar conditions. The conductimetrically measured rate constants listed in Table 4, therefore, correspond to the ionization rate constants k_1 defined in Scheme 1.

Table 4. Conductimetrically measured solvolysis rate constants (25 °C) of the benzhydryl alkyl carbonates (**6**–**11**)-LG in different solvents.

Solvent[a]	LG	Electrofuge	k_1 [s^{-1}]
50A50W	OCO_2Me	**10**	4.87×10^{-2}
		11	1.24×10^{-1} [b]
	OCO_2iBu	**6**	1.09×10^{-4}
		7	4.81×10^{-4}
		8	1.20×10^{-3}
		9	7.16×10^{-3}
		10	2.13×10^{-2}
		11	5.97×10^{-2}
60A40W	OCO_2Me	**10**	1.91×10^{-2}
		11	4.66×10^{-2} [b]
	OCO_2tBu	**8**	6.06×10^{-5}
		9	3.89×10^{-4}
		10	1.51×10^{-3}
		11	3.92×10^{-3}
70A30W	OCO_2Me	**10**	6.87×10^{-3}
		11	2.45×10^{-2} [b]
60E40W	OCO_2iBu	**6**	2.31×10^{-4}
		7	1.00×10^{-3}
		8	2.24×10^{-3}
		9	1.66×10^{-2}
		10	5.40×10^{-2}
	OCO_2tBu	**8**	3.94×10^{-4}
		9	3.05×10^{-3}
		10	8.54×10^{-3}
		11	2.15×10^{-2}
80E20W	OCO_2Me	**10**	4.72×10^{-2}
	OCO_2tBu	**8**	1.50×10^{-4}
		9	1.15×10^{-3}
		10	3.96×10^{-3}
		11	1.07×10^{-2}
90E10W	OCO_2Me	**10**	2.33×10^{-2}
	OCO_2iBu	**7**	1.81×10^{-4}
		8	5.80×10^{-4}
		9	4.53×10^{-3}
		10	1.45×10^{-2}
		11	4.14×10^{-2}
60AN40W	OCO_2tBu	**8**	9.87×10^{-5}
		9	8.28×10^{-4}
		10	2.76×10^{-3}
		11	7.13×10^{-3}

[a] Mixtures of solvents are given as (v/v); solvents: A = acetone, AN = acetonitrile, E = ethanol, W = water. [b] Stopped-flow kinetics.

Correlation Analyses: From the plots of logk_1 vs. $\Sigma\sigma^+$, one derives Hammett reaction constants of $-2.9 < \rho < -2.4$ for the solvolysis reactions of benzhydryl carbonates in 60E40W (Figure 4). The magnitudes of the reaction constants ρ suggest transition states, which correspond to the carbocations.

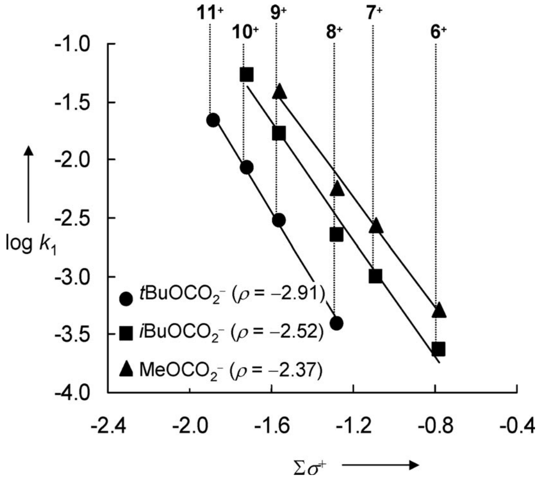


Figure 4. Plots of logk_1 of the solvolysis reactions of the benzhydryl alkyl carbonates in 60% aqueous ethanol (60E40W) vs. Hammett's substituent constants $\Sigma\sigma^+$ (k_1 for $tBuOCO_2^-$ and $iBuOCO_2^-$ from Table 4, k_1 for $MeOCO_2^-$ from ref.[4], σ^+ from ref.[12]).

In previous work[5] we have demonstrated that Equation (4) can be used for the calculation of the heterolysis rate constants k_1 of benzhydryl derivatives in various solvents.

$$\log k_1\ (25\ ^\circ\text{C}) = s_f\,(N_f + E_f) \tag{4}$$

In Equation (4) k_1 is a first-order rate constant (s^{-1}), s_f and N_f are nucleofuge-specific parameters (referring to combinations of leaving groups and solvents), and E_f is a carbocation-specific electrofugality parameter.

Plots of logk_1 (from this work and ref.[4]) for the solvolysis reactions of various substituted benzhydryl carbonates vs. the electrofugality parameters E_f of the benzhydrylium ions (see Table 3) are linear as exemplified in Figure 5 for the solvolyses of benzhydryl *tert*-butyl carbonates in different aqueous solvents (Table 5). For analogous correlations of isobutyl and methyl carbonates see Supporting Information. From these correlations one can extract the nucleofugality parameters N_f as the negative intercepts on the abscissa (E_f axis) and the s_f parameters as the slopes of the correlations. The nucleofugality parameters for methyl carbonate are in very good agreement with those published by Denegri and Kronja,[4] which were based on a smaller data set.

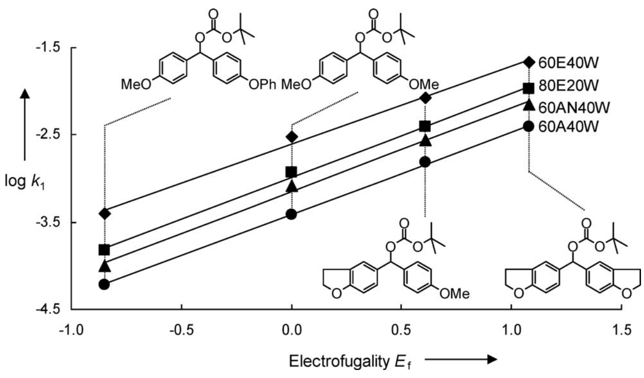


Figure 5. Plots of the first-order rate constants $\log k_1$ of the solvolyses of substituted benzhydryl *tert*-butyl carbonates in different solvent mixtures against the electrofugality parameters E_f [mixtures of solvents are given (v/v); W = water, E = ethanol, AN = acetonitrile, A = acetone].

Table 5. Nucleofugality parameters N_f and s_f of organic carbonates in different solvent mixtures.

Solvent[a]	N_f / s_f OCO_2Me	OCO_2iBu	OCO_2tBu
50A50W	–2.13/0.86[b]	–2.51/0.87	
60A40W	–2.56/0.88[b]		–3.62/0.94
70A30W	–2.83/0.94[b]		
60E40W	–1.59/0.89[b]	–2.04/0.89	–2.91/0.89
80E20W	–1.96/0.95[b]		–3.12/0.96
90E10W	–2.20/0.98[b]	–2.46/0.98	
60AN40W			–3.28/0.96

[a] Mixtures of solvents are given (v/v); W = water, E = ethanol, AN = acetonitrile, A = acetone. [b] These parameters differ slightly from previously published values which were based on a smaller data set for the correlation (ref.[4]).

With these nucleofugality parameters it now becomes possible to directly compare the leaving group abilities of various carbonates with other commonly used leaving groups. As the slope parameters s_f of different leaving groups differ only slightly ($\Delta s_f \leq 0.08$), it appears justified to compare the nucleofugalities of these leaving groups on the basis of N_f (Figure 6).

As depicted in Figure 6, phenyl carbonate which has previously been studied by Denegri and Kronja[4] is the most reactive carbonate investigated so far, ionizing about one order of magnitude faster than methyl carbonate. This difference in reactivity has been explained by the more efficient delocalization of the negative charge in phenyl carbonate.[4] Replacement of the methyl group by an isobutyl group reduces the reactivity by half an order of magnitude, and *tert*-butyl carbonate (*t*BocO) is the weakest nucleofuge of this series, approximately 10 times less reactive than isobutyl carbonate. Sterically hindered solvation of the *t*BocO⁻ anion can be assumed to account for its low nucleofugality. In conclusion the carbonate reactivity can be altered by about 2.5 orders of magnitude by changing the substituent from phenyl (most reactive) to *tert*-butyl (least reactive), i.e., the half-life of 4-methoxybenzhydryl phenyl carbonate in 80% aqueous ethanol at room temperature is about 4 min, whereas the half-life of the corresponding *tert*-butyl carbonate is about 19 h. Figure 6 furthermore shows that *t*BocO has a smaller leaving group ability than *p*-nitrobenzoate (PNB) or 3,5-dinitrobenzoate (DNB) in various solvents.[7]

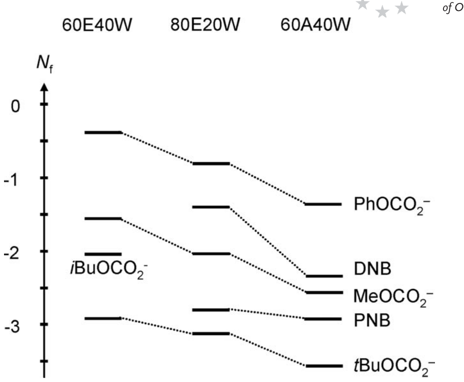


Figure 6. Comparison of the nucleofugalities of leaving groups in various solvents (DNB = 3,5-dinitrobenzoate, PNB = 4-nitrobenzoate from ref.[5]).

Conclusions

The great synthetic value of the *t*Boc protecting group has generally been assigned to the ease of deprotection under acidic conditions. This work has demonstrated an additional advantage of the *t*Boc group. The *tert*-butoxycarbonyloxy group $t\mathrm{BuOCO_2}^-$ is a considerably weaker nucleofuge than phenyl carbonate or other alkyl carbonates with the result that the *tert*-butyl carbonates $t\mathrm{BuOCO_2}$-R are much less sensitive toward heterolytic cleavage of the O–R bond than other carbonates. The higher lability of *tert*-butyl carbonates under acidic conditions is thus combined with greater stability under neutral and basic conditions.

Experimental Section

General: Acetonitrile (VWR, ≥ 99.9%) and acetone (VWR, ≥ 99.8%) were used as purchased. Water was purified by using a Millipore MilliQ (final specific resistance ≥ 18.2 MΩ/cm). The benzhydrylium tetrafluoroborates were synthesized according to literature procedures.[8a]

Tetra-*n*-butylammonium methyl carbonate was synthesized by bubbling CO_2 through a tetra-*n*-butylammonium methoxide solution in methanol as reported in ref.[13] As the crude product still contained some methoxide, complete conversion of methoxide to methyl carbonate was achieved by treatment of a solution of the crude material in toluene with a stream of CO_2. The benzhydryl methyl and isobutyl carbonates were prepared by esterification of the corresponding benzhydrols with methyl or isobutyl chloroformate, whereas the benzhydryl *tert*-butyl carbonates were prepared by reaction of the corresponding lithium diarylmethoxides with Boc_2O. In some cases the crude products were contaminated with starting material (benzhydrol) or decarboxylation product (benzhydryl alkyl ether). Details of the syntheses and characterization of the benzhydryl alkyl carbonates are described in the Supporting Information.

Determination of the Rates of the Combination of Benzhydrylium Ions with $MeOCO_2^-$: Solutions of benzhydrylium tetrafluoroborates in CH_3CN were mixed with solutions of $n$$Bu_4N^+MeOCO_2^-$ in CH_3CN in a stopped-flow instrument (Applied Photophysics SX.18MV-R), and the decay of the benzhydrylium absorbance was followed by UV/Vis spectrometry. All experiments were performed under pseudo-first-order conditions (excess of $MeOCO_2^-$). The temperature was kept constant at 25 °C in all experiments by using a circulating water bath.

Laser-Flash Photolysis: For determining the rates of the reactions of Ar_2CH^+ with $MeOCO_2^-$ with reaction times below 10 ms, benzhydrylium ions were generated by laser-flash photolysis of benzhydryl tri-*n*-butylphosphonium tetrafluoroborates in acetonitrile at 25 °C with an Innolas SpitLight 600 Nd:YAG laser (fourth harmonic at $\lambda = 266$ nm, power/pulse of 40–60 mJ, pulse length 6.5 ns) in a quartz cell.[9] The rate constants were determined by observing the time-dependent decay of the UV/Vis absorptions of the benzhydrylium ions.

Determination of Ionization Rates: The ionization rates of the benzhydryl alkyl carbonates were monitored by following the increase of the conductivity of the reaction mixtures using a conventional conductimeter (Tacussel CD 810, Pt electrode: WTW LTA 1/NS). Typically, each run was repeated at least once; the reported rate constants are the arithmetic means. For faster reactions, a stopped-flow conductimeter (Hi-Tech Scientific SF-61 DX2, platinum electrodes, cell volume 21 µL, cell constant 4.24 cm^{-1}, minimum dead time 2.2 ms) was used. In order to achieve a complete ionization of the liberated weak acid, 2 to 40 equiv. of 1,8-bis(dimethylamino)naphthalene or piperidine was used as additive. The temperature was kept constant at 25 °C in all experiments using a circulating water bath.

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

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