methanol, toluene, heptane, and acetic acid all eluted at the same time (t_0). The capacity factors (k'), separation factors (α), and the number of theoretical plates (N) were calculated according to standard chromatographic procedures[43] as $k'_D = (t_D - t_0)/t_0$, $\alpha = k'_L/k'_D$, and $N_D = 5.54\ (t_D/t_{1/2})^2$, where t_D is the retention time of the D enantiomer, t_0 the void elution time, and $t_{1/2}$ the width of peak at half-height. Resolution (R_s) was calculated according to Wulff et al.[3]

NMR Investigation. The samples for the titration study were prepared in sample tubes (5-mm o.d.) by adding 0.50 mL of a 100 mM solution of the print molecule dissolved in acetonitrile-d_3 or a mixture of acetonitrile-d_3 and EDMA of the same composition as in the preparation of the polymers. To this was added MAA with a gas-tight 50-μL syringe to obtain samples with desired acid concentrations.

The samples were degassed by sonication. All spectra were recorded at room temperature and at 60 °C, with a Varian XL-300 NMR spectrometer operating at 300 MHz. To obtain the spectra, 32 FIDs were accumulated by using 30° pulses with 10-s pulse intervals. All shifts are relative to the central peak of the CHD_2CN heptet at 1.980 ppm (relative to TMS).

Acknowledgment. We are grateful to Dr. Torbjörn Drakenberg, Dr. Torbjörn Frejd, Dr. Ingmar Persson, Prof. Bertil Törnell, Rolf Servin, Dr. Roland Isaksson (all at the Chemical Center, University of Lund), and Prof. Margaret C. Etter (University of Minnesota) for valuable discussions and assistance. This work was supported in part by the National Swedish Board for Technical Development and by the Swedish National Science Foundation to K.M.

Registry No. (EDMA)(MAA)(L-PheOEt) (copolymer), 114395-75-4; (EDMA)(MAA)(L-p-NH_2PheOEt) (copolymer), 114422-53-6; (EDMA)(MAA)(L-PheNHPh) (copolymer), 114395-77-6; (EDMA)(MAA)(L-PheNHEt) (copolymer), 114395-79-8.

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[43] Poole, C. F.; Schuette, S. A. *Contemporary Practice of Chromatography*; Elsevier: Amsterdam, 1984; pp 1-8.

Radiation Chemical Production, Lifetimes, and Structure-Activity Relations for α-Dialkoxyalkyl Carbocations in Aqueous Solutions: Importance of Solvation for Cation Reactivity

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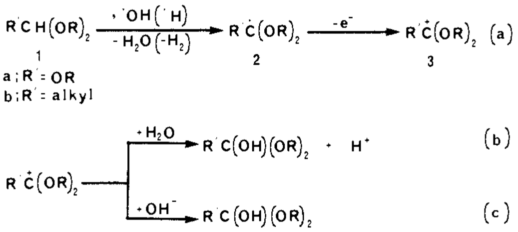
Abstract: α-Dialkoxyalkyl carbocations $R'C(OR)_2^+$ were produced in aqueous solution by H abstraction from acetals by OH and H radicals followed by one-electron oxidation of the so-formed α-dialkoxyalkyl radicals. Rate constants for the reactions of the cations with H_2O (and in some cases OH^-) have been determined by using time-resolved conductance techniques. For example, $MeC(OMe)_2^+$ reacts with water with a rate constant of $1.3 \times 10^5\ s^{-1}$ and with OH^- with a rate constant of $3.7 \times 10^8\ M^{-1}\ s^{-1}$. Rate constants for the hydration of 30 open-chain and cyclic aliphatic cations have been measured, enabling structure-activity relations to be seen. For substitution in the OR group a reactivity order OMe > OEt > O-i-Pr is observed with a good correlation versus σ^* encompassing a number of ions of different structural type with a ρ^* of +4.4. However, substitution of R′ (directly on the carbocation center) does not follow the expected steric/electronic order, t-$BuC(OEt)_2^+$, for example, reacting with water 2.3-fold *more* rapidly than $MeC(OEt)_2^+$. The reaction with water of these cations is a very close model of the rate-limiting step of H^+-catalyzed ester hydrolysis, the defining reaction for the E_s steric substituent constant. The observation that the effects of alkyl substituents at C_α are described neither by their σ^* nor by their E_s constants is explained in terms of solvation effects. A consequence of this is that solvational effects, in particular on the equilibrium protonation step of ester hydrolysis, must also play an important role in determining the E_s parameter. This parameter is therefore not a pure measure of steric effects.

In a previous paper, a radiation chemical technique was described for the production of trialkoxymethyl carbocations **3a** in aqueous solution, with subsequent direct measurements of lifetime.[1] The ions were formed by one-electron transfer to an oxidant from trialkoxymethyl radicals **2a**, which were produced by hydrogen abstraction from orthoformates **1a**. The overall reaction consists of removing a hydride ion from the precursor in a step-wise fashion, i.e. by consecutive removal of a hydrogen atom and an electron (eq 1a). Time-resolved conductance measurements provided rate constants for the reactions of **3a** with water and hydroxide ion (eq 1b,c).

Hydrogen abstraction from acetals **1b** to produce radicals **2b** is also well established,[2] and thus dialkoxy carbocations **3b** should be accessible through the same procedure. These cations are probably of greater interest and relevance to physical organic chemistry, since they are intermediates in the mechanistically well-studied reaction of ortho ester hydrolysis.[3] They are also models for hydroxyalkoxyalkyl cations, the intermediates of acid-catalyzed ester hydrolysis.



$$\underset{1}{R'CH(OR)_2} \xrightarrow[-H_2O(-H_2)]{+\cdot OH(\cdot H)} \underset{2}{R'\dot{C}(OR)_2} \xrightarrow{-e^-} \underset{3}{R'\overset{+}{C}(OR)_2} \quad (a)$$

a; R′ = OR
b; R′ = alkyl

$$R'\overset{+}{C}(OR)_2 \xrightarrow{+H_2O} R'C(OH)(OR)_2 + H^+ \quad (b) \quad (1)$$

$$R'\overset{+}{C}(OR)_2 \xrightarrow{+OH^-} R'C(OH)(OR)_2 \quad (c)$$

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[1] Steenken, S.; Buschek, J.; McClelland, R. A. *J. Am. Chem. Soc.* **1986**, *108*, 2808.

[2] Eibenberger, J.; Schulte-Frohlinde, D.; Steenken, S. *J. Phys. Chem.* **1980**, *84*, 704.

[3] Cordes, E. H. *Prog. Phys. Org. Chem.* **1967**, *4*, 1. Fife, T. H. *Acc. Chem. Res.* **1972**, *5*, 264. Cordes, E. H.; Bull, H. G. *Chem. Rev.* **1974**, *74*, 581.

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Aqueous solution lifetimes of dialkoxy carbocations stabilized by charge delocalization to aromatic rings have been measured, usually with stopped-flow spectroscopy.[4] For lifetimes of purely aliphatic cations, however, only estimates are available.[5] We report here that simple alkyl dialkoxy carbocations can be produced in nucleophilic solvents, i.e. under "solvolytic conditions" by step-wise hydride transfer from acetals, and lifetimes for a large series of such ions are presented. These reactivity data are a valuable addition to the detailed knowledge that exists on the structure of carbocations as obtained from studies in superacids.[6]

Experimental Section

Acetals not commercially available were prepared by following standard procedures.[7] (A) Dimethyl acetals, diethyl acetals, and acetaldehyde diisopropyl acetal were prepared by mixing the commercially available aldehyde with an equivalent amount of the appropriate trialkyl orthoformate in the presence of a trace of *p*-toluenesulfonic acid. (B) 2-Alkyl-1,3-dioxolanes and 2-alkyl-1,3-dioxanes were prepared in a similar way with an equivalent amount of ethylene glycol or 1,3-propanediol also present. (C) 2-Alkoxytetrahydrofurans and 2-alkoxytetrahydropyrans were prepared by the addition of 2,3-dihydrofuran or 3,4-dihydro-2*H*-pyran, respectively, to a slight excess of alcohol containing a trace of *p*-toluenesulfonic acid. (D) 2-Alkyl-4,4,5,5-tetramethyl-1,3-dioxolanes were prepared by stirring the aldehyde, pinacol, and 85% phosphoric acid for 2 days. Workup for method D involved separation of the organic phase away from the aqueous acid phase, followed by washing with aqueous sodium bicarbonate, drying with magnesium sulfate, and fractional distillation at reduced pressure. For methods A–C, anhydrous potassium bicarbonate was added upon completion of the reaction (as judged by ^{1}H NMR spectroscopy), and the mixture was fractionally distilled. Ethyldimethyl orthoformate was prepared by mixing trimethyl orthoformate and triethyl orthoformate in equimolar proportions and adding a trace of *p*-toluenesulfonic acid. This establishes an equilibrium with, as judged by NMR spectroscopy, all four possible combinations present in statistical amounts—trimethyl:ethyldimethyl:diethylmethyl:triethyl = 1:3:3:1. The acid was neutralized by addition of anhydrous sodium carbonate and the mixture fractionally distilled through a 2-m column to yield the above ortho ester. Isopropyldimethyl orthoformate was prepared in a similar way from the trimethyl and triisopropyl ortho esters. (2,2,2-Trifluoroethoxy)diethoxy orthoformate was prepared by mixing at 0 °C equimolar quantities of 2,2,2-trifluoroethanol and diethoxymethyl acetate (Aldrich). After 15 min, the mixture was taken up in diethyl ether and extracted with cold 1 M sodium hydroxide to remove acetic acid. After removal of ether, the mixed ortho ester was purified by distillation. All compounds had appropriate ^{1}H NMR spectra and mass spectral parent ions and were judged by gas chromatographic analysis to be greater than 99% pure.

The pulse radiolysis system and experimental conditions have been described in detail previously.[1] Aqueous solutions containing 0.2–1.5 mM oxidant [$K_3Fe(CN)_6$ and K_2IrCl_6] were saturated with N_2O in order to convert e^-_{aq} into OH radicals. Immediately before pulse radiolysis 10–50 mM acetal was added and the mixture adjusted to pH 4–5.5 with aqueous $HClO_4$ or pH 9–10.5 with aqueous $Ba(OH)_2$. The solutions were subjected to a 0.1–0.4-μs electron pulse with a dose such that ≈2 μM OH (90%) + H (10%) were produced. Detection was by AC or DC conductance techniques. Conductance amplitudes were calibrated with a N_2O-saturated solution of 0.1 M methanol and 0.5 mM oxidant for which $G(OH + H) = G(H^+) = G(ox^-) = 6.6$.

Results and Discussion

Production of Dialkoxy Carbocations. The pulse radiolysis method for the generation of oxy carbocations was discussed in detail in our previous paper.[1] The same procedure was employed here; for illustrative purposes, experiments leading to the 1,1-dimethoxyethyl cation will be described. The precursor is acetaldehyde dimethyl acetal. Upon H abstraction from this compound by OH and H radicals (produced by the electron pulse) in the presence of $IrCl_6^{2-}$ or $Fe(CN)_6^{3-}$ as oxidants and the pH at 5.0, a two-component buildup of conductance was observed [see Figure 1 for the trace with $Fe(CN)_6^{3-}$]. The rate of the fast increase depends upon oxidant concentration, and nature, while the slow increase is independent of concentration, and within experimental error, has the same first-order rate constant with the two oxidants—$(1.3 \pm 0.1) \times 10^5$ s^{-1} for $Fe(CN)_6^{3-}$ and $(1.4 \pm 0.2) \times 10^5$ s^{-1} for $IrCl_6^{2-}$. With the latter oxidant the amplitudes of the fast and slow buildups have an 80:20 ratio and the total change accounts for 100% of the initial •OH + •H radicals. With $Fe(CN)_6^{3-}$ the fast to slow ratio is 70:30 and the total change represents only 60% of the initial radicals.[8]

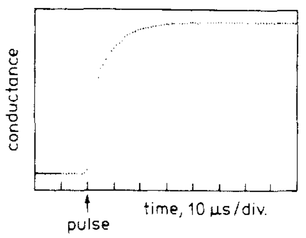
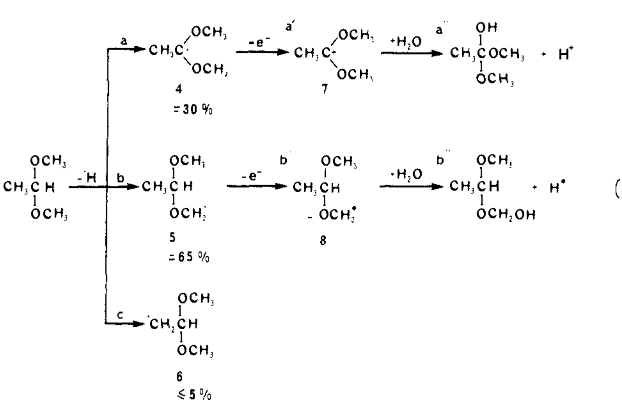


Figure 1. Conductance change observed on producing $CH_3C^+(OCH_3)_2$ by using •OH, 50 mM $CH_3CH(OCH_3)_2$, and 0.5 mM $Fe(CN)_6^{3-}$ at pH 5.0.

The explanation for these observations is given in eq 2. As shown, three carbon-centered radicals can in principle be produced



(2)

from the acetal by H abstraction. The α-alkoxy radicals **4** and **5** are expected on the basis of previous studies[9] to be rapidly oxidized by $IrCl_6^{2-}$ by electron transfer, while the alkyl radical **6** should be oxidized by ligand transfer. The latter process does not produce conductivity increases.[9] The ≈100% conductivity increase observed with $IrCl_6^{2-}$ as oxidant therefore implies that only the radicals **4** and **5** are produced in the initial H abstraction, i.e. that the yield of **6** is ≤5%. This high selectivity of H abstraction by OH is in accord with previous observations[1,2,9,10] made with ethers and acetals.

The electron-transfer oxidations produce the cations **7** and **8**. Detailed determinations of the rate constants for these reactions were not undertaken here but the values are $\approx 4 \times 10^9$ M^{-1} s^{-1}, similar to those observed with radicals produced from orthoformates.[1] The cation **8**, being a monoalkoxy carbocation, is expected to be short-lived, with an estimated rate constant for reaction with water $\geq 10^7$ s^{-1}.[1] Therefore, with this cation the formation step is rate-limiting and not the hydration.[11] In

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(4) McClelland, R. A.; Ahmad, M. *J. Am. Chem. Soc.* **1978**, *100*, 7027. McClelland, R. A.; Alibhai, M. *Can. J. Chem.* **1981**, *59*, 1169. McClelland, R. A.; Moreau, C. *Ibid.* **1985**, *63*, 2673.

(5) McClelland, R. A.; Ahmad, M. *J. Am. Chem. Soc.* **1978**, *100*, 7031.

(6) For reviews see: (a) Bethell, D.; Gold, V. *Carbonium Ions*; Academic: London, New York, 1967. (b) Olah, G. A.; White, A. M.; O'Brien, D. H. *Chem. Revs.* **1970**, *70*, 561. (c) *Carbonium Ions*; Olah, G. A., Schleyer, P. v. R., Eds.; Wiley-Interscience: New York, London, 1976; Vol. 5. (d) Olah, G. A. *Chem. Scr.* **1981**, *18*, 97. (e) Perst, H. *Oxonium Ions in Organic Chemistry*; Verlag Chemie/Academic: Weinheim, 1971.

(7) Vogel, A. I. *A Text Book of Practical Organic Chemistry*; Longmans, Green: London, 1948; p 318. Loudon, G. M.; Smith, C. K.; Zimmerman, S. E. *J. Am. Chem. Soc.* **1974**, *96*, 465. Blicke, F. F.; Anderson, F. E. *Ibid.* **1952**, *74*, 1733.

(8) The less than 100% total conductance change may mean that oxidation of the radical **5** occurs partially by ligand transfer (cf. ref 1, 9).

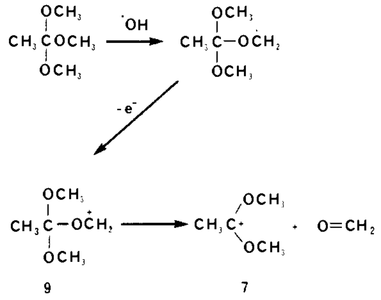
(9) For a discussion of oxidations of alkyl radicals, see: Steenken, S.; Neta, P. *J. Am. Chem. Soc.* **1982**, *104*, 1244.

(10) Schuchmann, M. N.; von Sonntag, C. *Z. Naturforsch. B: Chem. Sci.* **1987**, *42*, 495.

contrast, the cation **7**, a dialkoxy carbocation, should be longer lived, and this expectation is supported by the observation that the slow conductance rise is independent of oxidant nature and concentration. Thus, the conclusion is that the *fast* and oxidant concentration *de*pendent buildup of conductance represents the conductivity increases resulting from the two electron-transfer steps 2a′ and 2b′ and from the hydration of the resulting short-lived **8** (eq 2b″). In the latter reaction H^+ is produced while the oxidations convert $IrCl_6^{2-}$ into the more conducting ion[1] $IrCl_6^{3-}$. In contrast, the slower and oxidant concentration *in*dependent increase is associated with H^+ released in the hydration of **7** (eq 2a″). The first-order rate constant obtained from this change reflects directly the hydration process and provides, therefore, a direct measurement of the lifetime of **7**. Correcting[1] the 80:20 ratio for the conductivities of the ions removed and formed results in a concentration ratio [**4**]:[**5**] = 1:2.

Experiments were also performed in weakly basic solutions (with $Fe(CN)_6^{3-}$ as oxidant). Under these conditions, the H^+ produced upon reaction with water reacts with the excess OH^- and a decrease in conductance is observed. As expected, this is two-component. The rate constant for the slow step is independent of oxidant concentration. It does, however, increase with increasing OH^- concentration (Figure 2) according to the equation $k_{obsd} = k(H_2O) + k(OH^-)[OH^-]$. The $k(H_2O)$ term—$(1.2 \pm 0.1) \times 10^5$ s^{-1}—has the same numerical value as observed in the experiments at acid pH and obviously represents the hydration of **7**. The $k(OH^-)$ term—$(3.7 \pm 0.2) \times 10^8$ M^{-1} s^{-1}—is explained by the reaction of this cation with OH^-, cf. eq 1c.

Another precursor to **7** is trimethyl orthoacetate through the sequence of reactions outlined in eq 3. The key step here is the C–O fragmentation of the primary cation **9** to give the tertiary cation **7**. The existence of such reactions was reported in our previous paper,[1] with tetraalkoxymethanes (orthocarbonates) serving as precursors for trialkoxy carbocations. Evidence that the orthoacetate undergoes a similar fragmentation was obtained through experiments with this ortho ester in base. Large oxidant-independent conductivity decreases were observed, with rate constants exactly corresponding to those obtained with the acetal (Figure 2).



(3)

The advantage of using trialkyl ortho esters as precursors for dialkoxyalkyl cations is related to the statistics and selectivity of the H-abstraction reaction by the OH radical. In the case of $CH_3C(OCH_3)_3$ there are only two types of abstractable hydrogens with a 9:3 statistical plus a polarity-related preference for formation of the precursor $CH_3C(OCH_3)_2OCH_2^{\bullet}$ which, after oxidation and fragmentation, gives the desired cation (see eq 3). In contrast, with $CH_3CH(OCH_3)_2$, the aldehydic hydrogen to be abstracted to finally give the cation is only 1 out of a total of 10 abstractable hydrogens. This statistically unfavorable situation is, however, alleviated somewhat by the polar and bond energy related factor, which favors abstraction of the aldehydic H. The one drawback with ortho esters is that their high acid hydrolytic reactivity[12] makes their study under acid conditions very difficult.

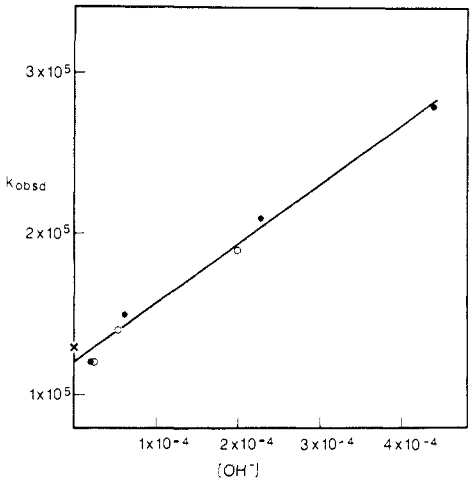
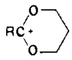
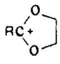
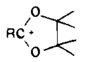
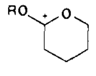
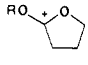


Figure 2. First-order rate constants for the reaction of $CH_3C^+(OCH_3)_2$ in weakly basic solution. (●) $CH_3CH(OCH_3)_2$ precursor; (○) $CH_3C(OCH_3)_3$ precursor; (×) pH 5.0 experiments, with acetal as precursor.

Table I. Rate Constants for the Addition of Water to α-Di- and Trialkoxy Carbocations in Aqueous Solution (20 ± 2 °C, pH 4–6)

cation	R	no.	k_{H_2O}, s^{-1}
$RC^+(OMe)_2$	Me	**7**	$(1.3 \pm 0.1) \times 10^5$
	Et	**10**	$(1.5 \pm 0.1) \times 10^5$
	n-Pr	**11**	$(1.2 \pm 0.2) \times 10^5$
	n-Bu	**12**	$(1.6 \pm 0.3) \times 10^5$
	i-Bu	**13**	$(1.9 \pm 0.5) \times 10^5$
	i-Pr	**14**	$(7.6 \pm 1.0) \times 10^5$
	s-Bu	**15**	$\approx 6 \times 10^5$
	t-Bu	**16**	$(6.2 \pm 1.1) \times 10^5$
$RC^+(OEt)_2$	Me	**17**	$(2.8 \pm 0.3) \times 10^4$
	Et	**18**	$(2.8 \pm 0.6) \times 10^4$
	n-Pr	**19**	$(2.3 \pm 0.3) \times 104$
	i-Pr	**20**	$(6.7 \pm 1.2) \times 10^4$
	t-Bu	**21**	$(6.5 \pm 0.3) \times 10^4$
$MeC^+(O\text{-}i\text{-}Pr)_2$		**22**	$(2.0 \pm 0.3) \times 10^3$
	Me	**23**	$(1.4 \pm 0.1) \times 10^5$
	Et	**24**	$(1.4 \pm 0.1) \times 10^5$
	i-Pr	**25**	$(1.6 \pm 0.2) \times 10^5$
	t-Bu	**26**	$(9.3 \pm 0.6) \times 10^4$
	Me	**27**	$(1.4 \pm 0.3) \times 10^6$
	t-Bu	**28**	$(1.5 \pm 0.1) \times 10^{6a}$
	Me	**29**	$(3.5 \pm 0.3) \times 10^4$
	Et	**30**	$(5.1 \pm 0.7) \times 10^4$
	i-Pr	**31**	$(5.9 \pm 0.3) \times 10^4$
	t-Bu	**32**	$(3.7 \pm 0.2) \times 10^4$
	Me	**33**	$(1.3 \pm 0.2) \times 10^5$
	Et	**34**	$(6.4 \pm 0.4) \times 10^4$
	i-Pr	**35**	$(2.4 \pm 0.4) \times 10^4$
	Me	**36**	$(1.2 \pm 0.1) \times 10^5$
	Et	**37**	$(4.0 \pm 0.3) \times 10^4$
	i-Pr	**38**	$(8.8 \pm 0.3) \times 10^3$
$(MeO)_2C^+OEt$		**39**	$(4 \pm 1) \times 10^2$
$(MeO)_2C^+O\text{-}i\text{-}Pr$		**40**	$(9.8 \pm 0.8) \times 10^1$
$(EtO)_2C^+OCH_2CF_3$		**41**	$(1.0 \pm 0.1) \times 10^4$

[a] Cation produced via a radical cation precursor by C–C fragmentation: Steenken, S.; McClelland, R. A., unpublished results.

With the appropriate acetals as precursors we have found that an almost complete[13] list of simple alkyldialkoxy carbocations can

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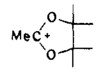
[11] We refer to the reaction of the cation with water as "hydration". (That this term is mechanistically justified is shown in section d.) With the conductivity method alone it cannot be distinguished whether the cations react by hydration (=addition) or by deprotonation (=elimination) from C_β. In the following it will, however, always be assumed that the α-alkoxyalkyl carbocations under consideration react with water exclusively by addition (=hydration). In support of this are the following observations and facts: (a) The α-ethoxyethyl cation reacts exclusively by addition, as concluded from the absence of ethyl vinyl ether among the products. See: von Sonntag, C.; Schuchmann, H.-P. In *The Chemistry of Functional Groups*; Patai, S., Ed.; Wiley: New York, 1980; Suppl. E, Part 2, p 935. (b) The same is true for $OCH_2CH_2OCH_2CH^+$, as judged by the absence of 1,4-dioxene as a product: Steenken, S., unpublished results. (c) Products derived from β-deprotonation reactions typically are not found in H^+-catalyzed ester, acetal, or ortho ester hydrolyses where α-alkoxy carbocations are assumed to be intermediate.

[12] Trimethyl orthoacetate, for example, has a half-life of only 5 s at pH 5.

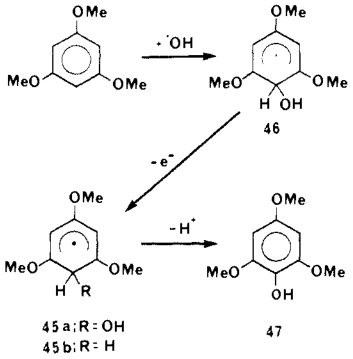
Table II. Rate Constants for the Addition of Hydroxide Ion to α-Di- and Trialkoxy Carbocations in Aqueous Solution (20 ± 2 °C)

cation	no.	$k(OH^-)$, $M^{-1}\ s^{-1}$
$MeC^+(OMe)_2$	**7**	$(3.7 \pm 0.2) \times 10^8$
$EtC^+(OMe)_2$	**10**	$(2.7 \pm 0.4) \times 10^8$
$MeC^+(OEt)_2$	**17**	$(9.2 \pm 0.3) \times 10^7$
$EtC^+(OEt)_2$	**18**	$(1.2 \pm 0.1) \times 10^8$
i-$PrC^+(OEt)_2$	**20**	$(1.3 \pm 0.1) \times 10^8$
$MeC^+(O$-i-$Pr)_2$	**22**	$(1.8 \pm 0.3) \times 10^7$
	**29**	$(5.1 \pm 0.3) \times 10^7$
$(MeO)_2C^+OEt$	**39**	$(5.7 \pm 0.1) \times 10^7$
$(MeO)_2C^+O$-i-Pr	**40**	$(1.8 \pm 0.1) \times 10^7$
$(EtO)_2C^+OCH_2CF_3$	**41**	$(1.5 \pm 0.2) \times 10^8$

be produced, and rate constants for their reaction with water have been measured. These are reported in Table I. Experiments in all these cases involved weakly acidic solutions. With each acetal precursor measurable amounts of dialkoxy carbocation were formed, the presence of a (slow) oxidant-independent conductivity increase being taken as evidence. Experiments were conducted with the two oxidants in all cases; rate constants in Table I are the average of values obtained with each. A limited number of cations were also studied in weakly basic solutions; the values of $k(OH^-)$ so obtained are given in Table II. Five cations were studied in weakly acidic solutions at temperatures in the 0–40 °C range. The activation parameters obtained from the Arrhenius plots ($r \geq 0.99$) are listed in Table III. Also reported in Tables I and II are rate constants for three trialkoxy carbocations prepared from mixed ortho esters.

Limitations. With this approach, the upper limit for cation reactivity measurements is $\sim 10^7\ s^{-1}$. This is imposed by the maximum oxidant concentrations of ~5 mM, above which the ionic strength of the solution is too high to perform conductance experiments. Assuming second-order rate constants of $\approx 2 \times 10^9\ M^{-1}\ s^{-1}$ leads to maximum pseudo-first-order rate constants of $\approx 10^7\ s^{-1}$ for the oxidation step (e.g., eq 2a′) under these conditions. Thus, with cations that react with water faster than this, the oxidation of the radical is rate-limiting, and no information about cation lifetime other than a lower limit can be obtained.

We have investigated four systems where this is true—the monoalkoxy carbocation i-$PrOC^+Me_2$ (**42**) generated from diisopropyl ether,[1] the hydrogen-substituted dialkoxy carbocation $(EtO)_2CH^+$ (**43**) from $(EtO)_2CH_2$, the *tert*-butyl cation **44** from $(Me_3C)_2SO$,[8] and the hydroxycyclohexadienyl cation **45a**. This last cation is formed by oxidation of the radical **46** formed upon

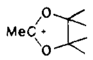


(4)

OH addition to 1,3,5-trimethoxybenzene. It reacts not by water addition but by proton loss to give the phenol **47**. Each of the cations **42**–**45a** is generated in substantial yield, but in each case the oxidation step forming them is rate-limiting even at high concentration, and all that can be said is that the cation reacts with a rate constant greater than $10^7\ s^{-1}$. This is not surprising in the case of the *tert*-butyl cation, for which Kresge has estimated a water rate constant of $10^{10}\ s^{-1}$.[14] For **45b** (R = H), an equilibrium constant has been measured in strong acids and a protonation rate constant measured in dilute acids by tritium exchange.[15] Combining these gives a deprotonation rate constant of $10^4\ s^{-1}$ for **45b**. On this basis we had anticipated being able to observe **45a**. There are two explanations for the failure. The cation **45a** has an OH substituent whose effect will be to inductively destabilize the cation and shorten its lifetime. Alternatively, the equilibrium constant[15] is in error because of the use of an inappropriate acidity function to extrapolate to water.

Structure–Activity Relations. Thirty dialkoxy carbocations have been examined in this study, with rate constants for reaction with water ranging from 2×10^3 to $1.4 \times 10^6\ s^{-1}$ (see Table I) and for reaction with OH^- from 2×10^7 to $4 \times 10^8\ M^{-1}\ s^{-1}$ (see Table II). The most conspicuous phenomenon is that the effect an alkyl substituent has on the reactivity of a dialkoxy carbocation depends on whether the alkyl substituent is in the alkoxy group or at C_α: Whereas replacement of methyl by ethyl or isopropyl in the alkoxy group leads to a pronounced *de*crease of the reactivity with H_2O (compare in Table I, e.g.: **7**, **17**, and **22**), it has no effect or even results in an *in*crease if the change is at C_α (compare, e.g.: **7**, **10**, **14**, and **16**; or **23**, **24**, **25**, and **26**, etc.). The same situation exists with respect to reactivity with OH^- (compare in Table II: **7**, **17**, and **22** for the effect of OR; and **17**, **18**, and **20** for the effect of R at C_α). In the following, various aspects of the structure–

Table III. Activation Parameters for the Addition of Water to Oxy Carbocations (pH 5–6)

cation	k_{H_2O}, s^{-1} (at 20 °C)	E_a, kcal mol^{-1}	A, s^{-1}	$\Delta S^\ddagger$, cal $mol^{-1}\ K^{-1}$
$MeC^+(OEt)_2$	2.8×10^4	6.9 ± 0.8	3.8×10^9	-16.7 ± 2.8
$EtC^+(OEt)_2$	2.8×10^4	7.35 ± 0.7	8.6×10^9	-15.1 ± 2.4
i-$PrC^+(OEt)_2$	6.7×10^4	5.5 ± 0.4	1.2×10^9	-19.1 ± 1.5
t-$BuC^+(OEt)_2$	6.5×10^4	1.4 ± 0.7	5.0×10^5	-34.5 ± 2.5
	3.5×10^4	7.2 ± 0.7	7.0×10^9	-15.5 ± 2.2
$(MeO)_3C^{+a}$	1.4×10^3	7.6 ± 1.3	6.4×10^8	-20.2 ± 4.4

[a] From ref 1.

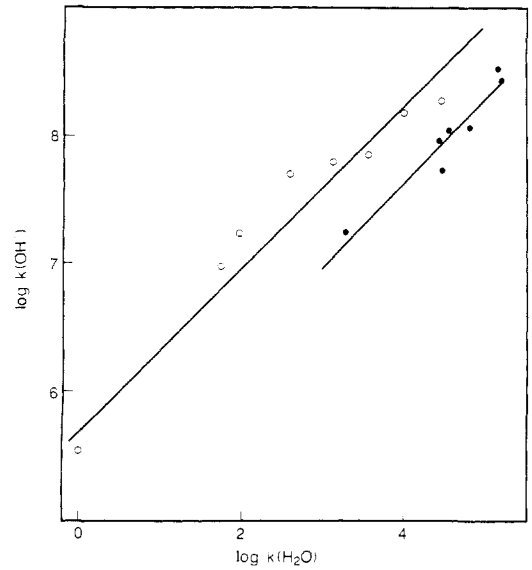


Figure 3. Correlation of hydroxide and water reactivities. Closed circles represent dialkoxy carbocations; open circles, trialkoxy carbocations. Lines drawn are linear (based upon) regression and have slopes 0.65 (○) and 0.66 (●).

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[13] The one type of cation that appears inaccessible is the O-t-Bu system. As shown by ESR this is because the precursor radical undergoes β fragmentation to give an ester and the t-Bu radical more rapidly than oxidation can occur: Steenken, S., unpublished results. See also: Steenken, S.; Schuchmann, H.-P.; von Sonntag, C. *J. Phys. Chem.* **1975**, *79*, 763.

[14] Chiang, Y.; Chwang, W. K.; Kresge, A. J.; Powell, M. F.; Szilagyi, S. *J. Org. Chem.* **1984**, *49*, 5218.

[15] Kresge, A. J.; Chen, H. J.; Hakka, L. E.; Kouba, J. E. *J. Am. Chem. Soc.* **1971**, *93*, 6174. Kresge, A. J.; Mylonakis, S. G.; Sato, Y.; Vitullo, V. P. *Ibid.* **1971**, *93*, 6181.

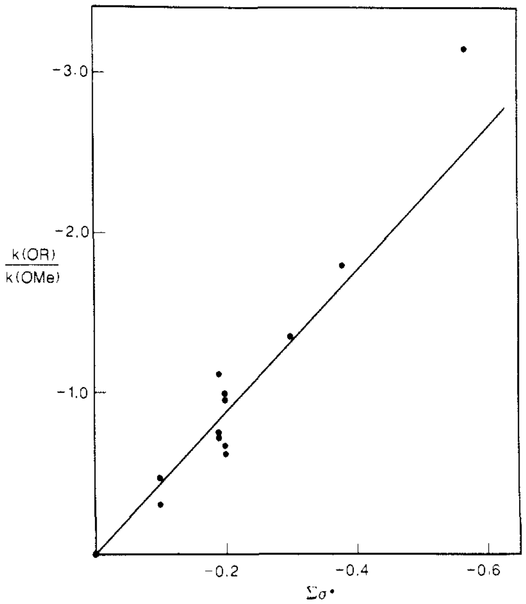


Figure 4. *O*-Alkyl correlation with Taft σ^* substituent constants. The line has been forced to go through the origin and has a slope (ρ^*) of +4.4.

activity dependence will be discussed.

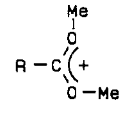
(a) Hydroxide Ion. Figure 3 shows the correlation of hydroxide ion rate constants with the water rate constants. Separate lines are clearly observed for di- and trialkoxy carbocations, but the slopes are quite similar. Richard and Jencks have argued that rate constants for oxy anions reacting with phenethyl cations reach a limit of $\sim 5 \times 10^8$ M^{-1} s^{-1}.[16] The trialkoxy carbocation series may possibly show some curvature consistent with such a leveling. This curvature is, however, not apparent with the more reactive dialkoxy carbocations, although admittedly the 5×10^8 limit has not quite been reached.

(b) *O*-Alkyl Effects. Significant differences in the reactivity with H_2O were observed with $(RO)_3C^+$, with the order MeO > EtO > *i*-PrO,[1] and this behavior continues at the dialkoxy carbocation level. In fact, as illustrated in Figure 4, the reactivity dependence on the structure of R is quantitatively the same. This figure combines all the available data for both types of cations in a plot normalized to the methoxy derivative, and although the correlation is not perfect, a single relationship is seen. In general, one ethoxy group retards the rate of water addition by a factor of ~3 relative to methoxy; a further factor of ~3 is seen on replacing ethoxy by isopropoxy. These effects are reasonably additive when multiple substitutions are considered. It is also noteworthy that the data correlate much better with the Taft electronic parameter ($\rho^* = 4.4$) than with the steric constant E_s. The latter predicts a much bigger difference between Et ($E_s = -0.07$) and *i*-Pr ($E_s = -0.49$) than between Me ($E_s = 0$) and Et. As seen in Table II and in Figure 3, the reactivity with OH^- parallels that with H_2O.

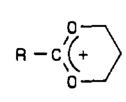
(c) Ring Effects. We observed previously[1] that the 2-methoxy-1,3-dioxolan-2-ylium cation is 5.9 times more reactive with water than the 2-methoxy-1,3-dioxan-2-ylium cation, and this trend is continued here, the five-membered **27** being 10 times more reactive than the six-membered **23**. A sizeable portion of the difference—a factor of ~3—can be explained by the previously mentioned *O*-alkyl effect. That is, the five-cycle is like a dimethoxy cation, while the six-cycle is like a less reactive methoxy, ethoxy derivative. However, taking this difference into account, the five-cycle is still more reactive. This order is opposite to that normally expected for nucleophilic addition to cyclic systems.[17] The ions under consideration here, however, have three centers undergoing sp^2 to sp^3 hybridization during reaction, whereas the general rule was formulated for cycloalkyl systems where only one center (with no heteroatoms attached) is involved. The intermediate situation, two centers in the ring undergoing a change, is represented by the pyran (**33–35**) and furan (**36–38**) type ions. These have the six-cycle more reactive, with the actual differences small and dependent upon the exocyclic alkoxy substituent.

(d) *C*-Alkyl Effects. The effects of alkyl substitution at C_α present perhaps the most surprising result of this study. The order for reactivity with water is Me ≈ Et ≈ *n*-Pr ≈ *n*-Bu ≈ *i*-Bu < *i*-Pr ≈ *s*-Bu ≈ *t*-Bu for the acyclic ions $RC^+(OMe)_2$ (**7–16**) and $RC^+(OEt)_2$ (**17–21**) (see Table I). Thus, in these series, there is a *lack* of (kinetic) stabilization on replacing Me by the more electron-donating and longer straight-chain substituents Et through *n*-Bu. If, however, *branched* substituents (R = *i*-Pr, *s*-Bu, *t*-Bu) are introduced, kinetic *de*stabilization results (compare, e.g., **14–16**, with **7** or **20–21** with **17**). In comparison, with the cyclic 1,3-dioxan-2-ylium ions (**23–26**) and the 4,4,5,5-tetramethyldioxolan-2-ylium ions (**29–32**), the rate constants for hydration are essentially *in*dependent of the nature of alkyl substituent (from R = Me to *t*-Bu). Obviously, on the basis of alkyl ability to (a) stabilize positive charge and (b) sterically hinder the access of a water molecule to C^+, a general reactivity order Me > Et > *i*-Pr > *t*-Bu is expected.

As shown by NMR superacids, the acyclic ions adopt the *Z,E* conformation.[18,19] Molecular models indicate that in the *Z,E* conformation steric interaction between the alkyl group and one alkoxyl substituent is possible if the alkyl group is larger than Me. In fact, with R = aryl there is experimental evidence for steric crowding preventing full coplanarity of the $RC(OR')_2$ system.[21] It is therefore possible that the enhanced reactivity of the acyclic *i*-Pr-, *s*-Bu-, and *t*-Bu-substituted cations is at least in part due to a sterically induced deviation from coplanarity. The cyclic systems, however, should have a fully planar π system with no steric interaction possible between the alkyl and alkoxyl substituents, and they should therefore show the expected reactivity pattern Me > Et > *i*-Pr > Bu. However, this is not observed.



Z, E



Z, Z

As is usually done when the normal alkyl order is not observed, solvation effects (the Baker–Nathan effect)[22] can be invoked. The argument here is that there is a solvation order Me > Et > *i*-Pr > *t*-Bu counter-balancing the opposite electronic/steric order, and differences end up being small and variable. On the basis of the activation parameters (Table III) there is in fact evidence for differences in solvation in going from Me to *t*-Bu. We have previously commented upon the negative entropy of activation for hydration of $(MeO)_3C^+$,[1] explaining this by the involvement of additional water molecules in the transition state, possibly with a mechanism involving concerted proton transfer to the solvent. The alkyl diethyoxy carbocations all have negative $\Delta S^\ddagger$, but there

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(16) Richard, J. P.; Jencks, W. P. *J. Am. Chem. Soc.* **1984**, *106*, 1373.

(17) Brown, H. C.; Ichikawa, K. *Tetrahedron* **1957**, *1*, 221.

(18) (a) Taft, R. W. *J. Am. Chem. Soc.* **1952**, *74*, 2729; *Ibid.* **1952**, *74*, 3120; *Ibid.* **1953**, *75*, 4231. Ramsay, B. G.; Taft, R. W. *J. Am. Chem. Soc.* **1966**, *88*, 3058. Hart, H.; Tomalia, D. A. *Tetrahedron Lett.* **1966**, *3383*. Borch, R. F. *Ibid.* **1968**, *90*, 5303. Dusseau, C. H. V.; Schaafsma, S. E.; Steinberg, H.; de Boer, T. J. *Tetrahedron Lett.* **1969**, 467. Paulsen, H.; Dammeyer, R. *Chem. Ber.* **1976**, *109*, 1837. (b) α-Dihydroxy- and hydroxyalkoxyalkyl carbocations (in superacids) show a similar preference for the *Z,E* conformation, cf. ref 6c,d for reviews.

(19) The corresponding *radical* cations also assume the *Z,E* conformation. See: Reference 20.

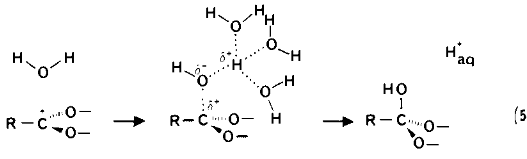
(20) Behrens, G.; Bothe, E.; Koltzenburg, G.; Schulte-Frohlinde, D. *J. Chem. Soc., Perkin Trans. 2* **1980**, 883; *Ibid.* **1981**, 143. Koltzenburg, G.; Behrens, G.; Schulte-Frohlinde, D. *Angew. Chem.* **1983**, *95*, 511; Angew. *Chem., Int. Ed. Engl.* **1983**, *22*, 500.

(21) Chiang, Y.; Kresge, A. J.; Salomaa, P.; Young, C. I. *J. Am. Chem. Soc.* **1974**, *96*, 4494.

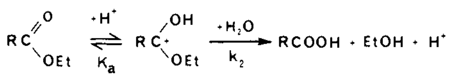
(22) Baker, J. W.; Nathan, W. S. *J. Chem. Soc.* **1935**, 1844. The effect results from steric hindrance to solvation. See, e.g.: Schubert, W. M.; Craven, J. M.; Minton, R. G.; Murphy, R. B. *Tetrahedron* **1959**, *5*, 194. Schubert, W. M.; Sweeney, W. A. *J. Org. Chem.* **1956**, *21*, 119. Brown, H. C.; Guedin, B. G.; Tekeuchi, K.; Peters, E. N. *J. Am. Chem. Soc.* **1975**, *97*, 610.

is a clear order, Me ≈ Et > *i*-Pr ≫ *t*-Bu, the *t*-Bu derivative in particular standing out. For an explanation it is suggested that the $\Delta S^{\ddagger}$ values reflect to a large extent the difference in solvation between the cation and the transition state for its hydration. On this basis, the strongly negative $\Delta S^{\ddagger}$ for $t\text{-BuC}^+(\text{OEt})_2$ compared to $\text{MeC}^+(\text{OEt})_2$ indicates that in the case of $t\text{-BuC}^+(\text{OEt})_2$ more water molecules are immobilized in going to the transition state.

An additional aspect is the effect the substituent has on the activation *enthalpies*. As seen from Table III, the substituent effect is of compensatory nature: As compared to Me or Et, *t*-Bu lowers the activation entropy, but this rate-decreasing effect is compensated by the rate-enhancing effect of the decrease of the activation enthalpy (to 1.4 kcal mol^{-1}). It is tempting to interpret this low value in terms of addition of a quasi OH$^-$ ion, formed by dissociation of a water molecule (eq 5). The resulting proton would be hydrated by adjacent water molecules, this giving rise to a large entropy loss. The OH$^-$, being a better nucleophile than H_2O, would react with C$^+$ with a lower activation enthalpy. In essence, this picture involves a dissociative polarization of a water molecule in the transition state of the hydration of the carbocation, with the transition state being more productlike in the case of the *t*-Bu derivative than with the methyl derivative.


(5)

These mechanistic concepts are relevant in connection with the fact that the hydration of $\text{RC}^+(\text{OEt})_2$ is a close model of the rate-limiting step k_2 in the H$^+$-catalyzed hydrolysis of ethyl esters.



$$\text{RC}(=\text{O})\text{OEt} \underset{K_a}{\overset{+\text{H}^+}{\rightleftharpoons}} \text{RC}^+(\text{OH})(\text{OEt}) \xrightarrow[k_2]{+\text{H}_2\text{O}} \text{RCOOH} + \text{EtOH} + \text{H}^+ \qquad (6)$$

It is precisely this overall reaction that is used to define the steric substituent parameters E_s. The assumption is made that electronic effects on the equilibrium and on the hydration steps k_2 cancel, leaving only the steric effect on the latter to determine rate differences.[23,24] To give an example, ethyl pivalate undergoes acid hydrolysis 35 times more slowly than ethyl acetate, so E_s (*t*-Bu) results as −1.54. However, with the dialkoxy carbocations the reactivity ratio is reversed, i.e. $t\text{-BuC}^+(\text{OEt})_2$ is 2.3 times *more* reactive than $\text{MeC}^+(\text{OEt})_2$, or $t\text{-BuC}^+(\text{OMe})_2$ is 6 times *more* reactive than $\text{MeC}^+(\text{OMe})_2$ (see Table I).

As shown in eq 7, rate constants for ester hydrolysis can be broken down into an equilibrium constant and the hydration rate constant. If k_2 ratios are similar to $\text{RC}^+(\text{OEt})_2$ rate ratios, then,

$$E_s = \log \frac{k_{\text{Hyd}}(\text{R})}{k_{\text{Hyd}}(\text{Me})} = \log \frac{k_2(\text{R})}{k_2(\text{Me})} + \text{p}K_a(\text{R}) - \text{p}K_a(\text{Me}) \qquad (7)$$

in contrast to the classic picture, the E_s order results not from an effect on the hydration step but from an effect on the equilibrium step. For example, if $k_2(t\text{-Bu})/k_2(\text{Me}) = 2.3$, then $\text{p}K_a(t\text{-Bu}) - \text{p}K_a(\text{Me}) = -1.90$. This means that ethyl pivalate is about 2 orders of magnitude more difficult to protonate than ethyl acetate. This is not an unreasonable result. For an explanation, a solvation argument can again be invoked. Protonated esters are expected to be strongly solvated through hydrogen bonding to their OH group. Bulkier R groups should hinder this solvation. There is literature evidence for this effect. With ^{1}H NMR spectroscopy to monitor protonation behavior, esters RCOOEt were found to exhibit a basicity order Me > Et > *i*-Pr,[25] in accord with the above prediction. In fact, the proposal was advanced in that work that the alkyl substituent on the ester carbonyl influences the basicity via its effect on the solvation of the protonated form.[25] Substituent-induced solvation differences are also seen with the protonated ketones, which have been more extensively investigated.[26] The conclusion then is that E_s does not measure pure steric effects but contains the substituent effects on the hydration pattern of the (protonated) ester.

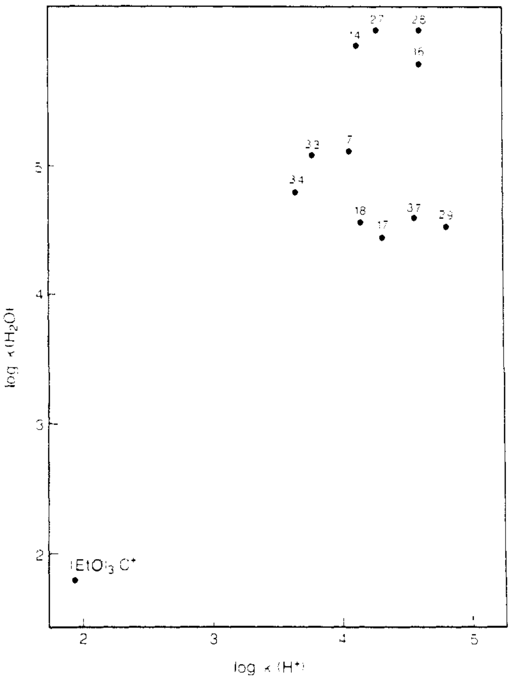
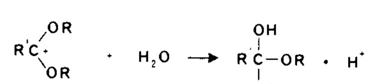
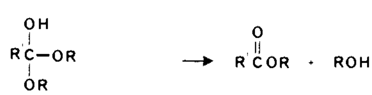


Figure 5. Correlation of cation hydration rate constants [$k(H_2O)$] with rate constants for H_3O^+-catalyzed formation from ortho esters. For cation identification, see Table I. Ortho ester leaving alcohol and source of $k(\text{H}^+)$ are as follows: **7**, OMe, ref 29a; **14**, OMe, ref 29b; **16**, OMe, ref 29b; **17**, OEt, ref 29c,d; **18**, OEt, ref 29c; **27**, OMe, ref 29a,e,f; **29**, OMe, ref 29e,f; **29**, OMe, ref 29e; **33**, OMe, ref 29g; **34**, OEt, ref 29g; **37**, OEt, ref 29g; $(\text{EtO})_3\text{C}^+$, OEt, ref 29c.

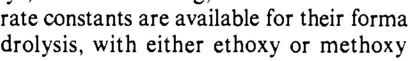
(e) Ortho Ester Hydrolysis. Dialkoxy carbocations are intermediates of the three-stage mechanism of ortho ester hydrolysis (eq 8–10).[3,27] The first stage of this reaction is normally, but not always,[27,28] rate-limiting, and for 10 of the cations listed in Table I, rate constants are available for their formation in an ortho ester hydrolysis, with either ethoxy or methoxy as the leaving group.[29] Except that the formation and hydration stages run in reverse directions, they are very similar. The first stage of ortho



$$\text{RC}(\text{OR})_3 + \text{H}^+ \longrightarrow \text{RC}^+(\text{OR})_2 + \text{ROH} \qquad (8)$$



$$\text{RC}^+(\text{OR})_2 + \text{H}_2\text{O} \longrightarrow \text{RC}(\text{OH})(\text{OR})_2 + \text{H}^+ \qquad (9)$$



$$\text{RC}(\text{OH})(\text{OR})_2 \longrightarrow \text{RC}(=\text{O})\text{OR} + \text{ROH} \qquad (10)$$

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[23] Taft, R. W. *J. Am. Chem. Soc.* **1952**, *74*, 2729; *Ibid.* **1952**, *74*, 3120; *Ibid.* **1953**, *75*, 4231.

[24] Obviously, the tacit assumption is made that change of substituents has *no* effect on the difference in *solvation* of the species in the reactant and the transition states.

[25] Lee, D. G.; Sadar, M. H. *J. Am. Chem. Soc.* **1974**, *96*, 2862.

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[27] Ahmad, M.; Bergstrom, R. G.; Cashen, M. J.; Kresge, A. J.; McClelland, R. A.; Powell, M. F. *J. Am. Chem. Soc.* **1977**, *99*, 4827.

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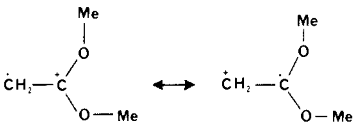
ester hydrolysis is subject to general-acid catalysis,[3] with proton transfer concerted with C–O bond breaking.[30] The negative ΔS^* values for cation hydration are consistent with an analogous picture in reverse eq 5, i.e. proton transfer concerted with C–O bond making. In fact, general-base catalysis of water addition to monoalkoxy carbocations has been suggested on the basis of trapping experiments.[31] Despite the mechanistic similarity, there is, however, no universal correlation in the rate constants for ortho ester hydrolysis and cation hydration (Figure 5). For example, $MeC^+(OEt)_2$ forms more rapidly and hydrates more slowly than $MeC^+(OMe)_2$. This is the behavior expected on the basis of cation stability, and there is a number of pairs that follow such a pattern. There are, however, equally many examples that do not. For example, the 2-methyl-1,3-dioxolan-2-ylium ion not only forms but also reacts more quickly than $MeC^+(OMe)_2$. In view of this, it may be unwise to interpret differences in rate constants for ortho ester hydrolysis in terms of differences in cation stabilities. Again, the explanation will probably involve the effect of the alkyl substituents on solvation and activation parameters.

Another comparison worth commenting upon involves di- and trialkoxy carbocations (Figure 5). The relative slowness with which the latter form from orthocarbonates was noted over 20 years ago,[29c] being attributed to the weaker basicity of the oxygen leaving group.[3] This effect, however, cannot be important in the hydration direction, where the order is much like one would expect on the basis of cation stability, $(EtO)_3C^+$, for example, reacting almost a 1000-fold more slowly[1] than $(EtO)_2C^+Et$. One explanation for this is that the transition state in eq 5 has proton transfer ahead of C–O bond breaking in the forward direction, so that basicity effects are important. This means that in the reverse direction C–O bond formation is ahead of proton transfer so that cation stability is important. However, the negative activation entropies show that proton transfer is not totally unimportant.

(f) Comparison with Aliphatic Radical Cations. Radical cations of a type that closely resemble α-dialkoxyalkyl carbocations have recently been described.[20] The acyclic radical cations assume in aqueous solution a *Z,E* conformation, and they decay by reaction with water or OH^- whereby OH^- attacks at C_α and the thus



formed hemi ortho ester radical eliminates alcohol to give, e.g. the ester radical $^\bullet CH_2CO(OMe)$.[20] What is interesting is the fact that the rate constants for reaction of the *radical* cations with water are 2–3 orders of magnitude *lower* than those for the cations, whereas the rate constants for reaction with OH^- are 1 order of magnitude *higher* for the *radical* cations than for the corresponding cations. This means that the two types of ion have a totally different selectivity in their reactions with the nucleophiles H_2O and OH^-. Another difference is that the *radical* cations are (kinetically) stabilized by increasing alkyl substitution at C_α/C_β, in contrast to the cations (see section d).

Summary and Conclusions

It has been shown that aliphatic α-dialkoxyalkyl carbocations can be produced in aqueous solution (i.e., under solvolytic conditions) from acetals and ortho esters as precursors by using the stepwise hydride-transfer method. The reaction of the cations with water was monitored via the production of H^+ by conductance techniques. On the basis of rate data obtained for 30 carbocations structure–activity relations could be established. For substitution in the alkoxyl group, the reactivity order is Me > Et > *i*-Pr with $\rho^* = +4.4$. For alkyl substitution at C_α, however, the usual steric/electronic order breaks down, and this is explained in terms of counteracting solvational effects. The reactivity order of the dialkoxyalkyl carbocations is discussed in connection with mechanistic schemes proposed for ester and ortho ester hydrolysis, and apparent inconsistencies between these areas are suggested to be due to neglect of solvational effects, the exact nature of which will still have to be established.

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Mechanisms of Decarboxylation of Carboxybiotin

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Abstract: Carboxylation is decarboxylated by two different mechanisms at low pH, where the N1′ carboxyl is protonated (pK 4.25 at 2 °C) and at high pH where it is ionized. The low-pH mechanism has a rate constant of 5.9×10^{-3} min^{-1} at 2 °C (activation energy 33 kcal/mol), while the high-pH one has a rate constant of 4.6×10^{-3} min^{-1} at 25 °C, with the two mechanisms showing equal rates at 25 °C at pH 6.4. At pH 8 the D_2O solvent isotope effect is 1.1 with a curved proton inventory, while at pH 3.4 the value is 1.6 with a linear proton inventory. The ^{13}C isotope effect on decarboxylation is 1.023 at pH 8.2, but 1.012 for the low-pH reaction. The low-pH mechanism probably involves concerted protonation of N1′ and C–N bond cleavage, with an early transition state in which proton motion is ahead of C–N bond breaking. The high-pH mechanism has a moderately early transition state and gives the enolate as the product, with the small solvent isotope effect presumably arising from changes in the fractionation factors of protons in water hydrogen-bonded to the ureido oxygen.

The cofactor biotin serves as a carboxyl carrier in many enzymatic carboxylations, mediating between the carboxyl group donor, usually bicarbonate, and acceptor, usually an α-keto acid or acyl-CoA thioester. Biotin-dependent enzymes show ping-pong kinetics, consistent with the formation of a discrete carboxybiotin intermediate. Although the structure of carboxybiotin remained

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