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Reaction Kinetics

Intramolecular Hydrogen-Bonding Modulates the Nucleophilic Reactivity of Ammonium-Peroxycarboxylates

Robert J. Mayer[a] and Armin R. Ofial*[a]

Abstract: The ammonium-peroxycarboxylic acid mesylates derived from γ-aminobutyric acid, β-alanine, and β-piperidinopropionic acid were synthesized and characterized by spectroscopic methods and X-ray crystallography. To study the nucleophilic reactivities of the corresponding ammonium- and aminoperoxycarboxylates, the kinetics of their reactions with a series of benzhydrylium ions (Ar_2CH^+) were investigated in alkaline, aqueous solutions at 20 °C. Using sequential-mixing stopped-flow UV/Vis photometry, the rates of the reactions of the short-lived nucleophiles with Ar_2CH^+ were determined and analyzed by the linear free energy relationship $\lg k = s_N(N + E)$ furnishing nucleophilicity parameters (N, s_N) of the peroxycarboxylates. Quantum chemical calculations indicate that the reactivity of the zwitterionic ammonium-peroxycarboxylates is attenuated by intramolecular N–H···O hydrogen bonding.

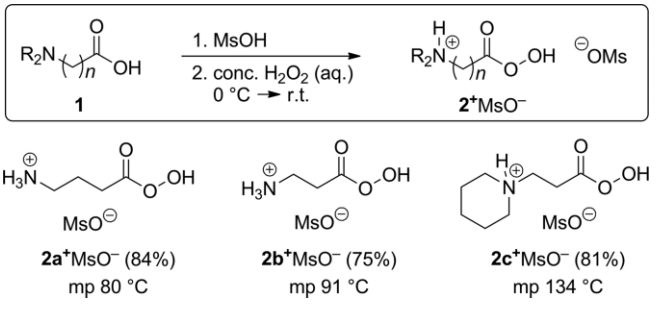
Introduction

Recent investigations into the nucleophilic reactivity of inorganic bleach reagents and peroxide anions showed that peroxycarboxylates possess distinctly higher reactivity than the anions of alkyl hydroperoxides (ROO^-) and hydrogen peroxide (HOO^-).[1,2] In this context, some patents on the use of amino-acid derived peroxycarboxylic acids intrigued us.[3a–3g] Quaternarization of the nitrogen by alkylation or protonation along with subsequent oxidation at the carboxyl group led to solid ammonium-peroxycarboxylic acids (APOCAs, with HSO_4^- or MsO^- counterions).[3a] These APOCA salts had been characterized by elemental analysis and, in some cases, melting points. In addition, their potential application as textile bleaches was reported.[3a–3g] One would, furthermore, expect that APOCA salts could serve as stable and well water-soluble precursors of highly nucleophilic peroxycarboxylate anions.

To enhance our understanding of their reactivities, we characterized a representative set of three APOCA salts by spectroscopic methods and X-ray analysis. We then evaluated the pH-dependent reactivity of aqueous solutions of APOCA salts toward benzhydrylium ions (as reference electrophiles) by kinetic methods to define the potential of APOCAs as nucleophilic oxidants and compare their reactivities with those of related oxidants.

Results and Discussion

Characterization of Ammonium-Peroxycarboxylates. Following a literature procedure,[3a] we synthesized three APOCA mesylates **2**$^+$MsO$^-$ as depicted in Scheme 1. Dissolving γ-aminobutyric acid (**1a**, GABA), β-alanine (**1b**), and β-piperidinopropionic acid (**1c**) in methanesulfonic acid and adding an excess of concentrated (> 85 %) aqueous hydrogen peroxide[3h] generated the APOCA mesylates **2a**$^+$MsO$^-$, **2b**$^+$MsO$^-$, and **2c**$^+$MsO$^-$, respectively, which precipitated when the reaction mixture was poured on ice-cold THF.



Scheme 1. Preparation of ammonium-peroxycarboxylic acid mesylates.

Beside their spectroscopic characterization (Supporting Information), **2a**$^+$MsO$^-$, **2b**$^+$MsO$^-$ and **2c**$^+$MsO$^-$ were investigated by single-crystal X-ray diffraction (Figure 1).[4] The oxygen–oxygen distances of 1.451 to 1.464 Å in **2a**$^+$, **2b**$^+$, and **2c**$^+$ are in the typical range reported for peroxycarboxylic acids.[5]

In crystals of **2a**$^+$MsO$^-$ and **2b**$^+$MsO$^-$ the C(O)–O–O–H groups adopt an almost identical conformation with C–O–O–H dihedral angles of 158.2° and 154.6°. In contrast, this dihedral angle is significantly lower in the piperidinium derivative **2c**$^+$MsO$^-$ (104.7°), probably owing to different hydrogen bonding patterns in the solid states of (**2a**–**c**)$^+$MsO$^-$. As exemplarily shown for **2a**$^+$MsO$^-$ in Figure 2, various hydrogen bonding interactions between O–H or N–H of the **2**$^+$ and the oxygen atoms of the mesylate counterions are the prevalent interactions found for all APOCA mesylates in crystalline state (Figure 2).

[a] *Department Chemie, Ludwig-Maximilians-Universität München, Butenandtstraße 5-13, 81377 München, Germany*
E-mail: ofial@lmu.de
URL: http://www.cup.uni-muenchen.de/oc/ofial/
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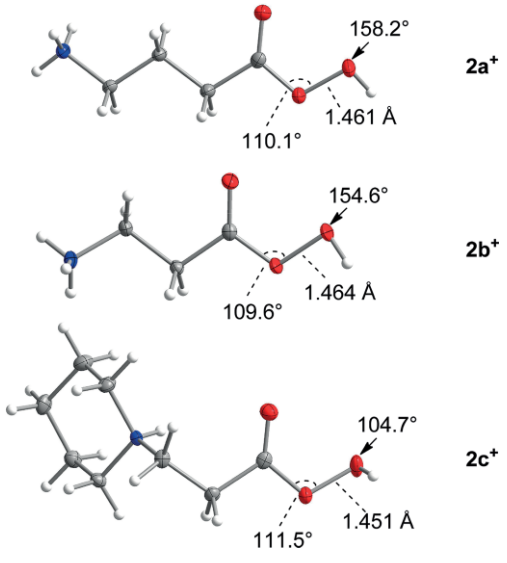


Figure 1. Solid-state structures of **2a**$^+$MsO$^-$, **2b**$^+$MsO$^-$ and **2c**$^+$MsO$^-$ (thermal ellipsoids are depicted at 50 % probability level at T = 100 K, counterion MsO$^-$ not shown).[4]

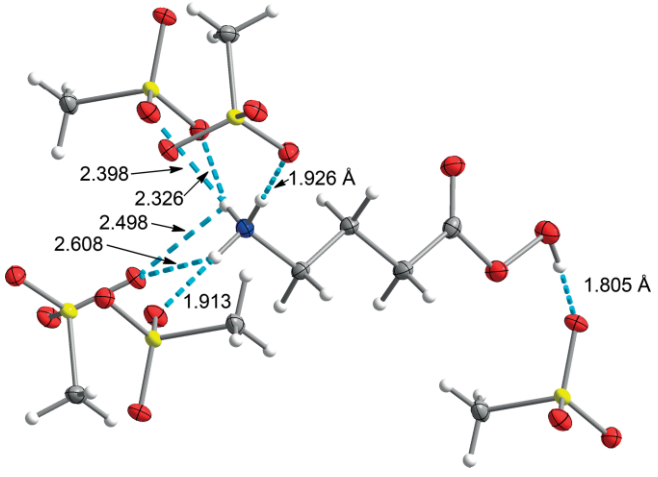
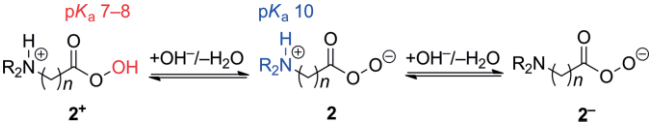


Figure 2. Hydrogen bonding in the solid-state structure of **2a**$^+$MsO$^-$ (thermal ellipsoids are depicted at 50 % probability level).

To characterize the acid/base behavior of **2**$^+$, we determined the Brønsted acidities (pK_a) of their peroxycarboxylic groups by potentiometric titration in water. The acidities of **2**$^+$ were found to be in the common range of pK_a 7–8 for aliphatic peroxyacids (see Table 1 below).[1] By assuming that the known pK_a of ammonium groups in protonated amino acids (pK_a ≈ 10) also apply for the APOCA cations **2**$^+$, it can be anticipated that amino-substituted peroxycarboxylic acids exist as cations (**2**$^+$), zwitterions (**2**), or anions (**2**$^-$) in aqueous solution (Scheme 2), depending on the pH and in analogy to the established equilibria for α-amino acids. As both, the peroxycarboxylate and the amino group, can act as the nucleophile, the reactivity of APOCA salt solutions is significantly affected by pH.

Kinetics. The nucleophilic reactivity of the amino group in aminocarboxylates derived from natural amino acids or small peptides has already been investigated.[6] Analogous N-nucleophilicities have also been determined for the deprotonated

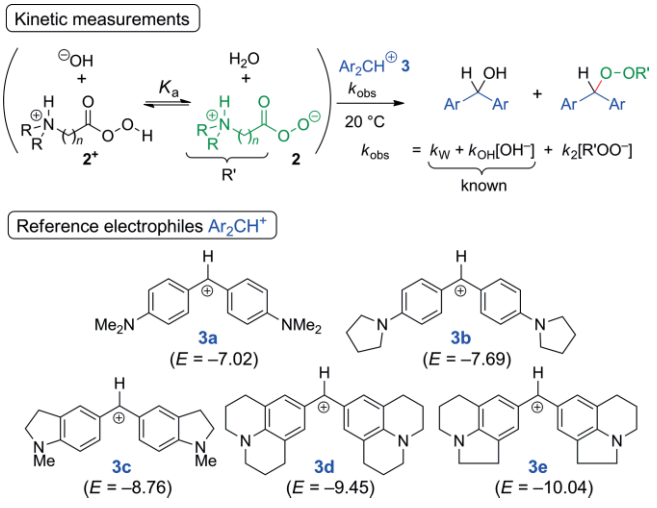


Scheme 2. Protonation equilibria of APOCAs.

forms of GABA (**1a**) and β-alanine (**1b**).[6] In this work, we set out to characterize the peroxycarboxylate groups of **2** and **2**$^-$ in alkaline, aqueous solution with the aim to compare the nucleophilic reactivities with those of other peroxide anions on the basis of Mayr's linear free energy relationship (1).[7–11]

$$\lg k_2(20\ ^\circ\mathrm{C}) = s_N(N + E) \quad (1)$$

In equation (1) the nucleophiles' reactivity is described by the solvent-dependent nucleophilicity parameter N and the nucleophile-specific susceptibility s_N. These parameters can be determined from kinetic measurements with a set of benzhydrylium ions as reference electrophiles (with known electrophilicity parameters E), employing the previously reported procedure.[1,6] As shown in Scheme 3, the kinetics were studied in alkaline, aqueous solution, in which zwitterions **2** were generated by equilibrium deprotonation of the corresponding cations **2**$^+$. The reactions of an excess of **2** with blue colored benzhydrylium ions Ar$_2$CH$^+$ **3**[12] under pseudo-first-order conditions yielded colorless reaction products, which enabled us to use stopped-flow UV/Vis photometry to monitor the reaction progress.



Scheme 3. Generation of nucleophilic zwitterions **2** in alkaline, aqueous solution and reactions of **2** with the benzhydrylium ions **3** (counterions: BF_4^- for **3**, MsO$^-$ for **2**$^+$, electrophilicities E from ref[11]).

Initial sequential mixing experiments showed that conditions successfully used to determine the nucleophilicity of various peroxide anions[1] could not be applied without modification to study the kinetics of the reactions of **3** with the ammonium-peroxycarboxylates **2**: When we generated **2a** in a first mixing step by dissolving **2a**$^+$MsO$^-$ ([**2a**$^+$]$_0$ = 4 × 10^{-4} M) in aqueous potassium hydroxide solution ([KOH]$_0$ = 4 × 10^{-4} M), then allowed the solution to age for a defined time and, in a second mixing step, added solutions of **3**-BF$_4^-$ ([**3**]$_0$ = 1.1 × 10^{-5} M),

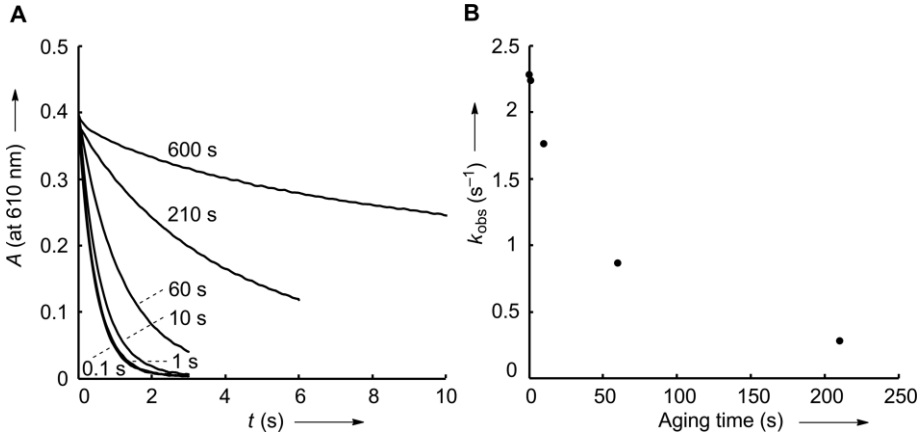


Figure 3. (A) Observed decays of benzhydryl absorbances (**3b**) for variable aging times of the nucleophile (**2a**) solutions and (B) dependence of the corresponding first-order rate constants k_{obs} on the aging times. [**2a**$^+$MsO$^-$]$_0$ = 4 × 10^{-4} M, [OH$^-$]$_0$ = 4 × 10^{-4} M, 20 °C. The slow reaction of **2a** with **3b** after 600 s aging time did not follow a mono-exponential decay.

we observed mono-exponential decays of the benzhydrylium absorbances under these pseudo-first-order conditions. However, the observed decay rates systematically decreased when the time between the first and the second mixing step, that is, the aging time of the nucleophile solution, was increased (Figure 3A). The dependence of the observed rate contants k_{obs} on the aging time indicated a first-order decomposition of the nucleophile on the seconds time scale at 20 °C ($\tau_{1/2}$ = 20–25 s, Figure 3B). The analogous variation of the aging times for reactions of reference electrophiles **3** with aqueous solutions of the nucleophilic zwitterions **2b** and **2c** (generated from **2b**$^+$MsO$^-$ and **2c**$^+$MsO$^-$, respectively) gave similar results but showed that the degradation proceeded somewhat slower ($\tau_{1/2}$ > 100 s, Supporting Information) than for **2a**.

In contrast, iodometric titration of an alkaline solution of **2a**$^+$MsO$^-$ showed that the total peroxide content of the reaction mixture decreased on the minute time-scale (Figure 4), thus, much slower than expected from the kinetic experiments shown in Figure 3.

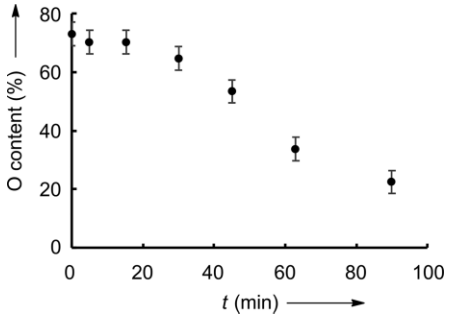
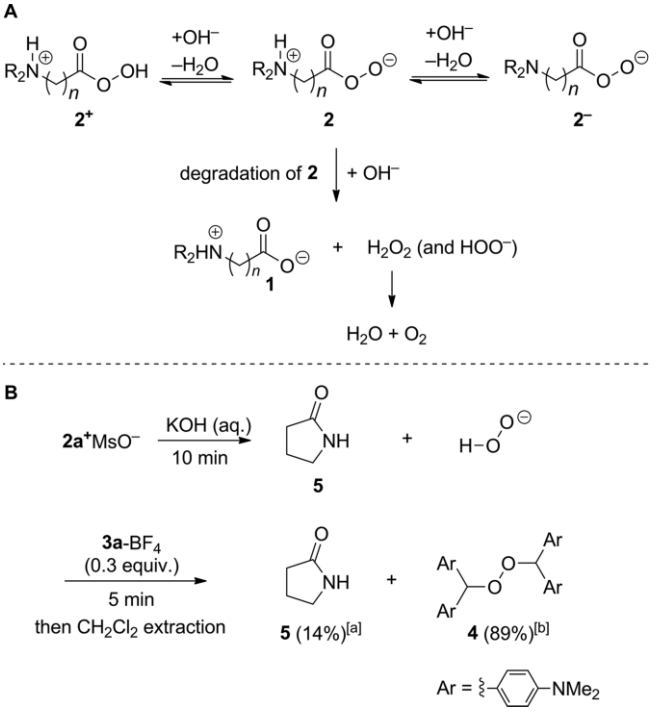


Figure 4. Peroxide content as determined by iodometric titration of an alkaline solution of **2a**$^+$MsO$^-$ (20 °C, [**2a**$^+$] = 1.4 × 10^{-3} M, [OH$^-$] = 5 × 10^{-2} M).

The NMR spectroscopic investigation of the alkaline, aqueous solutions showed that degradation of the peroxycarboxylate to the carboxylate group by attack of hydroxide ions at the carboxyl carbon is a common decomposition pathway for all investigated zwitterions **2** (Scheme 4A). This reaction path liberates hydrogen peroxide, which decomposes slowly to molecular oxygen and water.



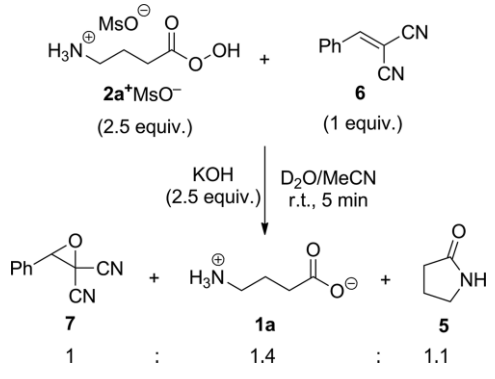
Scheme 4. (A) General degradation of **2** to **1** in alkaline solution. (B) Formation of the lactam **5** by ring closure of **2a**$^+$MsO$^-$ in alkaline solution and partial trapping of thus liberated hydrogen peroxide by **3a**. Yields were determined by using added dimethyl fumarate as integration standard. [a] The hydrophilic lactam **5** was only partially extracted by dichloromethane, which resulted in a low yield of **5** (yield refers to **2a**$^+$MsO$^-$). [b] Yield refers to **3a**-BF_4.

The peroxy version of GABA (**2a**) decomposed significantly faster than **2b** or **2c** owing to an additional option: As indicated by ^{1}H NMR spectroscopy, a mixture of the lactam **5** and the peroxide **4** was isolated after dichloromethane extraction of an aqueous, alkaline solution of **2a**$^+$MsO$^-$ that, after 10 min of aging at ambient temperature, was treated with **3a**-BF_4 (Scheme 4B). We conclude that **2a** not only degrades because of the hydroxide ion attack shown in Figure 4A but also undergoes ring closure to give γ-butyrolactam (**5**) under *alkaline* reac-

tion conditions (pH 13). A stoichiometric amount of hydrogen peroxide anions is released in this self-condensation, which is interceptable by the known reaction with **3a**[2] to yield the bis(benzhydryl)peroxide **4**. Degradation by ring closure was not observed for **2b**, presumably because this intramolecular reaction would lead to a strained β-lactam.

To gain evidence for the oxidation of electrophiles by APOCAs, we studied the reaction of benzylidene malononitrile **6** with $\mathbf{2}^+$ under alkaline conditions (Scheme 5). When **6** was treated with an excess of $\mathbf{2a}^+MsO^-$ (2.5 equiv.), the electrophile was almost quantitatively converted into the corresponding epoxide **7**. Additionally, the formation of the corresponding GABA zwitterion **1a** and γ-butyrolactam **5** (both in comparable ratio) were observed by NMR spectroscopy. The outcome of this reaction corroborates our mechanistic outline: After quantitative generation of **2a** by deprotonation of $\mathbf{2a}^+$ under the alkaline conditions, one part of **2a** (2.5 equiv.) reacts with **6** (1 equiv.) in a nucleophilic epoxidation to furnish **7** (1 equiv.) and **1a**. The remaining 1.5 equivalents of the peroxycarboxylate **2a** decompose to hydrogen peroxide and the lactam **5**.

We, therefore, conclude that the zwitterions **2** decompose rapidly in alkaline, aqueous solution after being generated from $\mathbf{2}^+$ (as seen in Figure 3). Independent of whether decomposition of **2** is initiated by hydroxide ions that react with the peroxycarboxyl group or by amino groups that intramolecularly attack at the carboxyl carbon, H_2O_2 is released. The iodometrically determined slow decrease of the overall peroxide content for alkaline solutions of $\mathbf{2}^+$ (Figure 4), therefore, reflects the subsequent, slow decomposition of the released H_2O_2.



Scheme 5. Reaction of $\mathbf{2a}^+MsO^-$ with malononitrile **6** as analyzed by ^1H NMR spectroscopy.

Figure 3 defines the conditions for the determination of the nucleophilic reactivities of **2**: First, solutions of **2** have to be mixed with their electrophilic reaction partners within 1 s after generation of **2** from $\mathbf{2}^+$. Second, the half-life times of the reactions should be 10 s or less to avoid noticeable degradation of **2** during the reactions with **3**. Determining the reaction kinetics by using the sequential mixing setup of the stopped-flow spectrometer was, therefore, instrumental to access the nucleophilicities of solutions of **2**: In a first step, aqueous solutions of the base and $\mathbf{2}^+MsO^-$ were mixed and allowed to age for 1 s. Then the reaction with the reference electrophiles **3** was initiated by mixing the solution of freshly generated **2** with that of **3**.

As the degree of deprotonation of $\mathbf{2}^+$ is adjustable by the chosen hydroxide concentration, different nucleophilic species can be addressed: Treating $\mathbf{2}^+$ with an equimolar amount of base generates the ammonium-peroxycarboxylates **2**. Under these conditions, the oxygen reactivity of zwitterions **2** can be measured selectively because the more basic amino group is still protected by protonation. Alternatively, a high concentration of base generates the amino-peroxycarboxylate $\mathbf{2}^-$ as the major species. Because anions $\mathbf{2}^-$ are ambident nucleophiles that attack via either nitrogen or oxygen at Ar_2CH^+, the determination of the nucleophilicities of $\mathbf{2a}^-$ and $\mathbf{2b}^-$ was not possible unequivocally. In $\mathbf{2c}^-$, however, the nitrogen of the tertiary amine is sterically hindered and does not react with highly stabilized benzhydrylium ions, such as **3b**–**e**.[13] This enabled us to quantify the oxygen-reactivity of amino-peroxycarboxylate $\mathbf{2c}^-$ without interfering reactivity of the piperidino group.

The analysis of the observed first-order rate constants k_{obs} (s^{-1}, Figure 5A) by equation (2) was performed as reported for the anions of organic peroxides:[1,2] Brønsted acidities (pK_a) of $\mathbf{2}^+$ were employed to determine the concentrations of peroxycarboxylates and hydroxide ions, that is, [**2**] (or [$\mathbf{2}^-$]) and [OH^-]. Then, [OH^-] and the known second-order rate constants k_{OH}

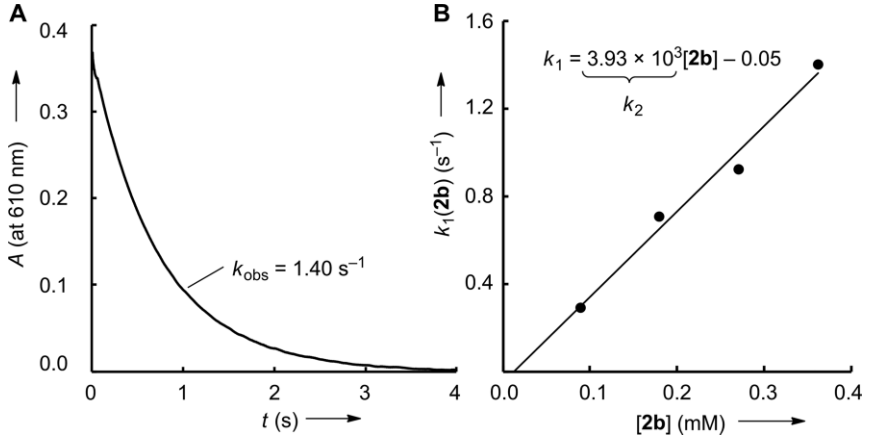


Figure 5. (A) Absorbance *A* (at 610 nm) vs. time for the reaction of **2b** (4.00×10^{-4} M) with **3b** (1.14×10^{-5} M) in aqueous solution (pH 9) at 20 °C. (B) The slope of the linear plot of the first-order rate constant k_1 (= $k_{obs} - k_{OH}[HO^-]$) vs. nucleophile concentration was used to derive the second-order rate constant k_2 for the attack of the zwitterion **2b** at the benzhydrylium ion **3b**.

(from ref[14]) were used for the calculation of the rates of consumption of the cations **3b**–**e** by the hydroxide ions. After subtraction of the contribution by hydroxide ions ($k_{OH}[OH^-]$) from the observed first-order rate constants k_{obs}, the first-order rate constant k_1 [in Equation (3)] reflect the reaction of the electrophiles **3** with the nucleophiles with only a very minor correction for the much slower background reaction of **3** with water (k_W).

$$k_{obs} = k_W + k_{OH}[HO^-] + k_2[R'OO^-] \quad (2)$$

$$k_1 = k_2[R'OO^-] + k_W = k_{obs} - k_{OH}[HO^-] \quad (3)$$

Thereby, the second-order rate constants for the reactions of **2** (or **2**$^-$) with benzhydrylium ions **3b**–**e** can be obtained from the slope of the linear correlation of the first-order rate constant k_1 (= $k_{obs} - k_{OH}[HO^-]$) with the nucleophile concentration.

In accord with equation (3) and as exemplified in Figure 5B for the reactions of **2b** with **3b**, the first-order rate constants k_1 increased linearly with increasing concentration of the nucleophile **2b**, and the slope of these correlations corresponded to the second-order rate constant (k_2, Table 1) for the attack of **2** (or **2**$^-$) at the benzhydrylium ions **3b**–**e**.

The resulting second-order rate constants k_2 of these reactions and the known electrophilicities E of **3b**–**e**[11] were then applied in equation (1): The linear correlations of lg k_2 with the electrophilicity E allowed us to determine the nucleophilicity parameter N and the nucleophile-specific susceptibilities s_N of the peroxide species **2a**–**2c** and **2c**$^-$ (Figure 6). The reactivities of the ammonium-peroxycarboxylates **2** vary only within less than one order of magnitude. It is noteworthy that **2** react 5 to 10 times slower with **3b**–**e** than structurally related peroxycarboxylates (such as phenylperoxyacetate or ε-phthalimido-peroxyhexanoate[1]). Deprotonation of zwitterion **2c** and generation of the anionic **2c**$^-$ increased the reactivity of the RCO_3^- group by a factor of four.

The nucleophilicities of the amino groups in deprotonated GABA **1a**$^-$ and β-alanine **1b**$^-$ were reported to be N = 13.3–13.5 (s_N = 0.56–0.58).[6] Such a level of reactivity can also be anticipated for anionic **2a**$^-$ or **2b**$^-$ that carry free amino groups in a similar molecular environment. We, therefore, analyzed the contribution of *N*-attack by **2**$^-$ at benzhydrylium ions **3** under the conditions of our kinetic experiments.

First, products of *N*-attack by the γ- and β-amino-carboxylates **1a**$^-$ and **1b**$^-$ at **3a**-BF_4^- were characterized by NMR spectroscopy (Supporting Information). The typical singlets at chemical shifts of 4.61–4.64 ppm for N-C*H*Ar$_2$ in **8a** and **8b** (Scheme 6) were then used to analyse product mixtures obtained for reactions of equimolar amounts of **2b**$^+$MsO$^-$ and **3a**-BF_4^- at variable pH. When 1 equiv. of KOH was used to convert **2b**$^+$ to **2b**,

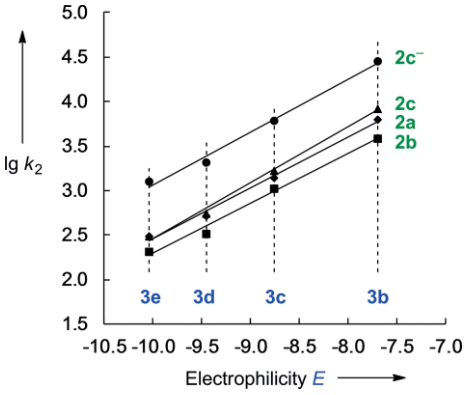
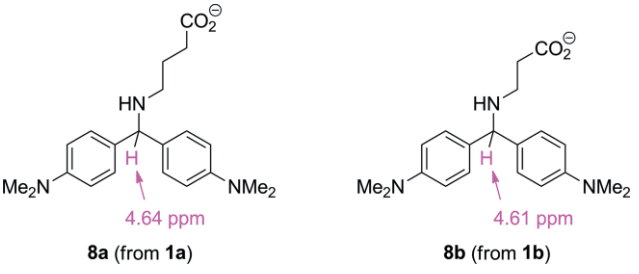


Figure 6. Correlation of lg k_2 for the reactions of nucleophiles **2a**–**c** (and **2c**$^-$) with the reference electrophiles **3b**–**e** (from Table 1) with the electrophilicity parameters E of **3**.

oxygen attack of **2b** at **3a** and subsequent Criegee rearrangements gave rise to various oxidation products of **3a**, such as 4-(dimethylamino)benzaldehyde, and the benzhydrol and benzophenone derivatives of **3a**.[15] Amine **8b**, which may form through nitrogen attack of **2b** at **3a** and subsequent degradation of the peroxycarboxylic to a carboxylic acid, was not detected by ^{1}H NMR spectroscopy under these conditions. However, when 2 equiv. of KOH were used, generation of **8b** became evident from the ^{1}H NMR spectrum of the reaction mixture, and **8b** was formed in even higher yields under more alkaline conditions, that is, reactions of **2b** with **3a** in the presence of 3 equiv. of potassium hydroxide (Supporting Information).



Scheme 6. Chemical shifts of the *N*-benzhydrylated amino acids **8a** and **8b** (in alkaline CD_3CN/D_2O = 4:3).

Owing to the fact that all rate constants for **2a**–**2c** collected in Table 1 were acquired by using only one equivalent of potassium hydroxide (relative to **2**$^+$MsO$^-$), we conclude that these kinetics describe exclusively the oxygen attack of the peroxycarboxylate groups of the zwitterions **2** at the cationic center of **3**. Nitrogen attack becomes only relevant at higher pH (that is, when > 1 equiv. of hydroxide ions relative to **2a**$^+$ or **2b**$^+$ are

Table 1. Basicities pK_{aH} and second-order rate constants k_2 for the oxygen attack of the ammoniumperoxycarboxylates **2** and the aminoperoxycarboxylate **2c**$^-$ at the reference electrophiles **3b**–**e** in alkaline, aqueous solution at 20 °C.

	pK_{aH}[a]	k_2 [M^{-1} s^{-1}]				N (s_N)
		3e	**3d**	**3c**	**3b**	
2a	7.77	3.10×10^2	5.20×10^2	1.39×10^3	6.33×10^3	14.33 (0.57)
2b	7.35	2.06×10^2	3.32×10^2	1.07×10^3	3.93×10^3	14.07 (0.56)
2c	7.48	3.08×10^2	5.55×10^2	1.66×10^3	8.45×10^3	13.94 (0.62)
2c$^-$	9.92[b]	1.26×10^3	2.10×10^3	6.07×10^3	2.89×10^4	15.17 (0.59)

[a] Determined by potentiometric titration. [b] Deprotonation of the piperidinium group.

used) as the more nucleophilic 2^- then starts to compete with **2** for the electrophile **3**. As nitrogen attack of **3** by $2c^-$ is unlikely[13] (see above), the kinetics of $2c^-$ refer to oxygen attack at **3**.

Quantum Chemical Calculations. Why are the nucleophilic reactivities of the ammonium-peroxycarboxylates lower than those of common peroxybenzoates or aliphatic peroxycarboxylates? The fact that the aminoperoxycarboxylate $2c^-$ is more nucleophilic than the ammoniumperoxycarboxylate **2c** led us to investigate whether intramolecular hydrogen bonding of the peroxycarboxylate moiety with the ammonium group reduces reactivity in zwitterions **2**. To investigate the effect of intramolecular H-bonding in **2**, quantum chemical calculations with the Gaussian software were performed to evaluate the conformational space of $2a^+$–$2c^+$.[16] Conformers were optimized with the M06-HF[17]/6-311++(d,p) method taking into account aqueous solvation by the SMD version of the Polarizable Continuum Model.[18] Several methods with the 6-311++G(d,p) basis were tested (including various DFT methods, HF, MP2 and MP3; see Supporting Information for details), but only classical HF and M06-HF gave the position of the intramolecular N–H···O hydrogen bond as expected from experimental basicities.

The calculations revealed that the formation of an intramolecular hydrogen bond is highly favored in **2a**–**2c** (Figure 7), which may attenuate the rates of attack of the peroxycarboxylate groups at the carbocationic centres of the electrophiles **3**.[19]

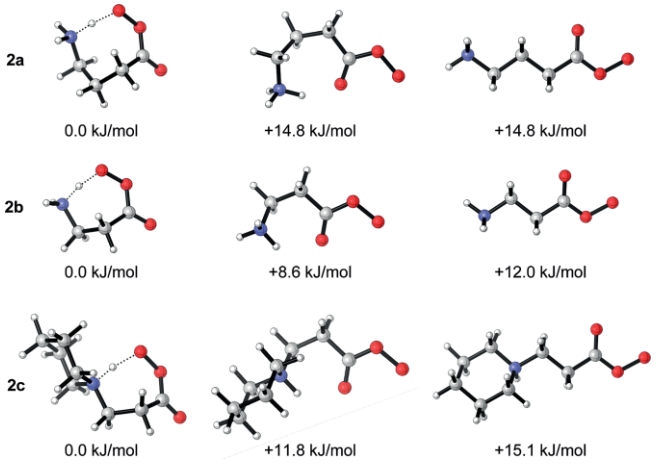


Figure 7. Relative Gibbs energies (at 298 K) of the conformers of **2a**–**2c** with the lowest Gibbs energy as calculated at the M06-HF/6-311++G(d,p) level of theory for aqueous solution (SMD).

Conclusions

Ammoniumperoxycarboxylic acid mesylates (APOCA mesylates) are easily preparable and stable peroxy compounds and, thus, a convenient source of active oxygen. At pH 8–9, ammoniumperoxycarboxylates, the corresponding zwitterions of APOCAs, can be generated, which are highly reactive epoxidation reagents. Their reactivities were characterized by Mayr's nucleophilicity parameters *N* and s_N, which allows for a direct comparison with reactivities of other peroxy anions (Figure 8) and further nucleophiles listed in Mayr's reactivity database.[10] Intramolecular N–H···O hydrogen bonding reduces the nucleophilic reactivity of β- and γ-ammonium-substituted peroxycarboxylates relative to structurally related peroxycarboxylates.

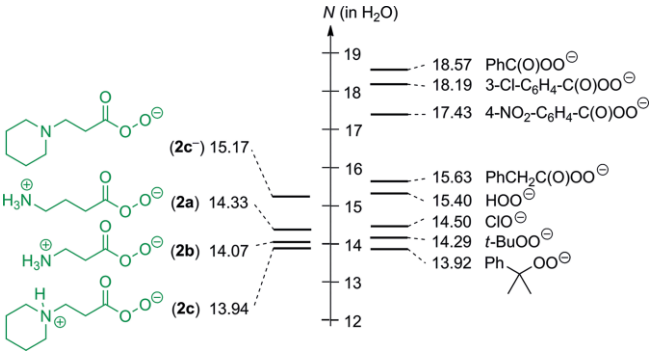


Figure 8. Comparison of nucleophilicity parameters *N* of **2** and 2^- with those of other anionic oxidants (from ref.[1,2,14]).

The application of APOCAs for oxygen transfer reactions in aqueous solution requires careful pH control, however, and is limited to very fast reactions with electrophiles because of the competing degradation to ammoniumcarboxylates and hydrogen peroxide under alkaline conditions.

A combination of the kinetic and thermodynamic data about APOCAs from this study with those for further aliphatic and aromatic peroxycarboxylic acids, hydroperoxides and related bleach reagents will provide a broad fundament for understanding structure-activity relationships, such as, for example, the so-called α-effect.[20]

Experimental Section

CAUTION: Pure peroxides may explode or detonate under influence of heat, shock, spark etc. All reactions or handling of peroxides should be carried out behind a blast shield as a precaution using open vessels while wearing appropriate safety equipment. Rotary evaporation of peroxides should be carried out carefully without excessive stirring at room temperature. Generally, all handling of peroxides should only be performed by experienced people trained in handling explosive compounds.

Analytics: Nuclear magnetic resonance spectra were recorded on 400 or 800 MHz NMR spectrometers. The following abbreviations and their combinations are used in the analysis of NMR spectra: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br. s = broad singlet. All ^{13}C NMR spectra were recorded under broadband proton-decoupling. NMR signals were assigned based on information from additional 2D NMR experiments (COSY, gHSQC, gHMBC, NOESY). Internal reference was set to the residual solvent signals.[21]

3-Carboperoxypropan-1-aminium Methanesulfonate ($2a^+MsO^-$): γ-Aminobutyric acid **1a** (400 mg, 3.88 mmol) was dissolved in methanesulfonic acid (2.03 mL, 31.3 mmol) with careful heating. The solution was cooled to 0 °C and H_2O_2 (0.28 mL of a 92 % aq. solution, 3 equiv.) was added dropwise. Then the reaction mixture was warmed up to room temperature. After 1 h the solution was poured into ice-cold THF (30 mL) and stirred for 30 min. The formed crystalline precipitate was collected by filtration and then washed with THF (5 mL) and diethyl ether (5 mL). Drying of the residue yielded

2a$^+$MsO$^-$ as a colorless, crystalline solid (704 mg, 84 %); m.p. 80 °C; active oxygen content: 100 % (iodometric titration). ^{1}H NMR (400 MHz, D_2O): δ = 7.68 (br. t, $^1J_{H,N} \approx$ 40 Hz, 0.02 H, $^+NH_3$), 3.05 (t, J = 7.8 Hz, 2 H), 2.79 (s, 3 H), 2.56 (t, J = 7.3 Hz, 2 H), 2.00 (quint, J = 7.4 Hz, 2 H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, D_2O): δ = 173.6 (C_q), 38.43 (CH_2), 38.36 (CH_3), 27.3 (CH_2), 21.8 (CH_2) ppm. IR (ATR, neat): $\tilde{\nu}$ = 3139, 2891, 1760, 1631, 1529, 1477, 1417, 1376, 1340, 1323, 1298, 1257, 1159, 1119, 1066, 1044, 995, 974, 968, 928, 872, 781, 763, 702, 660 cm^{-1}. HRMS (FAB$^+$): m/z calcd. for [$C_4H_{10}NO_3^+$]: 120.0665, found 120.0675. Elemental Analysis: Calcd: C, 27.90; H, 6.09; N, 6.51; S, 14.90; found: C, 27.94; H, 6.15; N, 6.49; S, 14.99.

2-Carboperoxyethan-1-aminium Methanesulfonate (2b$^+$MsO$^-$): β-Alanine **1b** (200 mg, 2.24 mmol) was dissolved in methanesulfonic acid (1.01 mL, 15.6 mmol) with careful heating. The solution was cooled to 0 °C and H_2O_2 (0.13 mL of a 85 % aq. solution, 2 equiv.) was added dropwise. Then the reaction mixture was warmed up to room temperature. After 1 h the solution was poured into ice-cold THF (20 mL) and stirred for 20 min. The formed crystalline precipitate was collected by filtration, washed with THF (10 mL) and diethyl ether (10 mL). Drying of the residue yielded **2b**$^+$MsO$^-$ as colorless, crystalline solid (365 mg, 81 %). The active oxygen content of this sample was determined by iodometric titration to be 91 %. Therefore, an overall yield of 74 % of **2b**$^+$MsO$^-$ was calculated. ^{1}H NMR (400 MHz, D_2O): δ = 7.85 (br. t, $^1J_{H,N} \approx$ 42 Hz, 0.01 H, $^+NH_3$), 3.38 (t, J = 6.6 Hz, 2 H), 2.91 (t, J = 6.6 Hz, 2 H), 2.83 (s, 3 H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, D_2O): δ = 171.5 (C_q), 38.4 (CH_3), 34.8 (CH_2), 28.2 (CH_2) ppm.

1-(3-Hydroperoxy-3-oxopropyl)piperidin-1-ium Methanesulfonate (2c$^+$MsO$^-$): 3-(Piperidin-1-yl)propanoic acid **1c** (197 mg, 1.25 mmol) was dissolved in methanesulfonic acid (0.81 mL, 12.5 mmol). The solution was cooled to 0 °C and H_2O_2 (0.15 mL of a 85 % aq. solution, 4 equiv.) was added dropwise. Then the reaction mixture was warmed up to room temperature. After 1 h the solution was poured into ice-cold THF (20 mL) and stirred for 60 min. The formed crystalline precipitate was collected by filtration, washed with THF (10 mL) and diethyl ether (5 mL). Drying of the residue yielded **2c**$^+$MsO$^-$ as a colorless, crystalline solid (291 mg, 86 %); m.p. 134 °C (ref:[3d] m.p. 132 °C); active oxygen content: 94 % (iodometric titration). Therefore, an overall yield of 81 % of **2c**$^+$MsO$^-$ was calculated. ^{1}H NMR (400 MHz, D_2O): δ = 8.72 (br. s, 0.06 H, $^+NH_3$), 3.53–3.50 (m, 2 H, 5-H), 3.44 (t, J = 7.1 Hz, 2 H), 2.99–2.93 (m, 4 H), 2.78 (s, 3 H), 1.96–1.87 (m, 2 H), 1.83–1.63 (m, 3 H), 1.53–1.39 (m, 1 H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, D_2O): δ = 170.9 (C_q), 53.4 (CH_2), 51.4 (CH_2), 38.4 (CH_3), 25.7 (CH_2), 22.6 (CH_2), 20.8 (CH_2) ppm. IR (ATR, neat): $\tilde{\nu}$ = 3021, 2961, 2775, 2721, 1773, 1480, 1451, 1349, 1208, 1139, 1122, 1087, 1066, 1037, 979, 944, 884, 845, 782, 733 cm^{-1}.

pK_a Determination: A Metrohm Titrando system (pH ± 0.001) was applied for automated titrations. Solutions of the acids in water were prepared at a constant ionic strength of I = 0.1 with a NaCl stock solution and titrated with 0.1 M KOH. The temperature during the titration was maintained constant at (20 ± 0.1) °C with a circulating bath thermostat. The titration curve was recorded automatically and the equivalence points were determined by the control software of the titration system. For every acid, the titration was repeated at least three times, the results were averaged and gathered in Table 1.

Kinetic Measurements: Kinetic measurements were performed on commercial stopped-flow UV/Vis photometry systems (Applied Photophysics SX.20). The temperature (20.0 ± 0.2 °C) was maintained constant by using circulating bath cryostats. To prevent alkaline decomposition of the peroxide solutions, the sequential-mixing setup of the instrument was employed. In a first step, equal volumes of a KOH solution and a solution of **2**$^+$MsO$^-$ were mixed. Kinetics aiming to characterize the reactivity of zwitterions **2** were carried out by mixing approx. equimolar amounts of **2**$^+$ and KOH in the first mixing step. Kinetics aiming to characterize the reactivity of the anionic **2c**$^-$ were performed by mixing **2**$^+$ [(2–5) × 10^{-4} M] with an excess of KOH (2.5 ×10^{-2} M) in the first mixing step. After 1 s ("aging time") these solutions were mixed at a second mixer with an equal volume of a solution of the electrophile **3**-BF_4. By using a high excess of the zwitterions **2** over the electrophiles **3**, the peroxide concentrations remained almost constant during the kinetic runs, resulting in mono-exponential decays of the electrophiles' absorptions. First-order rate constants k_{obs} (s^{-1}) were obtained by least-squares fitting the time-dependent absorbances with the single-exponential function $A_t = A_0 \exp(-k_{obs}t) + C$. After converting k_{obs} to k_1 by applying equation (3), the second-order rate constants for the reactions of **2** (or **2**$^-$) with benzhydrylium ions **3b**–**e** were obtained from the slope of the linear correlation of the first-order rate constants k_1 with the nucleophile concentration.

Details of the individual kinetic measurements are given in the Supporting Information.

Computational Analysis: First, all studied species were subjected to a conformational search with the OPLS3 force field[22] as implemented in the Macromodel software package[23] applying a MCMM search. The thus obtained set of conformers was subsequently optimized with the M06-HF/6-311++G(d,p) method[17] taking aqueous solvation into account by the SMD model.[18] Thermal corrections were obtained at the same level of theory from vibrational frequencies and are unscaled. Selection of an appropriate theoretical method for the structural optimization in the Gaussian software package[16] was found to be difficult as most methods are not able to correctly represent the position of the N···H···O hydrogen bond in a way that is in accord with experimental results (the amino group has the higher pK_{aH} value than the peroxycarboxylate, therefore the hydrogen should be located closer to nitrogen). Calculations in gas-phase as well as standard DFT (and MP) methods in solution (water) localize the hydrogen atom at the oxygen site. Geometries were all optimized with the 6-311++G(d,p) basis both in gas phase and aqueous solution (SMD and IEF-PCM were tested). Of the investigated methods (HF, B3LYP, B3LYP-D3, B2PLYPD, M06-2X, M06-HF, ωb97xd, MP2, MP3) only HF and M06-HF in combination with aqueous solvation were able to correctly locate the hydrogen bond.

Details of the conformational analysis and calculated geometries are given in the Supporting Information.

Acknowledgments

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Keywords: Nucleophilicity · Kinetics · Bleaching · Peroxides · Linear-free energy relationships

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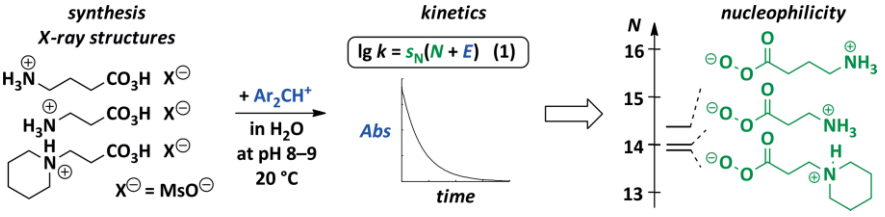
Reaction Kinetics



The kinetics of the reactions of ammonium-peroxycarboxylates with benzhydrylium ions (Ar_2CH^+) were investigated in aqueous solutions at 20 °C (pH 8–9). Application of the Patz–Mayr equation (1) furnished their nucleophilicity parameters (N, s_N). Quantum chemical calculations indicate intramolecular N–H···O hydrogen bonding in β- and γ-ammonium-substituted peroxycarboxylates, which accounts for their attenuated nucleophilicities relative to those of other peroxycarboxylates.

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