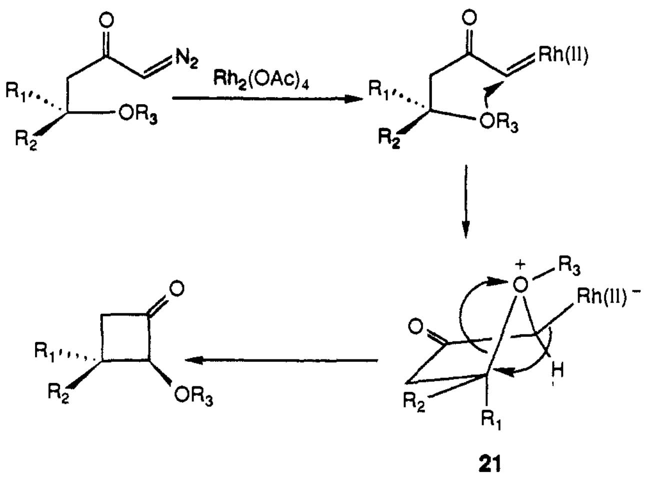
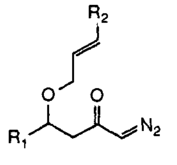
Scheme II

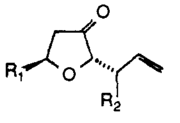


suitable candidates for the [2,3]-sigmatropic process. When **13** was treated with rhodium acetate it was found to undergo a rearrangement to yield furanones **14** and **15** (93:7) (65%). The preference for [2,3]-sigmatropic rearrangements over 1,2 migrations is additionally demonstrated by the results of reactions of **16** and **18** which provided **17** and **19**, respectively. Such rearrangements could be also extended to provide pyrans, e.g., **20**.



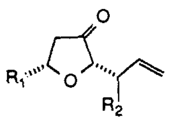
13 $R_1 = CH_3$ $R_2 = H$

16 $R_1 = H$ $R_2 = CH_3$

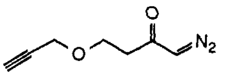


14 (60%)

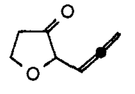
17 (63%[d])



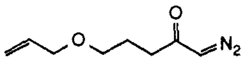
15 (5%)

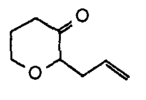


18



19 (74%)

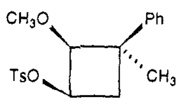




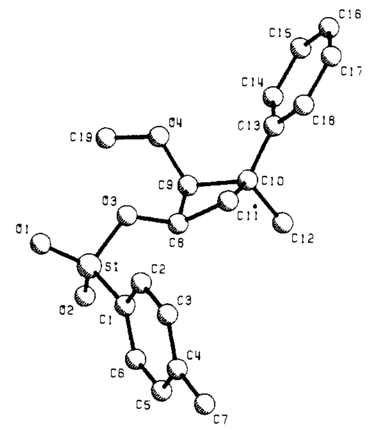
20 (61%)

Several detailed mechanisms are readily conceivable for the observed rearrangements. The most obvious, a direct C–O insertion by the carbene, can be ruled out, since it fails to account for the [2,3]-sigmatropic rearrangement products. Two other mechanisms involving metal carbenoids which react with the oxygen lone pair to form an intermediate of the type **21** must then be considered. Such an intermediate could decompose via several routes to yield the observed products: (i) loss of the metal to form an enolate, (ii) formation of a metallocycle which would then undergo a reductive elimination to regenerate the catalyst and form the carbon–carbon bond, or (iii) a direct formation of the carbon–carbon bond proceeding with inversion of configuration of the carbon–metal bond and retention of configuration of the oxonium–carbon bond. On the basis of our observation that ratios of **11** and **12** formed from **10** vary from 1:3 to 10:1 depending on the catalyst used,[8] the "free enolate" mechanism seems unlikely.

Diazoketone **10** (prepared optically pure from (*S*)-3-methoxy-3-phenylbutanoic acid) upon treatment with rhodium acetate gave cycloubutanones **11** $[\alpha]^{D}_{25}$ +62.1° (*c* 1.0, $CHCl_3$) and **12** $[\alpha]^{D}_{25}$ −33.8° (*c* 0.56, $CHCl_3$) in a ratio of 3:1 (yield 74%). The absolute configuration at the quaternary center in **11** was established by conversion to (*S*)-dimethyl-3-methyl-3-phenyl-1,4-dibutanoate.[9] The relative configuration of the methoxy group was established by X-ray crystallography of the derived tosylate **22**.



22



Cyclobutanone **11** was formed with complete retention of configuration at the quaternary center. The data currently available appear consistent with the hypothesis that the cyclobutane formation proceeds in the manner illustrated in Scheme II. The observed sigmatropic reactions could occur in a similar fashion.

The results herein described suggest that oxonium ylides should receive considerable attention in synthetic chemistry. We are continuing to explore the synthetic and mechanistic aspects of this chemistry.[10]

Acknowledgment. This work was supported by a grant from the National Science Foundation. We are grateful to Dr. Mary Jane Heeg of the Wayne State University Central Instrumentation Facility for the X-ray structure determination.

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[8] Catalyst selectivity for **11** vs. **12**: $Rh_2(OAc)_4$, 3:1; $Cu(acac)_2$, 1:6; $Rh^{I}Cl(Ph_3P)_3$, 1:10.

[9] Abbayes, H.; Dabard, R. *Tetrahedron* **1975**, *31*, 2111.

[10] This work was presented at the Third International Kyoto Conference on New Aspects of Organic Chemistry, Nov 1985; Abstr O-43, p 113.

Dioxygenyl Hexafluoroantimonate: A Useful Reagent for Preparing Cation Radical Salts in Good Yield

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Organic cation radicals have been prepared by using Brønsted acids, Lewis acids, halogens, and metal salts.[1] These methods suffer from a reaction stoichiometry that is either variable or unknown and often provide a cation radical in which the counteranion is ill-defined. Thus, only rarely can one use chemical oxidation procedures to prepare isolable cation radical salts. Although electrochemical oxidation procedures have also been developed for preparing cation radicals,[2] the utility of the method for preparing stable cation radical salts is quite limited.[3]

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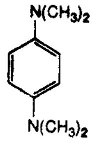
Recently, nitrosonium salts (e.g., $NO^+BF_4^-$) have been employed to prepare cation radical salts.[4] Here, the stoichiometry can be controlled, and the counteranion is both clearly defined and easy to vary. An additional feature of this oxidant is that its reduced form is a gas, thus potentially easy to remove. Even this reagent, however, has its drawbacks since oxidations are often accompanied by nitrosation and even nitration.[4b,5] Most seriously, nitric oxide appears to react with some cation radicals (vide infra).

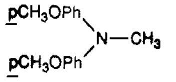
We have encountered some of these problems in attempts to prepare several cation radical salts. To circumvent them we examined dioxygenyl hexafluoroantimonate (1) as a one-electron oxidant. It shares the desirable features of NO^+ salts and has two additional advantages. First, $O_2^{\bullet+}$ is a considerably stronger oxidant than NO^+.[6] Second, dioxygen appears less reactive toward cation radicals than nitric oxide.

$O_2^{\bullet+} SbF_6^-$

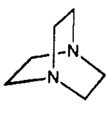
1



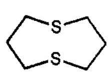
2



3



4



5

The first dioxygenyl cation salt was prepared in 1962 as the hexafluoroplatinate;[7] this discovery was followed by the preparation of several other stable salts.[8] The literature contains only two examples of successful one-electron oxidations using $O_2^{\bullet+}$ salts; hexafluorobenzene[9a] and pentafluoropyridine[9b] were converted into their stable cation radical salts. *We have found that in Freon solvents dioxygenyl hexafluoroantimonate cleanly oxidizes organic molecules to their cation radicals at low temperature.* This protocol constitutes a convenient preparation of organic cation radical salts. Described below are the oxidations of **2**–**5** and characterizations of the oxidation products.

N,N,N,N-Tetramethyl-*p*-phenylenediamine (**2**) was chosen as the first substrate for oxidation since its cation radical salts (Würster's Blue) are well characterized.[1,10] A typical oxidation follows. Inside a N_2 purged glovebox, **1** (0.17 mmol) and **2** (0.17 mmol) were each loaded into the separate chambers of a Pyrex U-tube, which were divided by a break seal. The chamber containing **1** was evacuated (10^{-5} torr) and sealed; $CHClF_2$ (2.4 mL) was transferred into the chamber containing **2**. After dissolution of **2**, the apparatus was cooled to −145 °C and then the break seal was shattered. Oxygen evolution ceased after 30 min and a deep blue solution remained. Solvent removal provided a blue solid in 97% yield (gravimetric). An EPR spectrum of the solid dissolved in CH_2Cl_2 was identical with that previously reported for the perchlorate salt of $\mathbf{2}^{\bullet+}$.[10d] The paramagnetic susceptibility of a CH_3OH solution of $\mathbf{2}^{\bullet+}SbF_6^-$ was measured by Evan's NMR shift method[11] and found to be 99% of that expected.[12]

Di-*p*-anisylmethylamine (**3**) was similarly converted to its cation radical salt at −120 °C in chlorodifluoromethane. Its −116 °C EPR spectrum in $CHClF_2$ agreed well with that obtained by electrooxidation under flow conditions in CH_3CN.[13] Solvent removal provided a green cation radical salt which was indefinitely stable at room temperature.[14] The yield of cation radical salt was determined by susceptibility measurements and found to be 89% of that expected.[12] Finally, reduction of the salt in CH_2Cl_2 with hydrazine produced **3** in 88% yield.

The preparation of 1,4-diazabicyclo[2.2.2]octane hexafluoroantimonate provides an example of a considerably less stable cation radical salt. Oxidation of **4** in $CHClF_2$ at −130 °C provided a vermillion solution of the cation radical which was stable at −130 °C for >6 h. An EPR spectrum of this solution was closely similar to that obtained by using flow techniques in CH_3CN.[15] The yield of cation radical salt as measured by the solution susceptibility was 40%.[12] Attempts to isolate $\mathbf{4}^{\bullet+}SbF_6^-$ have not yet been successful. Although solvent removal below −100 °C provided a cherry red solid, warming above this temperature caused rapid decolorization. The color of $\mathbf{4}^{\bullet+}SbF_6^-$ was similarly lost upon warming a $CHClF_2$ solution of it above −50 °C. The major product of both decompositions was the ammonium salt of **4** (68%).

A comparison between NO^+ salts and $O_2^{\bullet+}SbF_6^-$ was provided by their oxidations of 1,5-dithiacyclooctane (**5**). Musker has described the oxidation of **5** by both $NO^+PF_6^-$ and $NO^-BF_4^-$ in CH_3CN.[4a,16] We obtained similar results from the $O_2^{\bullet+}SbF_6^-$ oxidation. The reaction of **5** with $O_2^{\bullet+}SbF_6^-$ in $CHClF_2$ at −130 °C produced a lemon yellow solution similar to that from the NO^+ oxidation. An EPR spectrum recorded at −80 °C in $CHClF_2$ was indistinguishable from that reported at −10 °C in CH_3CN.[16b]

Interestingly, oxidation of **5** by $NO^+SbF_6^-$ in $CHClF_2$ or in CH_2Cl_2 produced a different result from the oxidations in CH_3CN described by Musker. In $CHClF_2$ at −130 °C, a crimson solution was formed which slowly precipitated a red solid. This same behavior was duplicated by first oxidizing **5** with $O_2^{\bullet+}SbF_6^-$ followed by degassing and introduction of NO. This latter result suggested that NO reacted with the cation radical of **5**, perhaps to form an *S*-nitroso salt.[17] Supporting evidence was provided by the oxidation of **5** by $NO^+SbF_6^-$ in CH_2Cl_2 at −80 °C. Here oxidation produced a red precipitate which did not dissolve upon warming to room temperature. Addition of CH_3CN, however, caused the red solid to rapidly dissolve, with a vigorous evolution of NO, to ultimately give a yellow solution. While all of the details of the NO^+ and the $O_2^{\bullet+}$ oxidations are not yet clear, one can at least conclude from these experiments that NO is more reactive with sulfide cation radicals than is dioxygen.[18]

Finally, we note one experimental detail regarding the stability of $O_2^{\bullet+}SbF_6^-$. The shelf life of $O_2^{\bullet+}SbF_6^-$ is somewhat limited by a slow decomposition which eventually produces the $Sb_2F_{11}^-$ salt.[19] Therefore, to prepare cation radical salts with a single

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counteranion, periodic purification by pyrolysis under a dynamic vacuum[20] is required. The purity of the salt was most conveniently monitored by iodometric titration. Typical titers using $n\text{-}\mathrm{Bu_4N^+I^-}$ in $\mathrm{CH_2Cl_2}$ were 98% of theory for freshly purified material and ~85% (based on $\mathrm{O_2^{\bullet+}SbF_6^-}$) for salt which was 6 months old.

The utility of **1** in organic cation radical chemistry is, of course, not limited to cases where the cation radical salts are isolable. The reagent may also provide important clues to the intrinsic reactivity of cation radicals which cannot be directly detected. For example, oxidations of simple trialkylamines with **1** do not give solutions of stable cation radical salts, but the results do suggest the their intermediacy.[21] The extreme oxidizing power[22] of $\mathrm{O_2^{\bullet+}}$ salts will undoubtedly prompt other applications.

Acknowledgment. We are grateful to R. W. Kreilick, S. P. Greiner, and D. L. Rowlands for their assistance in recording EPR spectra and to J. A. Kampmeier for his valuable encouragement. Support was provided by the Research Corporation and by the Camille and Henry Dreyfus Foundation for research and by the National Science Foundation for an instrumentation grant (CHE78-03089).

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(22) An approximate calculation reveals that the reduction of $\mathrm{O_2^{\bullet+}}$ is exothermic by ca. 5.3 V vs. SCE! This was calculated by using an ionization potential for $\mathrm{O_2}$ of 12.08 eV[6b] and Miller's empirical equation (Miller, L. L.; Nordblom, G. D.; Mayeda, E. A. *J. Org. Chem.* **1972**, *37*, 916). The Ag/$\mathrm{AgNO_3/CH_3CN}$ electrode potential so obtained was converted to the SCE electrode potential by adding 0.34 V.

Observation of the Visible Absorption Spectrum of Cobalt(II)-Carbonic Anhydrase III during Catalytic Hydration of CO_2

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Received March 31, 1986

We have prepared Co(II)-substituted carbonic anhydrase III from bovine skeletal muscle and observed its visible absorption spectrum during catalysis of $\mathrm{CO_2}$ hydration using a stopped-flow spectrophotometer. The optical spectrum of the homologous Co(II)-substituted carbonic anhydrase from red cells (isozyme II) shows a variability depending on pH and the ligands of the metal and is a sensitive measure of the status of the active center.[1] The spectrum of the cobalt-bound hydroxide form has distinctive features with maxima near 620 and 640 nm; for isozyme II the spectra of the cobalt-bound water form and the $\mathrm{HCO_3^-}$ complex are similar and rather featureless.[1] The spectrum of the cobalt-bound water form of carbonic anhydrase III has not yet been observed since this isozyme is believed to have a pK_a for the metal-bound water below 5,[2–4] a region in which the protein denatures. We report here changes in the visible spectrum of Co(II)–carbonic anhydrase III after mixing with $\mathrm{CO_2}$ which are consistent with the accumulation of the cobalt-bound water form of this isozyme during the catalysis. This is the first observation of a spectral property of the active center of carbonic anhydrase during the catalytic progress curve for $\mathrm{CO_2}$ hydration and is compatible with the hypothesis of a rate-contributing proton transfer in step 4 of eq 2. This hypothesis is also based on solvent

$$>\mathrm{ZnOH^-} + \mathrm{CO_2} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} >\mathrm{Zn(OH^-)CO_2} \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} >\mathrm{ZnHCO_3^-} \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} >\mathrm{ZnOH_2} + \mathrm{HCO_3^-} \tag{1}$$

$$>\mathrm{ZnOH_2} \underset{k_{-4}}{\overset{k_4}{\rightleftharpoons}} >\mathrm{ZnOH^-} + \mathrm{H^+} \tag{2}$$

hydrogen isotope effects and inhibition of the catalysis[5,6] and is analogous to an hypothesis for the catalytic mechanism of carbonic anhydrase II which is believed to proceed with a maximum velocity limited by a proton-transfer step.[1,7] In its most fundamental representation, the rate-contributing proton transfer is in step 4 of eq 2, the step in which the zinc-bound hydroxide at the active site is regenerated following a hydration sequence.

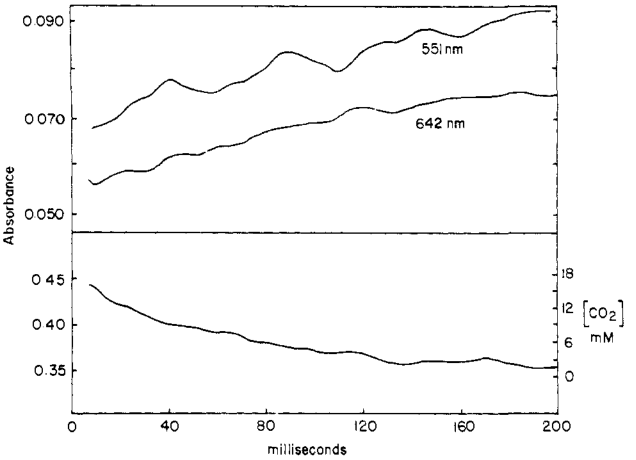

Figure 1. (Top) Absorbance change at 642 and 551 nm as a function of time after mixing Co(II)-substituted bovine carbonic anhydrase III and $\mathrm{CO_2}$. Initial pH after mixing was 7.5 with the concentration of $\mathrm{CO_2}$ and Co(II)–carbonic anhydrase at 0.017 and 1.4×10^{-4} M, respectively. (The estimated contamination by zinc-containing carbonic anhydrase III was 1.5×10^{-5} M.) Hepes sulfate was present at 100 mM with $\mathrm{Na_2SO_4}$ at 15 mM. The path length of our optical cell was 2 cm. (Bottom) Absorbance change at 559 nm as a function of time after mixing of solutions identical with those described above except the enzyme solution contained phenol red. The concentration of this indicator after mixing was 7.5×10^{-6} M. The ordinate also shows the concentration of $\mathrm{CO_2}$ calculated from the known initial value and rate of change of absorbance of indicator (see ref 11).

Carbonic anhydrase III was obtained from bovine flank steak by gel filtration and anion-exchange chromatography.[8] Apoenzyme was prepared by addition of the chelator 2-carboxy-1,10-phenanthroline to a solution of enzyme followed by dialysis against excess $\mathrm{CoCl_2}$ as described by Engberg and Lindskog.[4] The total concentration of carbonic anhydrase III (both the zinc and cobalt forms) was estimated at 280 nm by using $\epsilon = 6.4 \times 10^4$ $\mathrm{M^{-1}\,cm^{-1}}$ and the concentration of cobalt(II)-substituted carbonic anhydrase III was estimated at 640 nm and pH 7.0 by using $\epsilon = 270$ $\mathrm{M^{-1}\,cm^{-1}}$.[4] By this comparison our sample of isozyme III was determined to be 90–93% in the cobalt form. Saturated solutions of $\mathrm{CO_2}$ (33.8 mM at 25 °C)[9] were prepared by bubbling $\mathrm{CO_2}$ gas into water. The progress curve and initial rate measurements were carried out on a Durrum-Gibson (D-110) stopped-flow spectrophotometer equipped with a Nicolet Explorer (Model 206) digital oscilloscope interfaced with an IBM XT

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