s), ca. 2.35–2.05 (2 H, m), 1.91 (3 H, s), ca. 1.9–1.4 (2 H, m), 1.37 (3 H, s); mass spectrum, m/z (relative intensity) 339 (M^+, 0.4), 308 (1), 184 (12), 167 (28), 91 (28), 72 (100), 43 (53). Anal. ($C_{16}H_{21}NO_5S$) C, H, N, S.

3-(1-Hydroxyethylidene)-6-methoxy-1-[(4-methylphenyl)sulfonyl]-2-piperidinone (6) and 3,4-Dihydro-2-methoxy-6-methyl-*N*-[(4-methylphenyl)sulfonyl]-2*H*-pyran-5-carboxamide (4c). Similar treatment of 740 mg (3.75 mmol) of TsNCO and 400 mg (3.12 mmol) of **2c** in 10 mL of THF, as described for **3a**, produced a brown foamy residue that was column chromatographed on 60 g of silica gel and eluted with CH_2Cl_2–MeOH (99.5:0.5) to yield 180 mg (0.55 mmol, 18%) of **6** as a colorless oil, which crystallized from Et_2O–hexane as white crystals, followed by 440 mg (1.35 mmol, 43%) of **4c** as a colorless oil. Compound **6**: mp 93–94 °C; IR (CH_2Cl_2) 3050–2450, 2940, 1625, 1600, 1350, 1165, 1085 cm^{-1}; IR (film) 3300–2300, 2950, 1600, 1405, 1350, 1260, 1160, 1080, 880, 800 cm^{-1}; NMR (200 MHz, $CDCl_3$) δ 13.80 (1 H, s, exchanges with D_2O), 7.90 (2 H, d, J = 8.4 Hz), 7.30 (2 H, d, J = 8.2 Hz), 5.70 (1 H, t, J = 2.9 Hz), 3.54 (3 H, s), 2.57 (1 H, apparent td, J = ca. 14, 5 Hz), 2.43 (3 H, s), 2.25 (2 H, apparent dd with further splitting, J = ca. 14, 5 Hz), 1.95 (3 H, s), 1.73 (1 H, apparent tdd, J = ca. 14, 5, 2.5 Hz); mass spectrum, m/z (relative intensity) 325 (M^+, 12), 293 (6), 265 (6), 261 (5), 218 (12), 155 (28), 153 (30), 138 (17), 128 (20), 111 (20), 108 (26), 96 (16), 91 (100), 71 (82), 65 (32), 58 (69), 43 (92). Anal. ($C_{15}H_{19}NO_5S$) C, H, N, S. Compound **4c**: IR (CH_2Cl_2) 3400, 2940, 1690, 1605, 1400, 1165, 1005 cm^{-1}; NMR (79.5 MHz, Me_2SO-d_6) δ 11.26 (1 H, br s, exchanges with D_2O), 7.80 (2 H, d, J = 8.3 Hz), 7.38 (2 H, d, J = 8.1 Hz), 4.97 (1 H, t, J = ca. 3.0 Hz), 3.33 (3 H, s), 2.36 (3 H, s), 2.3–2.0 (2 H, m), 1.88 (3 H, s), 1.8–1.5 (2 H, m); mass spectrum, m/z (relative intensity) 325 (M^+, 4), 293 (5), 170 (13), 153 (58), 111 (28), 91 (43), 58 (100), 43 (68). Anal. ($C_{15}H_{19}NO_5S$) C, H, N, S.

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Registry No. **1a**, 37642-94-7; **1b**, 110-87-2; **2a**, 4454-05-1; **2b**, 64331-95-9; **2c**, 28194-35-6; **3a**, 87937-93-7; **3b**, 87937-94-8; **4a**, 87937-95-9; **4b**, 87937-96-0; **4c**, 87937-97-1; **6**, 87937-98-2; TsNCO, 4083-64-1.

Ascorbic Acid. 2. Nucleophilic Reactivity of Ascorbate Anion toward Acyl Carbon and Phosphorus

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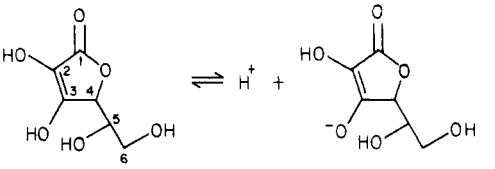
There has been great attention to the nutritional value of ascorbic acid (vitamin C).[1] However, biochemists have not been able to find clear evidence of essential roles. The commonly cited role of ascorbate in prolyl hydroxylase may be due to the need for a reducing agent in order to keep the essential iron atom in the Fe^{II} state, not due to direct involvement in the mechanism of action of this enzyme.[1-3] Ascorbic acid (**1**) and the anion **2** are interesting, polyfunctional species.[4] Ultimately, we should be able to understand the molecular basis of the function of ascorbate as we now understand thiamin, niacin, pyridoxal, and other vitamins.

Table I. Data for Reaction of 2,4-Dinitrophenyl Acetate by Several Nucleophiles at 30 °C

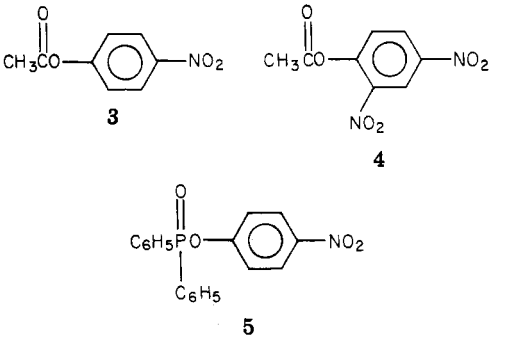
nucleophile[a]	pH	10^2k_2,[b] min^{-1} M^{-1}
$ClCH_2CO_2^-$	4.2	0.251
HCO_2^-	4.5	6.17
$CH_3CO_2^-$	5. 7	4.63
ascorbic acid anion	5.3	70

[a] In all cases a 10:1 ratio of anion to acid provided buffering. [b] Based upon three runs for the carboxylates and four runs for ascorbate.



1 2

Ascorbic acid (**1**), pK_a 4.2, will be present predominantly as the anion **2** at pH 7. The anion is stabilized by delocalization of charge over both the 1- and 3-oxygens.[5,6] We anticipated that **2** might be unusually reactive since both the 2-OH and the side chain at C-4 could potentially solvate certain transition states. For example, on the basis of its structure, the anion might be effective as an acyl transfer agent. Therefore, we have examined the nucleophilic reactivity of ascorbate monoanion **2** toward acyl carbon and acyl phosphorus centers **3–5**.



3 4 5

Experimental Section

p-Nitrophenyl acetate (**3**) was recrystallized from hexanes; mp 76.8 °C. 2,4-Dinitrophenyl acetate (**4**) was prepared by adding 1 equiv of 2,6-lutidine to 2,4-dinitrophenol, crushing the orange solid to a powder, and slowly adding 1 equiv of acetyl chloride. After cooling, the yellow-white solid was brought to a melt and allowed to recool. The solid was then crushed and removed with water, filtered, washed with 0.1 M bicarbonate, and recrystallized in acetone–heptane; mp 71–71.5 °C. *p*-Nitrophenyl diphenylphosphinate (**5**) was prepared by our method.[7]

All reactions were followed on a Cary 16 spectrophotometer with the cell compartment temperature maintained at 30 °C.

(1) C. G. King and J. J. Burns, Eds., *Ann. N.Y. Acad. Sci.*, **258** (1975).
(2) G. J. Cardinale and S. Udenfriend, *Adv. Enzymol.*, **41**, 245 (1974).
(3) R. Myllylä, E. Kuutti-Savolainen, and K. I. Kivirikko, *Biochem. Biophys. Res. Commun.* **83**, 441 (1978).
(4) B. M. Tolbert, R. Myllylä, E. Kuutti-Savolanien, and K. Kivirikko, *Ann. N.Y. Acad. Sci.*, **258**, 48 (1975).
(5) J. Hvoslef, *Acta Crystallogr. B*, **25**, 2214 (1969).
(6) C. D. Hurd, *J. Chem. Ed.*, **47**, 481 (1970).
(7) G. H. Hurst and P. Haake, *J. Am. Chem. Soc.*, 88, 2544 (1966).

0022-3263/84/1949-0197$01.50/0

Table II. Rate Constants for Reactions of Oxyanion Nucleophiles with *p*-Nitrophenyl Acetate (PNPA), 2,4-Dinitrophenyl Acetate (DNPA), and *p*-Nitrophenyl Diphenylphosphinate (PNPDPP) at 25 or 30 °C, Ionic Strength 1.0 M or Unadjusted[a]

anion	pK_a[b]	k, M^{-1} min^{-1} PNPA	DNPA	PNPDPP
OH^-	15.75	5.70×10^2	3.22×10^4	
CH_3O^-	15.5	2.9×10^4	1.92×10^5	
$HC{\equiv}CCH_2O^-$	13.55	1.08×10^4	6.8×10^4	
$F_3CCH_2O^-$	12.37	3.85×10^3	2.4×10^4	
p-$CH_3C_6H_4O^-$	10.07	1.13×10^2	1.24×10^3	20.4
$C_6H_5O^-$	9.86	5.8×10^1	7.3×10^2	50.6
$ClC_6H_4O^-$	9.28	4.1×10^1	5.7×10^2	11.1
$(CH_3)_3CCO_2^-$	5.05		1.07×10^{-1}	
$CH_3CO_2^-$	4.76	3.8×10^{-4}	3.4×10^{-2}, 4.6×10^{-2}	6.45×10^{-3}
ascorbate anion	4.17	3.6×10^{-2}	7.0×10^{-1}	2.81×10^{-1}
HCO_2^-	3.77		6.2×10^{-2}	
$CH_3OCH_2CH_2O^-$	3.43		6.8×10^{-3}	
$ClCH_2CO_2^-$	2.86		2.5×10^{-3}	
HPO_4^{2-}	6.9	7.4×10^{-3}		
$HAsO_4^{2-}$	6.8	4.1×10^{-2}		
$C_6H_5CO_2^-$	4.20			1.3×10^{-3}
o-$CH_3C_6H_4O^-$	10.2			7.5×10^{-2}

[a] The data are from our work and from W. P. Jencks and M. Gilchrist, *J. Am. Chem. Soc.*, **90**, 2622 (1968). [b] pK_a of the conjugate acid of the anion.

Wavelengths were set to follow product formation: 355 nm for 2,4-dinitrophenol, 320 nm for *p*-nitrophenol, and 410 nm for *p*-nitrophenolate anion. Most reaction solutions were buffered by having neutral species present along with the nucleophilic anion. Two sets of runs employed pivalate buffer at pH 6.0 ± 0.02, which was useful because we showed pivalate anion to be unreactive, presumably due to steric hindrance.

All reactions were followed for at least 1 half-life. Pseudo-first-order rate constants and infinity points were calculated from large numbers of points by using a nonlinear estimation program based upon Taylor's expansion.[8] Second-order rate constants were calculated from the slopes of plots of the first-order rate constants vs. anion concentration. Our nonlinear estimation program has been found to be a reliable and accurate way to avoid the problems of a drifting infinity point, frequently observed in slow reactions possibly due to oxidation of the phenolic product.[8]

Results and Discussion

We measured rate constants for the reaction of ascorbate with *p*-nitrophenyl acetate at pH 5.2, 30.0 °C, with [ascorbate] = 0.11–0.55 M. It was not necessary to study other nucleophiles because of the available wealth of data.[9] A plot of k_{obsd} vs. [ascorbate anion] gave an intercept near 0 and a slope of 3.6×10^{-2} M^{-1} m^{-1}. Table I contains data for several oxyanions reacting with the more reactive acyl carbon substrate 2,4-dinitrophenyl acetate (**4**). The second-order rate constants are obtained from plots of k_{obsd} vs. [nucleophile] in order to have data to compare with ascorbate. The intercepts are >0 due to rate terms involving water and hydroxide,[9] which are held constant in these buffered solutions. Data for other oxyanion nucleophiles are in the literature and are tabulated in Table II.

Data for reaction of nucleophiles with *p*-nitrophenyl diphenylphosphinate (**5**) were obtained as for **3** and **4**. Plots of k_{obsd} vs. concentration gave the k_2 values in Table II. We showed that pivalate ion reacted very slowly with **5**. Therefore, in some cases, we used pivalate buffers in order to hold the pH constant but have a nonreactive buffer anion. The reproducibility and accuracy of these rate constants appear to be more than adequate for the log k vs. pK_a comparison.

We correlated our data for **3** and **4** plus data from the literature (Table II) according to the Brønsted equation, $\log k = \beta(pK_a) +$ constant. Rates of reaction at acyl carbon and phosphorus are well-known to correlate with basicity.[10] In order to avoid problems due to different kinds of nucleophiles,[11] we used only data for oxy anions; slopes of 0.93, 0.80, and 0.70 were found for **3**, **4**, and **5**, respectively. We suspect that these oxyanions (Table II) react as nucleophiles with **5** because of the high affinity of phosphorus centers for oxygen nucleophiles probably due to the high bond energy for P–O bonds. In support of this, we found a very low rate of reaction by the *o*-cresolate anion as expected due to the steric hindrance in nucleophilic attack. Such steric hindrance does not inhibit general-base catalysis so strongly.[12]

The Brønsted correlations demonstrate that **2** reacts with **4** about 40 times faster than expected from its pK_a and it reacts with **3** and **5** nearly 300 times faster than expected from the pK_a. The 2-OH function in **2** is acidic (pK_a = 11) and probably is the source of this rate acceleration. Because ascorbic acid has a much lower pK_a than *p*-nitrophenol, it seems likely that the rate-determining step in reactions with **3** and **5** will be the breakdown of the intermediate. This problem has been discussed in an earlier paper.[13] The most likely source of the rate acceleration is intramolecular acid catalysis by the 2-OH in the departure of the leaving group. Of course, it also is possible for ascorbate anion to be a bifunctional reagent in the formation of the tetrahedral intermediate from **3** or the pentaccordinate intermediate from **5**.

We have been able to synthesize the 2-diphenylphosphinyl ester of **1**.[14] It shows a hydrogen bond between the 3-OH and the P=O oxygen by crystallographic analysis.[15] Although **2** should react at the 3-oxygen, this crystal structure demonstrates that it would be possible for the adjacent OH group to directly catalyze the breakdown of

(8) P. C. Turley, Ph.D. Thesis, UCLA, 1966.
(9) (a) V. Gold, D. G. Oakenfull, T. Riley, *J. Chem. Soc. B*, 515 (1968); (b) W. P. Jencks and J. Carriulo, *J. Am. Chem. Soc.*, **82**, 1778 (1960); (c) W. P. Jencks and M. Gilchrist, *ibid.*, **90**, 2622 (1968).
(10) (a) J. O. Edwards, *J. Am. Chem. Soc.*, **76**, 1540 (1954); (b) J. O. Edwards and R. G. Pearson, *ibid.*, **84**, 16 (1962).
(11) A. Williams and R. A. Naylor, *J. Chem. Soc. B*, 1971 (1967).
(12) F. Covitz and F. H. Westheimer, *J. Am. Chem. Soc.*, **85**, 1773 (1963).
(13) R. D. Cook, C. E. Diebert, W. Schwarz, P. C. Turley, and P. Haake, *J. Am. Chem. Soc.*, **95**, 8088 (1973).
(14) K. Kessler and P. Haake, research in progress.
(15) Structure by J. Springer and K. Hoogsteen, Merch & Co. Research Laboratories.

the intermediate.[16] Clearly, ascorbate is an unusually effective nucleophile despite being an oxyanion with a rather low basicity. Our results raise the question of the involvement of ascorbate anion in biological acyl-transfer reactions.

Acknowledgment. This research was supported by Wesleyan University. NMR spectra, essential to the research, were taken on an instrument purchased with support from The Dreyfus Foundation, The National Science Foundation, and Wesleyan University.

Registry No. Ascorbate anion, 299-36-5; *p*-nitrophenyl acetate, 830-03-5; 2,4-dinitrophenyl acetate, 4232-27-3; *p*-nitrophenyl diphenylphosphinate, 10259-20-8.

(16) See also the related structure of a 3-ester; J. Jernow, J. Blount, E. Oliveto, A. Perrotta, P. Rosen, and V. Toome, *Tetrahedron*, **35**, 1483 (1979). Unfortunately the 2-OH hydrogen is not shown but the structure suggests hydrogen bonding between the 2-OH and the P=O groups.

Molybdenum-Catalyzed Oxidation of Allylic Alcohols Using *t*-BuOOH. Regioselective Cleavages of the Double Bond and the Adjacent Single Bond with a Hydroxyl Group

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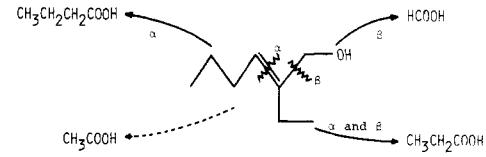
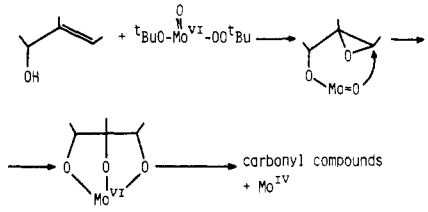
There have been many procedures for oxidative cleavage of olefinic double bonds to produce carbonyl compounds,[1] e.g.: (a) ozonolysis;[2] (b) oxo–metal reagents, such as permanganate[3,4] and ruthenium tetraoxide;[5] (c) for certain nucleophilic olefins, the O_2–copper system[6] and singlet molecular oxygen.[7] The transition metal–alkyl peroxide systems have attracted much interest because of the useful reagents for selective oxidations.[8] In the metal-catalyzed epoxidation of olefins, the hydroxyl group at the allylic position accelerates the regio-, stereo-, and enantioselectivity.[8-10] However, there are few reports concerning the olefinic double bond cleavage reaction using these transition metal–alkyl peroxide systems. Recently, we have found that the double bond of silyl enol ethers undergoes oxidative cleavage with the $MoO_2(acac)_2$–*t*-BuOOH system.[11] Here, we show that molybdenum complexes can be used to catalyze the oxidative cleavage of olefinic double bonds by use of excess *t*-BuOOH and that the allylic hydroxyl group exerts the directing effect for the regioselectivity. Molybdenum compounds appear specific in the present cleavage reaction.[12]

Scheme I. Oxidative Cleavage of 2-Ethyl-2-hexen-1-ol



Scheme II. Possible Mechanism of the Cleavage Reaction



In the molybdenum-catalyzed oxidation of allylic alcohol, the effects of metal valency and ligands on the catalytic activity were examined. These results are shown in Table I. Profound differences in both catalytic activity and the product selectivity were not observed among the homogeneous molybdenum complexes; 1-octen-3-ol gave hexanoic acid of two less carbons as a major product accompanying a small amount of valeric acid from a loss of three carbons. The heterogeneous MoO_3 catalyst showed low activity (run 4). Probably it takes a long time for MoO_3 to dissolve in the reaction medium. $MoO_2(acac)_2$ complex is used as a representative catalyst because of its availability and facility in handling as well as activity.

The reaction of 2-ethyl-2-hexen-1-ol gave butyric acid and propionic acid as major products (Scheme I). The cleavage at the α-position leads to the formation of butyric acid, and both α and β cleavages give propionic acid. Formic acid is derived from the β cleavage. A small amount of acetic acid was also observed. It is notable that the cleavage occurs selectively at the two positions of the double bond and adjacent single bond with the hydroxyl group in the allylic alcohol oxidation. The results of allylic alcohol and isolated olefin oxidations using the $MoO_2(acac)_2$–*t*-BuOOH system are summarized in Table II. 2-Octen-1-ol (internal olefin) gave hexanoic acid formed from the cleavage of the double bond. The regioisomers of 1-phenyl-2-propen-1-ol and cinnamyl alcohol produced the same product, benzoic acid, in good yields. Acyclic and aromatic allylic alcohols showed high reactivity for the present reaction, whereas cyclic allylic alcohols afforded dicarboxylic acids in poor yields. In the case of isolated olefins without hydroxyl groups, aromatic olefins gave the double bond cleavage products in moderate yields. Aliphatic olefins with allylic hydrogens showed low reactivity for the cleavage reaction, and the lower carboxylic acids were formed as overoxidation products.[13] It is clear that the allylic hydroxyl group can accelerate the molybde-

(1) Sheldon, R. A.; Kochi, J. K. "Metal-Catalyzed Oxidations of Organic Compounds"; Academic Press: New York, 1981.
(2) Bailey, P. S. "Ozonation in Organic Chemistry"; Academic Press: New York, 1978; Vol. 1.
(3) Permanganate oxidation without phase-transfer catalysts. (a) Lemieux, R. U.; Ludoloff, E. *Can. J. Chem.* **1955**, *33*, 1701. (b) Sharpless, K. B.; Lauer, R. F.; Repic, O.; Teranishi, A. Y.; Williams, D. R. *J. Am. Chem. Soc.* **1971**, *93*, 3303.
(4) Permanganate oxidation with phase transfer catalysts. (a) Starks, C. M. *J. Am. Chem. Soc.* **1971**, *93*, 195. (b) Sam, D. J.; Simmons, H. E. *Ibid.* **1972**, *94*, 4024. (c) Krapcho, A. P.; Larson, J. R.; Eldridge, J. M. *J. Org. Chem.* **1977**, *42*, 3749. (d) Lee, D. G.; Chang, V. S. *Ibid.* **1978**, *43*, 1532.
(5) (a) Wolfe, S.; Hasan, S. K.; Campbell, J. R. *J. Chem. Soc., Chem. Commun.* **1970**, 1420. (b) Ayres, D. C.; Hassan, A. A. M. *Ibid.* **1972**, 428.
(6) Kaneda, K.; Itoh, T.; Kii, N.; Jitsukawa, K.; Teranishi, S. *J. Mol. Catal.* **1982**, *15*, 349 and references cited therein.
(7) Wasserman, H. H.; Murray, R. W., Eds. "Singlet Oxygen"; Academic Press: New York, 1979.
(8) Sharpless, K. B.; Verhoeven, T. R. *Aldrichimica Acta* **1979**, *12*, 63 and references cited therein.
(9) Itoh, T.; Jitsukawa, K.; Kaneda, K.; Teranishi, S. *J. Am. Chem. Soc.* **1979**, *101*, 159.
(10) (a) Katsuki, T.; Sharpless, K. B.; *J. Am. Chem. Soc.* **1980**, *102*, 5974. (b) Martin, V. S.; Woodard, S. S.; Katsuki, T.; Yamada, Y.; Ikeda, M.; Sharpless, K. B. *Ibid.* **1981**, *103*, 6237.
(11) Kaneda, K.; Kii, N.; Jitsukawa, K.; Teranishi, S. *Tetrahedron Lett.* **1981**, *22*, 2595.
(12) By use of the epoxidizing catalyst $VO(acac)_2$ in place of $MoO_2(acac)_2$, a small amount of cleavage products was observed, and an epoxy alcohol was the major product.
(13) This phenomenon was reported on the potassium permanganate oxidation of terminal olefins (see ref 4c).

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