Ascorbic Acid. 2. Structural Determination and Synthesis of 2- and 3-Acyl Derivatives of 5,6-*O*-Isopropylidene-L-ascorbic Acid[1]

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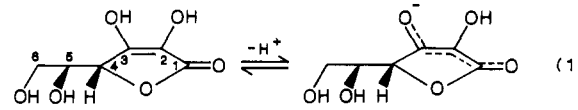
The development of methods for the synthesis and spectroscopic identification of 2-O or 3-O carbon and phosphorus derivatives of 5,6-*O*-isopropylidene-L-ascorbic acid (IAA) is reported. Noncrystallographic structural identification has been established by pK_a determinations based upon pH-dependent UV spectra and by ^{13}C NMR spectra of phosphorus esters which show phosphorus couplings to C1, C2, and C3 for the O2 esters and couplings to C2, C3, and C4 for O3 esters. UV spectra of O2 and O3 esters both demonstrate red shifts of near 26 nm upon ionization. The O2 esters absorb less intensely than their anions, but the reverse is true for O3 esters. Infrared spectra are particularly useful for structural assignments: O3 esters have bands for carbonyl stretching near 1784 cm^{-1} and olefinic stretching at 1700–1710 cm^{-1}; O2 esters have corresponding bands near 1778 cm^{-1} and 1680–1690 cm^{-1}, respectively. In compounds with a 3-*O*-acyl group, the carbonyl stretch is more intense than the olefinic stretch but the reverse is true in compounds with a 3-OH group. The ^1H NMR spectra of H4, H5, H6, and H6′ indicate first-order ABCD coupling. A value of near 1 Hz has been found for the long-range J_{P-H4} in the phosphorus esters. The monoanion of IAA, which is generated in situ by reacting 1 equiv of IAA with triethylamine, reacts in aprotic solvents to produce predominantly O3 esters. Reactions in aprotic solvents with neutral IAA appear to give 2-esters, which can be prepared nearly quantitatively when 6–10 equiv of methanol are present.

The structure and function of ascorbic acid (eq 1) has been addressed in several recent publications.[1-9] A particular problem has been the selective preparation of derivatives and the proof of their structure.[10-29] The ionization in eq 1 has led to the frequent prediction, based on the expectation that the anion will react, that reaction



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with an acylating agent will give the 3-acyl derivative, but later work has demonstrated in some cases that the isolated product was the 2-acyl derivative.[5,6,11-29] Both the 2-OH and 3-OH are enolic and might be expected to be quite reactive. Incisive spectroscopic evidence for distinguishing 2-O- and 3-O-substituted compounds has not been available. In this paper, we describe the use of acidity constants, ultraviolet spectra, ^{13}C, ^1H, and ^{31}P NMR spectra, and infrared spectra to distinguish the point of substitution in a series of carbon and phosphorus esters (**2–15**) of isopropylideneascorbic acid (**1**) (Chart I). We have utilized compound **15** as a 3-ester for which there is crystallographic proof of structure.[23]

Experimental Section

Organic analytical reagent-grade solvents were distilled from BaO under nitrogen and stored over molecular sieves. Deuteriated solvents were used without further treatment and stored under nitrogen atmosphere. Aqueous solutions were prepared with deionized water.

Nuclear magnetic resonance spectra were recorded with Varian XL-200 and XL-400 spectrometers. All frequencies were taken from a digital output printer. Unless noted otherwise, all chemical shifts were referenced to internal tetramethylsilane. Infrared spectra were recorded with a Perkin-Elmer 1500 Fourier transform infrared spectrometer using a 0.1-mm sealed NaCl cell and protonated or deuteriated chloroform as the solvent. Ultraviolet spectra were recorded with a Hewlett-Packard 8451A diode array spectrophotometer.

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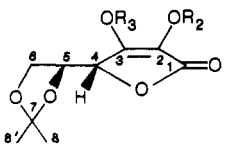
Chart I



	R_2	R_3
1	H	H
2	H	$(C_6H_5)_2P(O)$
3	H	$C(CH_3)_2CH(CH_3)C(CH_3)_2P(O)$
4	H	$(C_6H_5O)_2P(O)$
5	H	$CH_3C(O)$
6	H	$(C_6H_5)_1C(O)$
7	$(C_6H_5)_2P(O)$	H
8	$C(CH_3)_2CH(CH_3)C(CH_3)_2P(O)$	H
9	$(C_6H_5O)_2P(O)$	H
10	$CH_3C(O)$	H
11	$(C_6H_5)_1C(O)$	H
12	$CH_3C(O)$	$CH_3C(O)$
13	$(C_6H_5)C(O)$	$(C_6H_5)C(O)$
14	p-$NO_2C_6H_4C(O)$	p-$NO_2C_6H_4C(O)$
15	H	$(CH_2CH_2OCH_2CH_2N)_2P(O)$

Determination of Acidity Constants. Buffered solutions were 0.05 M phosphate and pH's were determined with a Radiometer pH Meter 26 fitted with a Beckman combination electrode 39505. Samples of 1 to 2 mL of fresh buffer at 25 °C were placed in cuvettes and reference spectra were recorded. Using microliter syringes, an aliquot of stock solution of a compound (ca. 0.015 M in acetonitrile or methanol) was injected into the reference buffer sample to yield concentrations between 10^{-4} and 10^{-5} M. The resultant solution was rapidly mixed and the absorbance spectrum immediately recorded from 190 to 360 nm. The experimental absorption readings, to which we applied eq 2 and 3, were taken at the wavelength of maximum extinction coefficient of the ionized compound. This wavelength varied from 260 to 268 nm depending upon the compound. In the case of aryl esters, the underlying absorption from low wavelength bands was subtracted by drawing a base-line absorption from minimum to minimum in the spectrum; e.g., see Figure 3.

The equilibrium equation representing ionization is $K = [H^+][B]/[A]$ where K is the equilibrium constant, A is the neutral acid, B is the monoanion, and H^+ is the negative antilog of the pH of the buffer. In our determinations of K, we were alert for problems due to a second dissociation or instability at the buffer basicity required to produce B. The experimental optical density (a) as a function of the buffer pH is equal to the sum of optical densities of acid and monoanion, $a = a_A + a_B$. Application of Beer's law yields eq 2, which can be rearranged to give eq 3.[31] Equation 3 was fitted to the data with a weighted linear least-squares program from which a_B and K are extracted; this method is useful because a_B need not be determined experimentally and is determined from the intercept; a second ionization or base-induced decomposition of substrate can make experimental determination of a_B uncertain.

$$K = [H^+]((a - a_A)/(a_B - a)) \quad (2)$$

$$[H^+](a - a_A) = -K(a) + K(a_B) \quad (3)$$

Solvents and amines were distilled from BaO under nitrogen. Analytical grade solvents were further dried over molecular sieves. Diphenylphosphinyl chloride, $(C_6H_5)_2P(O)Cl$ (DPC), was prepared by bubbling O_2 through a neat solution of freshly distilled diphenylchlorophosphine. The product distilled as a colorless liquid at 140 °C/0.1 mmHg (lit.[32] 135–136 °C/0.07 mmHg). Diphenyl *phosphorochloridate*, $(C_6H_5O)_2P(O)Cl$ (DPP), was purchased from Aldrich Chemical Co. and was purified by distillation, 125–130 °C/0.25 mmHg. 2,2,3,4,4-Pentamethyltrimethylenephosphinyl chloride (PTPC) was prepared according to a reported method[33] and recrystallized from petroleum ether, mp 70–72 °C. 5,6-*O*-Isopropylidene-L-ascorbic acid (1) was prepared according to the method of Ward and Tolbert[34] by using 2,2-dimethoxypropane, 93% yield. Carbon and hydrogen analyses were done by Mic-Anal Organic Microanalysis, Tucson, AZ.

3-*O*-(Diphenylphosphinyl)-5,6-*O*-isopropylidene-L-ascorbic Acid (2). Under nitrogen, freshly distilled triethylamine (2.6 mmol) was added dropwise from a syringe to 1 equiv of 5,6-*O*-isopropylidene-L-ascorbic acid in 20 mL of vigorously stirred dry acetone at 22 °C. Addition of the amine solubilized the acid and within moments caused the precipitation of the amine salt of the acid. Diphenylphosphinyl chloride (1 equiv) in 5 mL of acetone was added in one portion to this mixture by passing it through a connecting L-shaped tube adjoining both flasks. The mixing of the two solutions was continued vigorously by moving the mixture between the two flasks for a period of 2 min. The solution first became clear; then amine hydrochloride precipitated. The mixture was filtered and the filtrate concentrated under reduced pressure, yielding eventually a white powder which, after drying for 24 h at room temperature, was washed in deionized water to remove remaining hydrochloride salt; mp 108–110 °C.

Anal. Calcd for $C_{21}H_{21}O_7P$: C, 60.6; H, 5.08. Found: C, 60.4; H, 5.06.

2-*O*-(Diphenylphosphinyl)-5,6-*O*-isopropylidene-L-ascorbic Acid (7). A mixture of 2.3 mmol of 5,6-*O*-isopropylidene-L-ascorbic acid and 1.0 equiv of 2,6-dimethylpyridine was prepared in 20 mL of acetone at 22 °C under nitrogen. Diphenylphosphinyl chloride (1 equiv) in 5 mL of acetone was added dropwise and the reaction stirred for 2 h, at which time 6 equiv of methanol were added. After stirring overnight, solvent was removed under vacuum. The oily product was dissolved in chloroform and amine hydrochloride extracted with water. The organic phase was then concentrated to a foam under reduced pressure and converted to a powder by taking it up in methylene chloride and precipitating with hexane. Crystals were obtained from acetone, acetone–ethanol, and acetone–ether solvent mixtures; mp 80–81 °C.

Anal. Calcd for $C_{21}H_{21}O_7P$: C, 60.6; H, 5.08. Found: C, 61.3; H, 5.38.

3-*O*-Benzoyl-5,6-*O*-isopropylidene-L-ascorbic Acid (6). A mixture of 5,6-*O*-isopropylidene-L-ascorbic acid (1 equiv) and triethylamine (1 equiv) was prepared in 7 mL of dry dimethylacetamide at 22 °C under nitrogen. One equivalent of benzoyl chloride was then added dropwise with a syringe; the reaction was stirred for 2 min, after which triethylamine hydrochloride was removed by filtration and the filtrate was concentrated under reduced pressure. Addition of 0.4 mL of acetonitrile to this concentrate and storage at 4 °C effected the crystallization of the amine salt. The ester crystallized on evaporation of solvent as a 1:1 mixture of ester/dimethylacetamide as demonstrated by an ^1H NMR spectrum and analysis; mp 95–97 °C.

Anal. Calcd for $C_{20}H_{25}N_1O_8$: C, 58.96; H, 6.19. Found: C, 58.47; H, 5.93.

2-*O*-Acetyl-5,6-*O*-isopropylidene-L-ascorbic Acid (10). Acetyl chloride (1 equiv) was added slowly to a mixture of triethylamine (2.3 mmol) and 5,6-*O*-isopropylidene-L-ascorbic acid (2.3 mmol) in 5 mL of acetone containing 1.1% H_2O at 22 °C under nitrogen. After 2.5 min, triethylamine hydrochloride was filtered and the filtrate concentrated under reduced pressure (0.01 mmHg). Addition of 0.2 mL of acetonitrile effected crystallization of a mixture of ester (88.1%) and triethylamine hydrochloride (11.9%) as indicated by ^1H NMR; we had difficulty obtaining pure ester by the methods used for other esters.

Results

Isopropylideneascorbic acid, IAA (1), was used to prepare acyl derivatives **2–15** in order to avoid interference by the 5- and 6-hydroxyls of ascorbic acid. Structure has been proved by crystallography for one 3-ester, **15**,[23] and one 2-ester, **7**.[30b]

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Table I. UV Spectroscopic Data for IAA and Some Derivatives (ε's in (cm M)$^{-1}$, λ's in nm, pK_a's determined at 25 °C)[a]

compd		pK_a	$10^3\epsilon_1$, $\lambda_{1\,max}$ (pH)	$10^3\epsilon_2$, $\lambda_{2\,max}$ (pH)	$\Delta\epsilon$ ($\epsilon_2 - \epsilon_1$)	$\Delta\lambda$ ($\lambda_2 - \lambda_1$)
1	2-Esters	3.95	10.4, 244 (2.15)	14.0, 268 (7.51)	3600	24
7		2.35	6.9, 244 (2.07)	12.7, 260 (6.08)	5700	16
8		2.76	9.2, 238 (1 N HCl)	15.7, 260 (6.11)	6600	24
10		2.68	11.6, 238 (1.54)	18.7, 256 (4.57)	7000	28
2	3-Esters	5.74	17.6, 228 (4.23)	10.1, 266 (7.41)	−7500	38
15		6.01	8.6, 238 (1 N HCl)	7.5, 268 (8.03)	−1100	30
6		$4.5 < pK_a < 5.7$				
12 (diester)		none	9.0, 224 (1.54)	9.8, 224 (7.54)	800	0

compd	previously determined pK_a's pK_a	ref	compd	previously determined pK_a's pK_a	ref
L-ascorbic acid	4.2, 11.6	33	**15**	6.22	23
L-ascorbate 2-sulfate	3.11	10	3-*O*-methyl-L-ascorbic acid	7.8	21
L-ascorbate 3-phosphate	3.40	17	3-*O*-acetylascorbic acid	3.6	29

[a] Absorption from low wavelength bands was subtracted by drawing a base line from minimum to minimum.

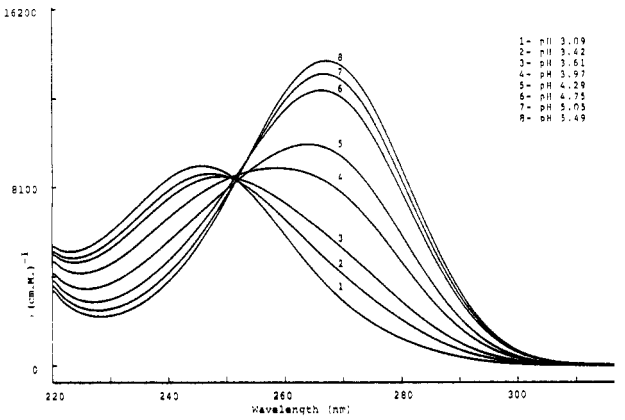

Figure 1. Ultraviolet spectra of 1 at various pH values.

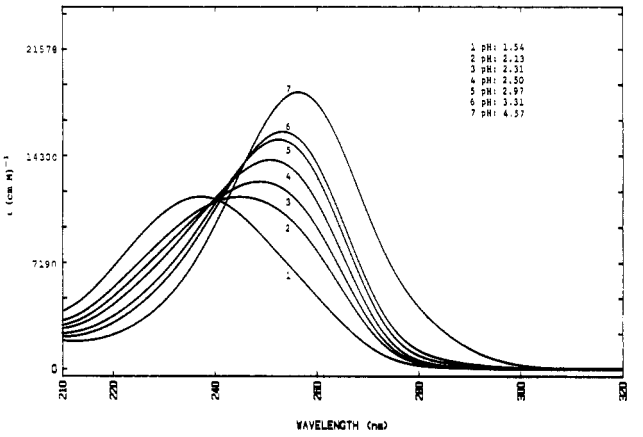

Figure 2. UV spectra of compound 10 at various acidities.

pH-Dependent Ultraviolet Spectra. For IAA and the acyl derivatives, there are absorption maxima for the neutral compound and, at longer wavelengths, for the anion at higher pH's. Typical sets of spectra are shown in Figures 1–4. Figure 1 demonstrates the effect of pH on the spectra of the unsubstituted ascorbate with the expected red shift of the $\pi \rightarrow \pi^*$ band as the neutral molecule is converted to the oxyanion. Figure 2 demonstrates the effect of acetyl substitution which we have determined to be a 2-acetyl ester as the rest of the results in this paper will demonstrate. The lack of a good isosbestic point indicates some degradation of the ester, although we made every effort to obtain these spectra very quickly after mixing the solutions. Figures 3 and 4 compare the 2- with the 3-diphenylphosphinyl derivatives. The 2-ester has a good isosbestic point as we anticipated from other spectroscopic studies (vide infra), but the 3-ester shows some deviation which is probably due to rearrangement to the 2-ester, a process which is also indicated by NMR and IR spectra.[30]

We did similar studies for all the compounds shown in Table I[30] and the indicated pK's were determined by eq 3. The diacetyl derivative 12 gave no significant change in spectrum between pH 1.5 and pH 7.5 in agreement with the structural assignment since there is no ionizable proton in a diester.

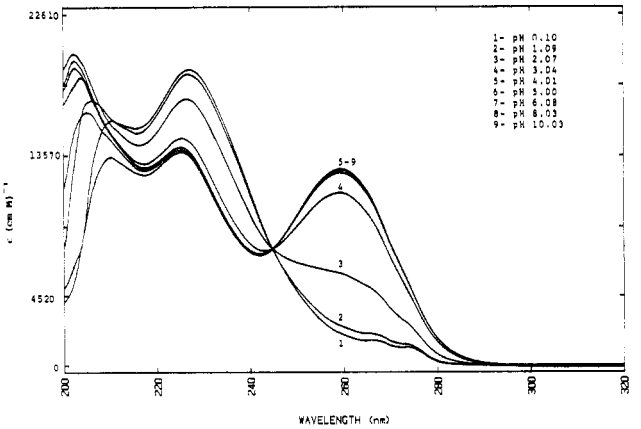

Figure 3. Ultraviolet spectra of 7 at various pH values.

Table I gives the pK's of the compounds for which spectra of the type shown in Figures 1–4 were obtained. We also present in Table I the absorption parameters for both neutral and anionic materials. Both the positions of

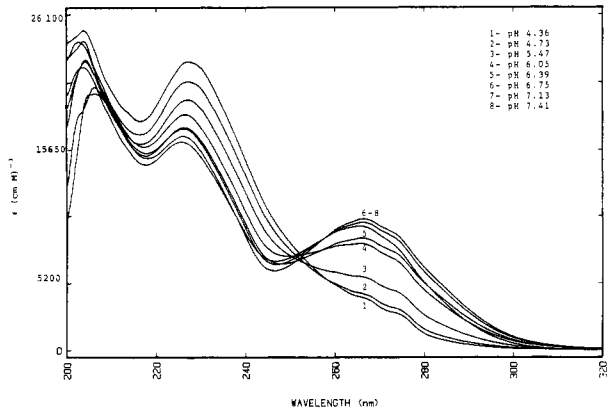

Figure 4. Ultraviolet spectra of **2** at various pH values.

Table II. IR Spectral Bands of Esters of IAA in $CDCl_3$ or $CHCl_3$ (with bands in cm^{-1})

compd	carbonyl stretch	double bond stretch	acyl carbonyl	approx ratio of carbonyl and double bond intensities of bands[a]
		O_3 Esters		
2	1784	1701		1.8
3	1781	1700		*b*
4	1790	1709		1.4
5	1784	1708	1733	1.6
6	1784	1704	1731	1.4
15	1785	1700		1.7
		O_2 Esters		
7	1776	1682		0.7
8	1777	1679, 88		*b*
9	1787	1688		0.5
10	1781	1687	1733	0.8
11	1778	1688	1729	0.5
		O_2,O_3 Diesters		
12	1794	1711	1784	1.6
13	1784	1708	1759	1.8
14	1793	1711	1767	3.2
		Unsubstituted		
1 (IAA)	1754	1665		0.7
IAA-$N(C_2H_5)_3$	1728	1604		0.4

[a] Ratio of $\epsilon(C{=}O)/\epsilon(C{=}C)$. [b] Compounds **3** and **10** are mixtures of diastereomers.

bands and the relative extinction coefficients appear to be useful for structural identification. In particular, the comparison of the 2- and 3-diphenylphosphinyl esters (**7** vs **2**) should be noted.

The absorption maximum of the anion compared to the neutral molecule ($\Delta\lambda$ in Table I) is much greater in 3-esters than in 2-esters. This is largely due to the lower wavelength absorption of the neutral 3-esters which makes sense because the 3-acyl group diminishes the conjugation in the 3-oxy-2,3-unsaturated carbonyl system.

The comparison of extinction coefficients also appears useful in structure determination. When extinction coefficients of the bands are estimated by measuring the peak intensity and subtracting the base due to other absorption bands, we find that the extinction coefficient for the 3-oxyanion is greater than for the 3-protonated neutral molecule, but the extinction coefficient for the 2-oxyanion is less than for the 2-protonated neutral molecule. That is, $\Delta\epsilon$ in Table I is positive for 2-esters but negative for 3-esters.

Acidity Constants. Ester pK_a values are presented in Table I; pK_a values greater than 4 for esters are consistent with O3 ester derivatives and the ionization of the 2-OH; pK_a values below 4 are consistent with ionization of the 3-OH and acylation at the O2 position. The pK_a value, 6.01, determined for compound **15** in this study agrees well with the value of 6.22 determined previously.[23] The pK's of 2.35 for compound **7** and 5.74 for compound **2** demonstrate the change in pK in structurally isomeric esters.

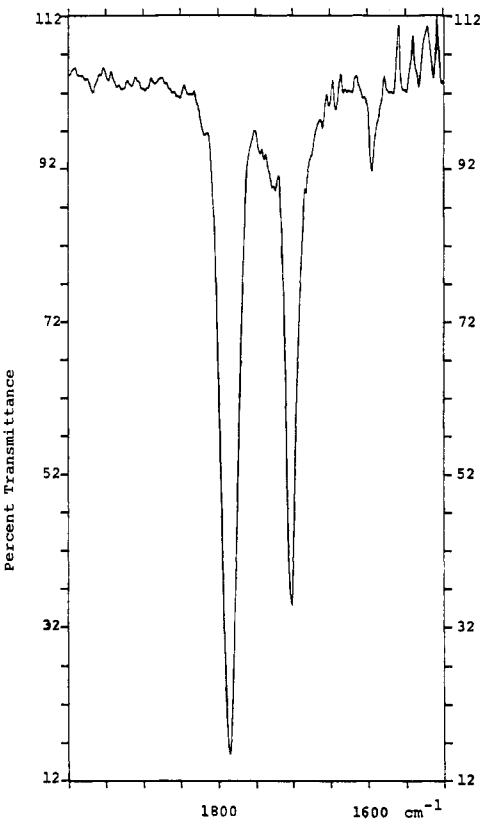

Figure 5. Infrared spectrum, 2000–1500 cm^{-1}, of **2** in $CDCl_3$.

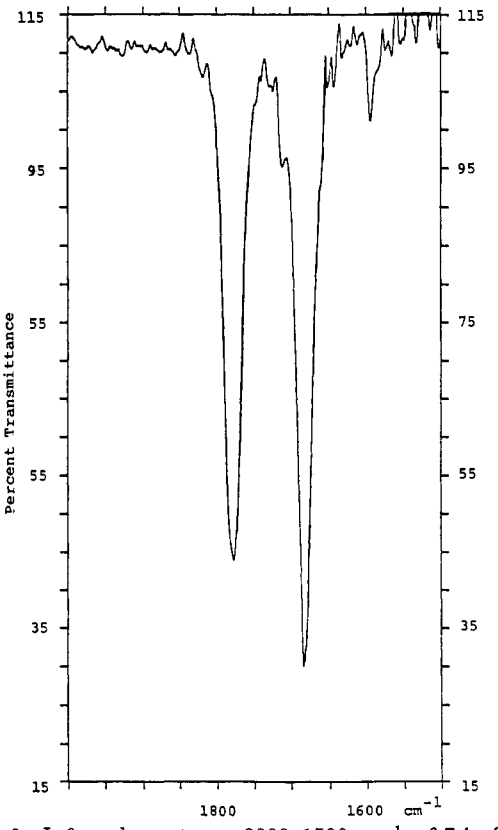

Figure 6. Infrared spectrum, 2000–1500 cm^{-1}, of **7** in $CDCl_3$.

Infrared Spectra. We have found that the positions of C=O and C=C stretching bands in the infrared are

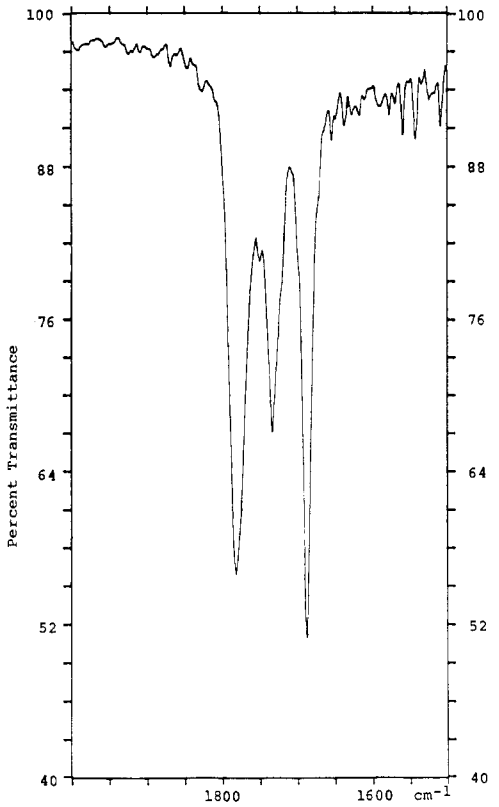

Figure 7. Infrared spectrum, 2000–1500 cm^{-1}, of **10** in $CDCl_3$.

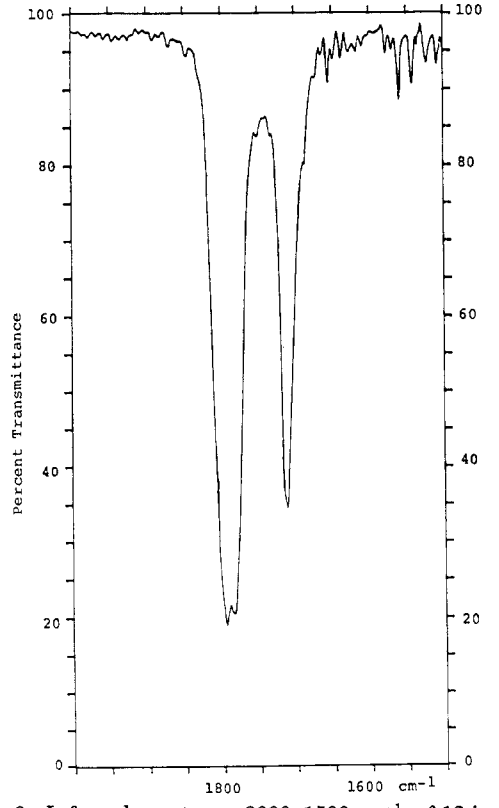

Figure 8. Infrared spectrum, 2000–1500 cm^{-1}, of **12** in $CDCl_3$.

useful for distinguishing 2- and 3-esters. Typical spectra are given in Figures 5–8 and all of the data obtained in our studies[30] are summarized in Table II.

Figures 5 and 6 compare infrared spectra of the 3- and 2-diphenylphosphinyl derivatives, respectively, in the double-bond and carbonyl stretching region. Two features of these spectra are useful in structure identification: First, the 2-ester **7** has an inversion of the normal intensity expectation; that is, in Figure 6 the carbonyl band is less intense than the double-bond band in contrast to the normal intensity ratio which is seen in Figure 5. Of course, these vibrational bands are mixed so that it is not strictly correct to speak about group vibrations, but for purposes of structure identification, it is useful. This intensity ratio which was first observed for compounds **2** and **7** has turned out to be maintained for all of the esters that we have studied as shown by the last column in Table II.

Table III. Proton-Decoupled ^{13}C NMR Spectral Data of IAA and Various Esters in $CDCl_3$ Referenced to Internal Tetramethylsilane[a]

		O_2 esters, δ (J)		O_3 esters, δ (J)	
C no.	IAA-$N(C_2H_5)_3$, δ	**7**	**8**	**15**	**2**
C_1	171.79	167.19 (6.3)	167.03 (5.5)	167.74	167.24
C_2	118.98	114.42 (7.8)	114.84 (10.7)	124.88 (4.3)	125.96 (4.6)
C_3	150.90	158.24 (4.4)	156.72 (4.4)	137.69 (6.4)	138.11 (8.8)
C_4	76.23	74.70	74.54	73.88 (7.9)	74.13 (5.9)
C_5	75.08	73.54	73.71	72.58	72.94
C_6	65.31	65.08	65.30	65.20	65.13
C_7	109.90	110.15	110.37	110.53	110.32
C_8	26.07	25.54	25.85	25.73	25.62
$C_{8'}$	24.59	24.19	25.60	25.68	25.51

[a] J's are due to ^{31}P–^{13}C. J values are in hertz.

Second, there are useful shifts in frequencies of the bands, especially for the double-bond stretching band. Table II demonstrates that carbonyl bands of the O3 esters lie near 1784 cm^{-1} (Figure 5) whereas those of the O2 esters lie near 1780 cm^{-1} (Figures 6 and 7), a small shift but expected because of the diminished conjugation in 3-esters. This pattern was also found for a mixture of 2-*O*- and 3-*O*-bis(trimethylsilyl)phosphinate esters of ascorbate when the other three hydroxyls are all protected with trimethylsilyl groups.[25] Only the bands of compounds **4** and **9**, the diphenyl phosphate monoesters, are at higher frequencies than the corresponding bands of other esters. Bands of 2,3-*O*-diacyl esters are at higher frequencies near 1790 cm^{-1} and show multiple bands due to overlap of the acyl and ring carbonyl stretching frequencies (Figure 8 and Table II).

The lower wavenumber band shown in Figures 5–8 and compiled in Table II, "the double bond stretching band", appears to be the most useful band for structure determination. The bands for the O3 esters are near 1700 cm^{-1} (Figure 5 and Table II) but the bands for the O2 esters are at significantly lower frequency, near 1684 cm^{-1} (Figures 6 and 7 and Table II). Individual double-bond stretching bands of O2 and O3 esters were resolvable in mixtures, which aided our synthetic work, since the bands are sharp and sufficiently separated so that product composition can be estimated. When one ester is predominant the band for the minor constituent still appeared as a shoulder.

^{13}C NMR spectroscopic data for the IAA–$N(C_2H_5)_3$ complex and four phosphorus esters in $CDCl_3$ are presented in Table III. Berger's work was useful in assignment of chemical shifts.[35] Coupling of phosphorus is particularly useful for structure determination in phosphorus esters. In both O2 esters, **7** and **8**, ^{31}P is coupled to C2, C3, and C1. In contrast, the two O3 esters, **15** and **2**, give couplings to carbons 2, 3, and 4. Therefore, the ^{13}C NMR spectra give a clear structural assignment which corrobo-

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Table IV. ^{1}H NMR Spectral Data (δ) for IAA and Esters (δ referenced to tetramethylsilane in $CDCl_3$ at 22 °C)

compd	δ H4	H5	H6	H6′	H8	H8′	acyl group
				O_3 Esters			
2	4.607	4.265	4.105	4.019	1.302	1.255	
3	4.569	4.376	4.186	4.117			
4	4.663	4.251	4.104	4.005	1.357	1.300	
5	4.840	4.339	4.177	4.057	1.386	1.366	2.358
6	4.994	4.441	4.229	4.132	1.391	1.363	
				IAA-N$(C_2H_5)_3$			
1	4.464	4.170	4.107	4.023	1.412	1.372	
				O_2 Esters			
7	4.603	4.297	4.120	4.015	1.261	1.213	
8	4.661	4.415	4.203	4.104	1.380	1.273	
9	4.632	4.251	4.153	4.062	1.369	1.354	
10	4.781	4.439	4.207	4.106	1.406	1.378	2.237
11	4.761	4.483	4.216	4.126	1.382	1.356	
				Diesters			
12	5.148	4.394	4.196	4.104	1.394	1.359	2.278, 2.311
13	5.492	4.533	4.262	4.197	1.426	1.374	
14	5.420	4.542	4.279	4.209	1.418	1.381	

Table V. H–H Coupling Constants for IAA and Ester Derivatives. Couplings Are from Spectra Recorded in $CDCl_3$ at 22 °C (in hertz)

compd	$^3J_{H4-H5}$	$^3J_{H5-H6}$	$^3J_{H5-H6'}$	$^2J_{H6-H6'}$	$^5J_{H4-P}$	$^4J_{H4-P}$
			O_3 Esters			
2	2.74	6.53	7.06	−8.34		1.48
3	3.47	6.88	6.35	−8.55		
4	2.19	7.03	6.73	−8.38		2.19
5	2.84	6.80	6.53	−8.67		
6	2.66	7.06	6.61	−8.47		
			O_2 Esters			
7	3.18	6.70	6.70	−8.60	1.27	
8	3.03	6.70	6.63	−8.53	1.05	
9	2.92	6.81	6.66	−8.50	0.96	
10	3.04	6.81	6.54	−8.48		
11	3.31	6.74	6.54	−8.70		
			O_2,O_3 Diesters			
12	2.03	6.78	6.06	−8.48		
13	2.5	6.75	6.08	−8.54		
14	2.06	7.0	6.19	−8.77		
IAA-N$(C_2H_5)_3$	4.80	6.47	7.33	−8.33		

rates the correlation of pK's and infrared spectra with structure. Although this method cannot be used for carboxylic esters, the data from phosphorus esters give us confidence that the assignments based on pK's and infrared spectra are correct for carboxylic esters.

^{1}H NMR chemical shifts and coupling constants of IAA and a variety of esters in $CDCl_3$ are presented in Tables IV and V. Most spin–spin couplings are first-order ABCD for H4, H5, H6, and H6′. Spin simulations, which were carried out with Varian XL-200 software, for **2**, **7**, **8**, and **15** verify this pattern. All esters indicate that derivatizations deshield all H4 and H5 protons. This is also observed for the majority of H6 and H6′. These gem protons at C6 are coupled to each other with negative coupling values as demonstrated by spin simulation (Table V). It was also found that O3 esters have $^3J_{H4-H5}$ under 3 Hz whereas those of O2 esters are above 3 Hz. The exception to this trend is noted with compounds **3** and **8** for which coupling values are reversed. Interesting long-range couplings $^nJ_{P-H4'}$ were observed for both the O3 esters (n = 4) and the O2 esters (n = 5). These couplings range from 0.96 to 2.19 Hz; two such couplings are shown in Figures 9 and 10 for the 2- and 3-diphenylphosphinyl esters (**2** and **7**).

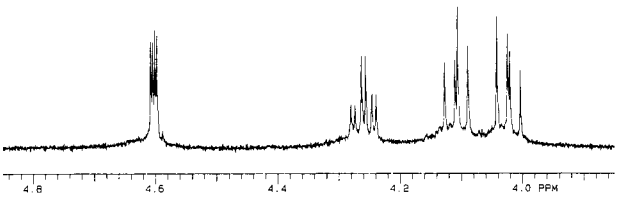

Figure 9. ^{1}H NMR spectrum of H4, H5, H6, and H6′ of **2** in $CDCl_3$ referenced to internal tetramethylsilane, at 400 MHz.

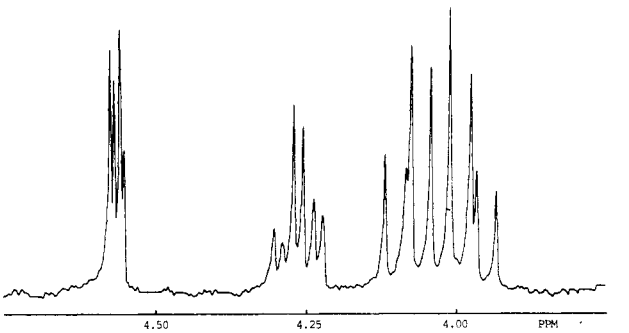

Figure 10. ^{1}H NMR spectrum of H4, H5, H6, and H6′ of **7** in $CDCl_3$ at 200 MHz, referenced to internal tetramethylsilane.

Discussion

Structure determination of acylated ascorbates has been one of several problems in the chemistry of ascorbic acid. There have been several syntheses of O2 derivatives that originally were thought to be O3 derivatives.[10–29] A major focus of this research was the development of useful methods for spectroscopic determination of structure of O2 and O3 derivatives. This has been achieved by a combination of spectroscopic methods. The crystallography on **7** and **15**, the ^{13}C NMR spectra of the phosphorus

esters, and the pK's in Table I give unambiguous structural assignments on which the other correlations are based.

Dissociation Constants. The pK_a's of ascorbic acid are 4.2 and 11.6;[36] the second pK_a represents ionization of the 2-OH to form a *dianion*. The typical pK of 2-esters (Table I) is approximately 2.6, a small increase in acidity compared to **1** (pK = 4.0) and ascorbic acid (pK = 4.2); this small effect is probably due to the electron-withdrawing acyl group at the 2 position. In 3-esters, the 2-OH has a typical pK of about 6, a large increase in acidity compared to the 2-OH of ascorbate anion because of the electrostatic difference between ionization to give a monoanion from the ester and a dianion from ascorbate.[37]

Based on these measurements of pK's in 2-esters and 3-esters, the inherent difference in acidity of the 3-OH and the 2-OH is about $10^{3.4}$. That difference must be due to greater delocalization of electron density in the 3-oxyanion compared to the 2-oxyanion as would be expected (eq 1).

Our findings in Table I are consistent with the pK's previously measured and listed at the bottom of Table I. The phosphate, sulfate, and acetate were thought to be 3-esters when first synthesized.[15,17-20,29] The correct assignments of structure for **15**, the phosphate, and sulfate were made definitively by crystallography so there is no question about the structure of these derivatives. The pK's of the sulfate and phosphate are somewhat higher than the 2-esters that we have synthesized, **7**, **8**, and **10**. This is undoubtedly due to the negative charges on the phosphate and sulfate groups which inhibit ionization of a proton at the 3-position. There is reasonable agreement between our determination of the pK of **15**, which we synthesized in order to have an authentic 3-ester for comparison studies, and the pK determined in the research in which the crystal structure of **15** was also reported.

In a previous report, synthesis of the 3-acetyl ester of **1** and a pK of 3.6 were reported.[28] Subsequently, ultraviolet spectra demonstrated that it was a 2-ester.[29] In this research, the ultraviolet spectra used to determine the pK of **10** showed evidence of probable degradation due to acid-catalyzed hydrolysis; Figure 2 demonstrates that there is no isosbestic point unlike Figures 1 and 3. Our spectra were taken with a diode array spectrometer which required only seconds for each spectrum so there was minimum degradation of **10** and the pK is fairly accurate. We believe that the previously reported pK is slightly in error due to hydrolysis during the titrations used to determine the pK, that the correct pK is close to 2.7 (Table II), and that the compound is definitely the 2-ester.[5,29,30] A pK of 2.7 or 3.6 is only consistent with a 2-ester;[5,29,30] infrared spectra (see below) support this assignment.

Infrared Spectroscopy. The positions of the carbonyl and double-bond stretching bands (Table II) are a result of the multiple effects of the ascorbate structure. It can be expected that the five-membered lactone will raise the frequencies and the conjugated double bond and the 2- and 3-OH groups will lower the frequencies.[38,39]

As indicated by the data of Table II, the IR spectra of IAA esters indicate that the spectral characteristics are dependent primarily on the position of the ester group in the structural isomers. Little dependence of the carbonyl and double-bond bands on the type of ester is indicated. Diesterification of **1** and monoesterifications at O3 and O2 increase the carbonyl frequencies by average values of 91, 85, and 79 cm^{-1}, respectively, above the frequency in **1**. The double-bond bands are similarly affected by esterification; changes in frequencies, relative to **1**, of 106, 100, and 81 cm^{-1} are displayed by diesters and O3 and O2 monoesters, respectively. These shifts to higher frequency are sufficiently different for 2- and 3-esters so that the double-bond band (Table II and Figures 5–8) can be used for structure determination.

Table VI. Distances of Some Bonds of Esters and L-Ascorbic Acid (AA) (in 10^{-8} cm) Determined by X-ray Crystallography[a-c]

compd	$R_{C_1=O_1}$	$R_{C_1=C_2}$	$R_{C_2=C_3}$
ascorbic acid[a]	1.216	1.452	1.338
calcium ascorbate[a]	1.233	1.416	1.373
15[b]	1.186	1.472	1.313
7[c]	1.176	1.480	1.331

[a] Reference 7. [b] Reference 23 and Cambridge Data File. [c] P. Haake, K. Kessler, and J. Springer, unpublished results; ref 30b.

In addition, in all the compounds we investigated, there is an unusual intensity inversion when the 3-position is *not* esterified: the double-bond band is more intense than the carbonyl band in contrast to the usual greater strength of carbonyl bands.[40] When the 3-position is esterified, this normal ratio of carbonyl to double-bond band intensities applies (Table II). Therefore, it appears that this intensity relation for infrared intensities can be useful for rapid determination of the point of acylation. We also found that infrared spectroscopy enabled a rapid analysis of reaction mixtures in order to determine whether the 2-OH or the 3-OH reacted more rapidly under a given set of conditions.

The shifts in frequencies of the carbonyl and olefinic bands have precedence in known effects of polar groups; it has been found that the frequencies of C—H bands, C=O bands, and C=C bands are strongly affected by polar groups.[40-42] Vinyl ethers give lower C=C frequencies than ethylene, but vinyl esters give higher frequencies.[42]

Structural changes are in agreement with the changes in position of the infrared bands as shown in Table VI. The anion, with delocalization as shown in eq 1, has a longer C1=O1 bond, shorter C1—C2 bond, and longer C2=C3 bond than ascorbic acid. The reverse effect is found in esters because delocalization of O2 and O3 lone pairs is reduced.

The carbonyl bond length order, based on crystal structures, is anion > **1** > O2 and O3 esters, Table VI. Hence, it is expected that the frequency of carbonyl bands of esters will be higher than the frequency for **1** and that the frequencies for O3 esters and O2 esters will be similar as is demonstrated by the data in Table II.

^{13}C NMR spectra were useful for structure determination of phosphorus esters due to J_{P-C} coupling constants (Table III): both 2- and 3-esters gave two- and three-bond couplings. Therefore, the C1 peak was a doublet in 2-esters and the C4 peak was a doublet in 3-esters, a clear method for distinguishing the structurally isomeric esters. Although this method cannot easily be applied to carboxylic esters, the unambiguous assignment of structure by pK's and ^{13}C NMR of phosphorus esters has enabled the development of infrared spectra as a rapid and simple method of structure identification for all esters.

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The chemical shift data in Table III are interesting. There is relatively little change in chemical shifts of C1, C4, C5, C6 and the carbons of the isopropylidene group, but the chemical shifts of C2 and C3 change considerably and in complimentary directions: in the O2 esters, **7** and **8**, C2 is shielded and C3 is deshielded, but in O3 esters, **15** and **2**, the reverse is true. That is, esterification causes deshielding at the carbon which is conjugated with the ester oxygen. This would be expected from the effect of esterification on enolic delocalization of electrons on O2 and O3. There is a stronger effect of esterification on the chemical shift at C2 than at C3 as would be expected from the very strong interaction of the O3 electrons with the double bond because O3 is directly conjugated with the 2,3-unsaturated carbonyl system. Crystallography of ascorbates demonstrates that the C1–C2 bond is shortened compared to a pure single bond and the C2–C3 double bond is lengthened compared to a pure double bond (Table VI).[7,30]

The ascorbic acid–triethylamine complex was used in order to improve the solubility of the ascorbic acid in deuteriochloroform so that the amount of NMR instrument time was not excessive. Carbons 1, 2, and 3 bear no hydrogens so there is slow relaxation of these carbons which necessitates a long delay time between pulses and this results in a need to use a large amount of time for a given number of pulses. We suggest that triethylamine improves solubility by disrupting intermolecular hydrogen bonding among ascorbic acid molecules. Because the ascorbic acid is a weak acid, we expect that in deuteriochloroform there is an amine–acid complex but proton transfer does not occur so that we are observing the spectra of the uncharged ascorbic acid. This is supported by the small changes in chemical shifts, compared to esters, except at carbons 2 and 3.

The shielding effect of the 2- or 3-OH groups is even stronger in the esters than in the ascorbic acid based on the chemical shifts of C2 an C3 in Table III. The largest shielding effect is at C3 in the 3-esters, **15** and **2**. This indicates that the 2-OH is more strongly conjugated with the double bond when O3 is esterified than when O3 is an OH and strongly conjugated with the double bond.

^{1}H NMR spectra were useful in purification of products but not definitive for structural identification (Table IV). Derivatization of IAA at either the O3 or the O2 causes an upfield shift in the methyls of the 5,6-*O*-isopropylidene group. These shifts are especially large for **2** and **7**, suggesting a shielding effect by one of the benzene rings of the $(C_6H_5)_2P(O)$ group. The difference in chemical shifts of H8 and H8′ has been used to distinguish between threo and erythro isomers when the hydroxyls are protected with isopropylidene groups.[43] The threo configuration at C1 of glycerol generates an isopropylidene ring which has chemical shift differences of ≤0.05 ppm. The erythro configuration generates a ring which has the difference value of ≥0.05 ppm. The 5,6-*O*-isopropylidene group of **1** and its esters is a terminal ring of a molecule with chiral C4 and C5. The differences of signals H8 and H8′ vary from 0.015 to 0.107 ppm in our compounds; therefore, our results do not follow the earlier correlation of chemical shifts.[43]

The proton chemical shifts of the O3 and O2 esters indicate that substituents at these positions significantly deshield H4 and H5 (Table IV). The H6 and H6′ chemical shifts are less affected. For example, compound **13**, the 2,3-*O*-dibenzoyl ester, has H4 deshielded by 1.028 ppm, whereas the deshielding of H5, H6, and H6′ are 0.372, 0.155, and 0.174 ppm, respectively. As reported above, the methyls of 5,6-*O*-isopropylidene of IAA are also different from those of the esters.

The steric effects on the structure of the compounds can be investigated through calculations of the average dihedral angles, at C4, C5, and C6, with a modified Karplus relation as applied successfully previously.[44,45] We used Abraham's

$$a \leq 120°: \; J_{cis} = k_1 \cos^2 a \quad (4)$$

$$a \geq 120°: \; J_{trans} = \tfrac{1}{2}(k_2 \cos^2(120 + a) + k_1 \cos^2(120 - a)) \quad (5)$$

constants,[44] $k_1 = 11.3$ and $k_2 = 11.8$, because of the structural similarity to the compounds he studied. The determined dihedral angles indicate, *approximately*, the extent of rotation about a C–C bond:

	dihedral angles, deg		
compd	H_5–C_5–C_5–H_6	H_5–C_5–C_6–$H_{6'}$	H_4–C_4–C_5–H_5
1-NET_3	41	144	49
2 (3-ester)	41	142	61
7 (2-ester)	40	140	58

These results demonstrate little effect of esterification on the ring or rotation about the C5–C6 bond but significant effects (**2** and **7** vs **1**) on rotation about the C4–C5 bond as would be expected due to interactions between the ester group and the isopropylidene ring.

Synthetic Methods. In addition to the methods described in the Experimental Section, a large number of reactions were run and assayed by infrared and NMR spectra.[30] Particularly useful were the 4-H signal and the isopropylidene signals in the NMR spectra and the carbonyl and olefinic stretching bands in the infrared spectra.

Generally, short reaction times at room temperature were most effective in producing the 3-ester. Rapid mixing of the acid chloride with a mixture of amine and IAA, stirring for a brief time, followed by workup, gave maximum yields of 3-ester and minimum contamination with 2-ester. It was very important to have dry solvent; deliberate contamination with water or methanol led to 100% 2-ester and no 3-ester: Either acetone or THF could be used in these experiments, although there was always more residual starting material (IAA) with THF than with acetone.

We compared triethylamine with 2,6-lutidine in this reaction with acetone as the solvent. Lutidine always produced 2-ester; triethylamine was required to produce 3-ester. Our hypothesis for this result involves the state of ionization of the ascorbic acid when it is exposed to the acid chloride: since triethylamine is a stronger base, it will produce more anion than lutidine.[46] There is experimental evidence in support of this: when lutidine is added to a slurry of IAA in acetone, it causes the IAA to become soluble, but when triethylamine is added, the initial solubilization is followed by an abundant precipitate which we presume to be the triethylammonium ascorbate salt. Therefore, the product distribution supports the concept that one needs to acylate ascorbate anion in order to produce a 3-ester.

Our results, then, indicate that ascorbate anions will react preferentially at the three position but neutral ascorbic acids react preferentially with acid chlorides at the 2-position. We have done a preliminary ab initio calcu-

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lation at the STO-3G level and find that neutral ascorbate has a higher electron density at O2 than at O3. An experimental indication comes from consideration of the dianion; in the dianion, it is clear that O2 is about 4 powers of 10 more basic than O3. There is synthetic evidence that in the dianion, reaction at O2 is more rapid.[6]

It is also clear that long reaction times or addition of protic solvents results in high yields of 2-ester. A reaction mixture which was predominantly 3-ester was converted to 2-ester if methanol was deliberately added. Therefore there is evidence that one reason for production of 2-esters is that a 3-ester can be initially produced but converted to a 2-ester.[29,47]

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Registry No. 1, 15042-01-0; 2, 116565-54-9; 3, 116565-55-0; 4, 32643-49-5; 5, 116565-56-1; 6, 14200-03-4; 7, 116565-57-2; 8, 116565-58-3; 9, 116565-59-4; 10, 116565-60-7; 11, 29881-30-9; 12, 109620-91-9; 13, 116565-61-8; 14, 116565-62-9; 15, 116565-63-0; $Ph_2P(O)Cl$, 1499-21-4.

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Organic Reactions of Reduced Species of Sulfur Dioxide[1a]

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Rongalite (sodium hydroxymethanesulfinate or sodium formaldehydesulfoxylate) reacts with organic halides in a variety of ways depending on the structure of the organic compound. Benzyl and other alkyl halides give sulfones in generally good yields; but in several cases, reduction (2,4-dinitrobenzyl bromide, phenacyl halides) or coupling (*p*-nitrobenzyl bromide under basic conditions, phenacyl bromide or iodide) of the halide occurs. Addition of sodium iodide to the mixture of Rongalite and phenacyl chloride changed the reaction from one of complete reduction to acetophenone to one of mainly dimerization to 1,4-diphenyl-1,4-butanedione. The amount of acetophenone from phenacyl bromide depends on the water content of the reaction mixture, more dimer being formed when little water is present. Diphenacyl sulfone is formed from phenacyl bromide and Rongalite in the presence of excess sulfur dioxide. The intermediate β-keto sulfinate is believed to normally lose sulfur dioxide very readily to give the enolate anion, which either is protonated to give acetophenone or reacts with phenacyl halide to give the butanedione. In the presence of excess sulfur dioxide, the loss of sulfur dioxide from the sulfinate is suppressed, allowing sulfone formation to occur by reaction of the sulfinate with phenacyl halide. *o*-Xylylene dibromide gave *o*-xylylene, trapped as the Diels-Alder adduct with norbornene, along with the expected cyclic sulfone and cyclic sulfinate ester (sultine). A convenient synthesis of the sultine in 78% yield is achieved by treatment of α,α'-dichloro-*o*-xylene with Rongalite and sodium iodide. Treatment of Rongalite in DMF-H_2O with sulfur dioxide gives the blue anion radical complex $(SO_2)(SO_2^{\bullet-})$. Anion radicals are produced from *p*-dinitrobenzene and *p*-nitrobenzoate ion when they are treated with Rongalite.

Introduction

Reduced species of sulfur dioxide such as $SO_2^{\bullet-}$ and SO_2^{2-} are formed by the interaction of sulfur dioxide with the dihydropyridine coenzyme NADPH[2] and also with 1-benzyl-1,4-dihydronicotinamide,[3] a model for the important pyridine nucleotide coenzymes. The production of these anions by the interaction of sulfur dioxide with biological reducing agents may be significant with respect to the toxic effects of this common pollutant on plants and animals, particularly since $SO_2^{\bullet-}$ is said to be formed in an aqueous medium.[4,5] While the reaction of sulfur dioxide with organic compounds has been widely investigated and while much significant and fascinating chemistry has been discovered,[6] there has been relatively little attention paid to the organic chemistry of reduced species of sulfur dioxide.[7,8a] The potential biological significance of these species is one reason for the study of their reactivity with organic compounds. In addition, these anions may be useful intermediates in organic chemistry.

In a search for a more accessible laboratory source of reduced species of sulfur dioxide (other than sulfur dioxide

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