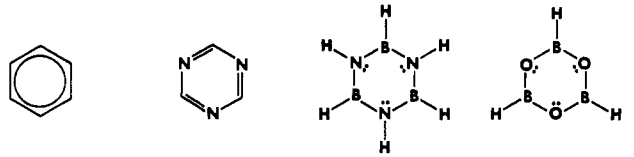
the uniform reference frame has uniform charge densities. Countless examples of such systems exist. For example, all π charge densities in benzene (**65**) are unity. The isoelectronic,



65 66 67 68

heteroatomic systems **66**, **67**, and **68** are all known. The topological charge stabilization rule suggests a decrease in stability through this series, following the trend of increasing localization of charge on more electronegative atoms.

Conclusion

The topological charge stabilization rule has potential value as a guide for synthetic efforts and as a quick way to rank the stabilities of positional isomers. It is easy to apply. Although more limited in its applicability, the rule is often more direct than a comparison of energy quantities because while energy is a properly of a molecule as a whole, charge density is a property of an atom in a molecule. From the pattern of charge densities one can sense what is right or wrong with the location of an individual atom in a particular structure. Much further work remains to be done to learn the limitations of the rule, including a more quantitative sense of the effect of the magnitude of differences in charge densities. More applications need to be made to systems of low symmetry, to chain and branched structures, and to three-dimensional structures.

Acknowledgment. This work was begun while I was a U.S. National Academy of Sciences exchange scientist in Yugoslavia, May 20–June 20, 1982. I am grateful to the staff of the Rudjer Bošković Institute, Zagreb, for their hospitality during my stay there. I am happy to acknowledge helpful discussions with Professor D. Sunko and Professor N. Trinajstić.

Successive Displacements of Phenoxy by Methoxy Groups in Triphenyl Phosphite Ozonide: Mechanism of the Accelerated Singlet Oxygen Formation with Pyridine and Methanol

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Abstract: The ozonides from triphenyl phosphite, methyl diphenyl phosphite, and phenyl dimethyl phosphite form a series (**1–3**) which liberate singlet oxygen thermally at rates increasing by an order of magnitude for each substitution of methoxy for phenoxy. Trimethyl phosphite ozonide (**4**) fits in this series, although the very low temperature limit of its stability has not been determined. When triphenyl phosphite ozonide (**1**) is treated with methanol and pyridine in methylene chloride[11] and yields singlet oxygen at an accelerated rate, the phenyl methyl phosphates **6** and **7** and trimethyl phosphate (**8**) are produced in a total amount corresponding to the singlet oxygen evolved. The lower the temperature, the greater the predominance of trimethyl phosphate (**8**) in the product. Each of the mixed phosphite ozonides **2** and **3** is in turn subject to accelerated singlet oxygen formation by the action of methanol and pyridine; in each case the phosphates formed contain at least one more methoxy group than the starting ozonide. These facts establish the mechanism of the accelerated singlet oxygen liberation as a successive displacement of phenoxy by methoxy groups on the initial phosphite ozonide, each newly formed aliphatic–aromatic phosphite ozonide decomposing thermally at its own increased rate.

Phosphite ozonides have acquired great mechanistic interest in connection with the thermal generation of singlet oxygen ($^1\Delta_g$). Triphenyl phosphite ozonide (TPPO, **1**) at its thermal decomposition point[3] of about −15 °C gives high yields of singlet oxygen,[4] which can be used preparatively with reactive singlet oxygen acceptors or diagnostically to identify the singlet oxygen component in complex photochemical reaction sequences.[5] Cyclic triaryl or trialkyl phosphite ozonides having the phosphorus atom at a bridgehead,[6,7] or the ozonides from triaryl phosphites having a quinoline nitrogen available for chelation with P,[8] show enhanced thermal stability, while triethyl phosphite ozonide can be detected only at −95 °C or below.[9]

Although a direct reaction has been observed between triphenyl phosphite ozonide and certain oxidizable substrates at temperatures far below the decomposition point of the ozonide,[10] the preparative and diagnostic usefulness of the phosphite ozonides centers about their use for the controlled thermal generation of singlet oxygen at temperatures where this can be made the dominant reaction. For that reason the usefulness of this way of generating singlet oxygen has been greatly increased by the discovery[11] of a simple way to generate singlet oxygen from triphenyl phosphite ozonide

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(2) Based on the Ph.D. Thesis of Charles M. Lonzetta, Harvard University, 1976.
(3) Thompson, Q. E. *J. Am. Chem. Soc.* **1961**, *83*, 845.
(4) Murray, R. W.; Kaplan, M. L. *J. Am. Chem. Soc.* **1968**, *90*, 4161.
(5) Bartlett, P. D.; Blakeney, A. J.; Combs, G. L.; Galloy, J.; Roof, A. A. M.; Subramanyam, R.; Watson, W. H.; Winter, W. J.; Wu, C. In "Stereochemistry and Reactivity of Pi Systems"; Watson, W. H., Ed.; Verlag Chemie: New York, in press.
(6) Brennan, M. E. *J. Chem. Soc. D* **1970**, 956.
(7) Stephenson, L. M.; McClure, D. E. *J. Am. Chem. Soc.* **1973**, *95*, 3074.
(8) Koenig, M.; El Khatib, F.; Munoz, A.; Wolf, R. *Tetrahedron Lett.* **1982**, *23*, 421.
(9) Murray, R. W.; Kaplan, M. L. *J. Am. Chem. Soc.* **1969**, *91*, 5360.
(10) (a) Barlett, P. D.; Mendenhall, G. D. *J. Am. Chem. Soc.* **1970**, *92*, 210. (b) Bartlett, P. D.; Mendenhall, G. D.; Schaap, A. P. *Ann. N.Y. Acad. Sci.* **1970**, *171*, 79. (c) Schaap, A. P.; Bartlett, P. D. *J. Am. Chem. Soc.* **1970**, *92*, 6055. Barlett, P. D.; Chu, H.-K. *J. Org. Chem.* **1980**, *45*, 3000.
(11) Bartlett, P. D.; Mendenhall, G. D.; Durham, D. L.; *J. Org. Chem.* **1980**, *45*, 4269. Mendenhall, G. D. Ph.D. Thesis, Harvard University, 1970.

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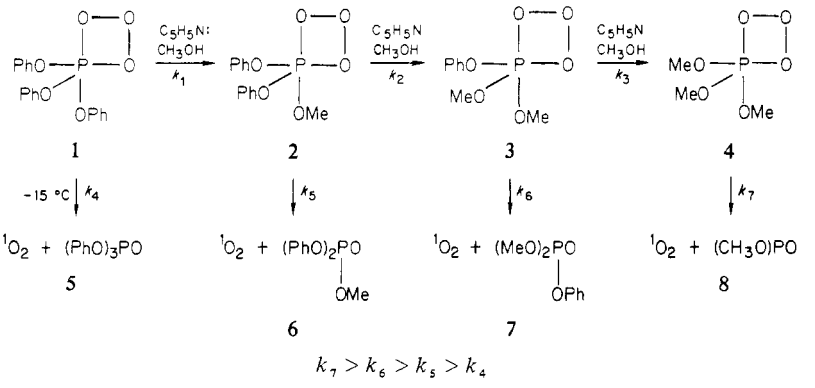
Table I. Rate of Thermal Decomposition of Phosphite Ozonides in Dichloromethane at Various Temperatures

ozonide	(ozonide) (mol/L)	temp, °C	first-order rate constant, 10^{-6}/s	correlatn coeff	no. of half-lives (range)
1	0.387 (0.020)	−55.6 (0.2)	60 ± 2	0.9997	3.6–5.8
1	0.283 (0.006)	−52.8 (0.6)	47.5 ± 2.5	0.9997	3.7–4.9
1	0.302 (0.014)	−33.8 (0.1)	585 ± 20	0.9999	2.7–4.3
1	0.422 (0.015)	−33.4 (0.1)	660 ± 30	0.9996	3.3–4.9
1	0.293 (0.012)	−32.0 (0.2)	790 ± 40	0.9998	3.0–4.0
1		−79.6	1.36[c]		
2	0.358 (0.025)	−80.5 (0.5)	8.3 ± 0.3	0.9992	0.60 (max)
2	0.322 (0.018)	−78.0 (0.5)	14.0 ± 1.0	0.9984	0.24 (max)
2	0.316 (0.019)	−52.7 (0.1)	1360 ± 50	0.9995	2.9–6.9
2	0.395 (0.025)	−51.8 (0.1)	1460 ± 40	0.9995	2.9–7.2
2		−79.6	9.91[c]		
3[a]	0.0618 (0.0085)	−79.5 (1.0)	194 ± 30	0.9970	1.9–3.5 (max)
3[b]	0.0790 (0.0070)	−79.6 (0.3)	185 ± 15	0.9970	2.9–4.5

[a] 74% GLPC pure dimethyl phenyl phosphite. [b] 95+% GLPC pure dimethyl phenyl phosphite. [c] Extrapolated.

Scheme I



$k_7 > k_6 > k_5 > k_4$

at any temperature from its normal decomposition point of −15 °C down to about −100 °C. The process consists in adding pyridine and methanol to triphenyl phosphite ozonide (**1**) in methylene chloride or any of a number of convenient solvents, at the desired temperature (below −20 °C), in the presence of the singlet oxygen acceptor.

We now report experiments proving that this accelerated generation of singlet oxygen proceeds by way of successive displacements of phenoxy by methoxy groups, resulting in a series of phosphite ozonides (**2–4**) which decompose to singlet oxygen and phosphates (**6–8**) in the same way as the original triphenyl phosphite ozonide (**1** → **5**) but at rapidly increasing rates as phenoxy groups are replaced by methoxy.

Results

We had to consider the possibility that the pyridine was catalyzing the TPPO decomposition by a direct nucleophilic or electron-exchange mechanism. It was found, however, that pyridine alone without the methanol had little or no effect when dry, while certain other amines which appeared to have an independent destructive effect on the ozonide never produced singlet oxygen, being quenchers for this excited species.

If methanol plus pyridine is uniquely essential to this process, an attractive mechanism is a nucleophilic displacement by methoxide on the phosphite ozonide, a phosphorane which should be subject to the mechanism established by Ramirez and coworkers.[12-14] These authors demonstrated equatorial attack of methanol and other alcohols, catalyzed by pyridine and other tertiary amines, on phosphoranes having 4- or 5-membered oxa rings on the phosphorus, the rings remaining intact during displacements of methoxy groups. It is also known that hexaarylphoshorus anions are reversibly formed by the attack of phenoxide ion on pentaarylphosphoranes.[15,16]

Thus, there is precedent for a direct displacement by methoxide (from methanol hydrogen bonded to pyridine) on the ozonide by attack at the phosphorane phosphorus atom, followed by decomposition of the new ozonide at its own increased rate. Such a mechanism implies that (a) separate experiments with the ozonides of mixed phenyl methyl phosphites should reveal rapidly increasing thermal decomposition rates within the series, (b) the recovered organic phosphates from an accelerated decomposition of **1** should be quantitatively consistent with this mechanism and should consist entirely of esters in which at least one of the phenoxy group has been displaced, and (c) the kinetic involvement of methanol in the process must be consistent with this mechanism.

Triphenyl phosphite, methyl diphenyl phosphite, and phenyl dimetyl phosphite were all prepared and ozonized at low temperature, and their thermal oxygen evolution followed by volume or pressure at the series of temperatures shown in Table I. For the triphenyl and methyl diphenyl phosphite ozonides **1** and **2**, Arrhenius plots are shown in Figure 1, indicating for the triphenyl phosphite ozonide $\Delta H^{\ddagger} = 12.7$ kcal and $\Delta S^{\ddagger} = -21.6$ eu and for methyl diphenyl phosphite ozonide $\Delta H^{\ddagger} = 15.3$ kcal and $\Delta S^{\ddagger} = -3.8$ eu.

The Arrhenius plots show that the first replacement of phenoxy by methoxy has an accelerating effect on oxygen evolution which declines from a factor of 18 at −55 °C to only 7.3 at −79.6 °C. At the latter temperature, however, **3** evolved oxygen 18.7 times as fast as **2** and 136 times as fast as **1**. Thus these rates are fully consistent with the displacement mechanism for the accelerated oxygen evolution produced by pyridine and methanol (see Scheme I).

At the lowest temperature used in these experiments (−88 °C) the lifetime of trimethyl phosphite ozonide **4** was too short to permit its detection in the ozonization of trimethyl phosphite.

(12) Ramirez, F.; Tasaka, K.; Desai, N. B.; Smith, C. P. *J. Am. Chem. Soc.* **1968**, *90*, 751.
(13) Ramirez, F.; Loewengart, G. V.; Tsolis, E. A.; Tasaka, K. *J. Am. Chem. Soc.* **1972**, *94*, 3531.
(14) Gillespie, P.; Ramirez, F.; Ugi, I.; Marquarding, D. *Angew. Chem., Int. Ed. Engl.* **1973**, *12*, 91.
(15) Lerman, C. L.; Westhekmer, F. H. *J. Am. Chem. Soc.* **1976**, *98*, 179.
(16) Phillips, D. I.; Szele, I.; Westheimer, F. H. *J. Am. Chem. Soc.* **1976**, *98*, 184.

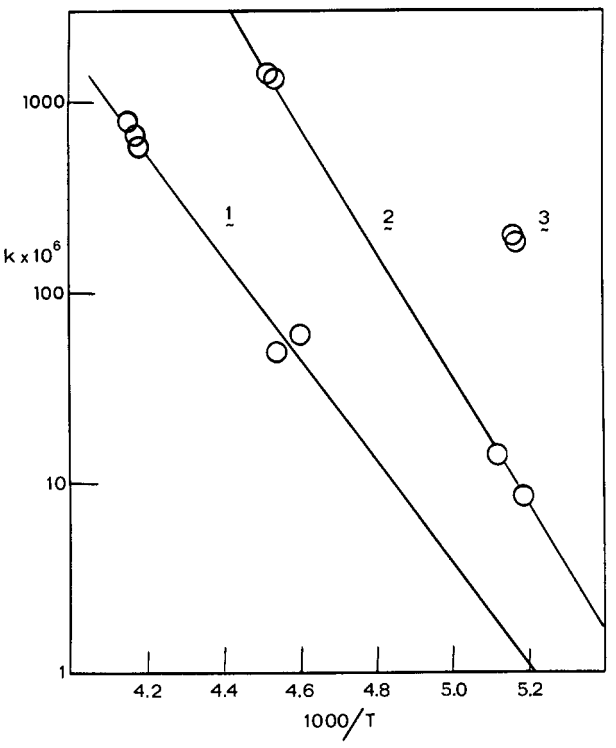


Figure 1. Arrhenius plot of the rate constant for oxygen evolution from triphenyl phosphite ozonide (**1**) and methyl diphenyl phosphite ozonide (**2**) in methylene chloride. Points for phenyl dimethyl phosphite ozonide at −79.6 °C are shown for comparison (**3**).

Table II. Products from TPPO + MeOH + Pyridine in CH_2Cl_2

t, °C	(CH_3OH), M	(C_5H_5N), M	$(CH_3O)_3PO$,[c] %	$(CH_3O)_2PO(OPh)$,[c] %	$(CH_3O)PO(OPh)_2$,[c] %
−57	1.48	0.74	4.8	93	2.5
−57.5	1.85	0.57	20	79	1
−56.1	2.18	1.30	24	75	<1
−57.0	2.34	1.17	18.5	81	<0.9
−55.3	2.23	1.10	23	77	<0.7
−78	4.87	1.95	90	8.1	1.4
−78	4.93	1.98	90	7.6	2.1
−80.7	4.86[a]	2.07	92	7.4	0.47
−80.5	4.81[a]	1.91	92	7.3	0.72
−54.5[a]	4.37[a]	1.86[b]	13	86	0.8
−53.0[a]	4.63[a]	0.84[b]	1.2	97	1.8

[a] Methanol dried by refluxing over $Mg(OCH_3)_2$ under argon. [b] Pyridine dried by reflux over CaH_2. [c] Based on phosphite ozonide consumed or, equivalently, on oxygen evolved.

In a series of experiments at temperatures between −53 and −80.7 °C, triphenyl phosphite ozonide (**1**) was allowed to decompose in methylene chloride in the presence of various concentrations of methanol and pyridine. After oxygen evolution had been completed, the products were separated by vapor chromatography. Table II lists the product compositions, which correspond to moles of each phosphate per mole of oxygen evolved. Since the TPPO was, in each case, freshly prepared in solution and not isolated, the reaction product may have included some unozonized triphenyl phosphite and some triphenyl phosphate resulting from oxidation of the phosphite by ozonide **1**. That none of the triphenyl phosphate **5** originated in the accelerated decomposition of the ozonide was indicated by the fact that phosphates **6**–**8** listed in Table II amounted to the same number of moles as the measured oxygen evolution, requiring that the triphenyl phosphate has arisen from a non-oxygen-producing source.

Table II shows emphatically that the accelerated oxygen evolution comes entirely from phosphite ozonides in which at least one of the original phenoxy groups has been replaced by methoxy. The lower the temperature of the decomposition, the better do successive displacements by methoxide compete with decomposition of the mixed ozonide, making trimethyl phosphate **8** the chief ester product at −78 °C. Phenyl dimethyl phosphate **7** becomes the main product at −53 °C, the highest decomposition temperature of this series.

Table III. Products from Diphenyl Methyl Phosphite Ozonide + MeOH + Pyridine in CH_2Cl_2

temp, °C	(CH_3OH), M	(pyridine), M	$(CH_3O)_3PO$,[a] %	$(CH_3O)_2PO(OPh)$,[a] %	$(PhO)_2PO(OCH_3)$,[a] %
−78	4.32	1.79	90	10	0
−78	4.63	1.90	94	6	0

[a] Yields based on phosphite ozonide consumed or, equivalently, on oxygen evolved.

In two experiments (Table III) with methanol and pyridine at −78 °C, where methyl diphenyl phosphite ozonide **6** is thermally stable, its accelerated decomposition gives a product in which all the evolved oxygen corresponds to the formation of phenyl dimethyl and trimethyl phosphates **7** and **8**, the latter being 90% or more of the product.

The product studies make it clear that every replacement of phenoxy by methoxy greatly increases the rate of singlet oxygen evolution from the resulting phosphite ozonide. Depending on the relative values of the individual rate constants and on temperature and reactant concentrations, the first such displacement might or might not be rate determining for the evolution of singlet oxygen from the ozonide.

It is intuitively apparent that it runs where the phosphate product is entirely phenyl dimethyl phosphate **7**, the rate-determining step should be the reaction between methanol and the methyl diphenyl phosphite ozonide **2** to form the precursor to the observed phosphate. Likewise, a product of pure trimethyl phosphate **8** could similarly correspond to a rate-determining reaction between methanol and phenyl dimethyl phosphite ozonide **3**. A steady-state treatment indicates that in each of these limiting cases the overall kinetics should be first order in TPPO (**1**), with the effect of methanol concentration within a run being minimized by a sufficient excess of methanol. It is thus not surprising that in a series of kinetic runs at −56 °C, where the prevailing ester product is phenyl dimethyl phosphate **7**, as well as at −78 to −80 °C, where the product is largely trimethyl phosphate **8** close fits to first-order kinetics are obtained.

This series of kinetic studies of the oxygen evolution was carried out in methylene chloride with TPPO concentrations from 0.136 to 0.0224 M, with methanol 2.74–5.91 M and pyridine 0.84–1.76 M. Points were taken numbering from 28 to 34 per run and covering from 2.8 to 5.0 half-lives. In each case the results fitted first-order kinetics in the ozonide **1** with correlation coefficients from 0.9978 to 0.9999. However, since the oxygen evolved at any moment is the sum of that coming from three different phosphite ozonides and is the result of as many as four successive reactions, the adherence to first-order kinetics is achieved only by maintaining a substantial excess of methanol over phosphite ozonide (about 18-fold in these runs).

Another circumstance might cause the oxygen evolution kinetics to be more purely first order than the multistep mechanism would suggest. If the displacement of phenoxy groups by methanol–pyridine has a lower activation energy than the ozonide decomposition, then at lower temperatures the starting material might go relatively fast to trimethyl phosphite ozonide (**4**), and the measured oxygen evolution would then be strictly that of this last intermediate. An indication favoring this interpretation is the similarity in rates at −78 °C between triphenyl and methyl diphenyl phosphite ozonides (Table IV). Of course, a special situation such as this would mean that the accelerated singlet oxygen evolution could not really fit the Arrhenius equation over a wide temperature range while the rate-determining step was changing. This point has not been further investigated.

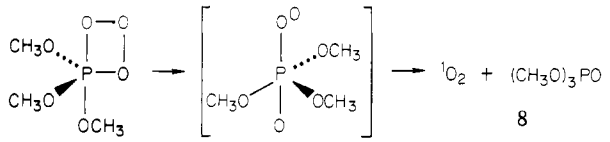
If the displacement reactions of the phosphite ozonides are of the type[12-14]

$$PX_5 + Y^- \rightleftharpoons PX_5Y^- \rightleftharpoons PX_4Y + X^-$$

Table IV. Oxygen Evolution from Phosphite Ozonides in the Presence of Methanol and Pyridine in Methylene Chloride

ozonide[a]	temp, °C	$(ozonide)_0$	$(CH_3OH)_0$	$(pyridine)_0$	$k_1 \times 10^{-4}$, s^{-1}
1	−80.7	0.299	4.86	2.07	5.48
1	−80.5	0.273	4.81	1.91	5.72
1	−78.0	0.293	4.87	1.95	8.00
1	−78.0	0.264	4.93	1.98	7.90
1	−78.0	0.294	3.67	1.71	4.90
1	−78.0	0.269	3.61	1.75	4.80
2	−78.0	0.244	4.63	1.90	6.20
2	−78.0	0.169	4.32	1.79	5.80
2	−78.0	0.175	3.54	1.74	5.15
1	−55.6	0.159	2.74	1.53	21.5
1	−56.1	0.159	2.74	1.53	21.0
1	−56.7	0.145	2.74	1.53	21.0
1	−56.8	0.145	2.74	1.53	21.0
1	−56.9	0.136	2.74	1.53	19.5

then the forward direction is favored by the greater anionic stability of phenoxide relative to methoxide. The favorable effect of methoxy groups on the singlet oxygen formation might be predicted in terms of the Stephenson–McClure mechanism[7] for TPPO decomposition, since methoxy groups accommodate better to the equatorial positions in the trigonal-bipyramid structure of **9**.



4 9 8

Experimental Section

The infrared spectra were recorded on a Perkin-Elmer 137 spectrophotometer. The proton nuclear magnetic resonance spectra were recorded on Varian A-60, T-60, and HA-100 spectrometers. The mass spectra were obtained by Dr. A. Baumstark on an AEI MS-9 double-focusing spectrometer. Refractive indices were measured with a Bausch and Lomb refractometer. The temperature for the kinetic studies was measured with an iron–constantan thermocouple, reference temperature 0 °C connected to a Leeds and Northrup potentiometer. The ozone, 3% in oxygen, was generated by a Welsbach T-23 ozonator (conditions: 6–8 psi of oxygen pressure, 110–120 volts, 0.01–0.02 ft^3/min flow rate of oxygen–ozone mixture).

The low-temperature kinetic runs were carried out in a methanol bath of 2.5–4.0 L in a styrofoam vessel with overhead stirring, cooled typically by a Neslabs Cryocool freon refrigerating unit. Temperature control at −60 or −52 °C was within ±0.2 °C.

The rate of oxygen evolution was measured by following the pressure as indicated by a capacitance manometer apparatus (Granville Phillips Co.), calibrated against the known outside pressure. Alternatively, the oxygen formation was followed by the change in volume in a water-cooled mercury-filled gas buret at constant pressure.

Analytical vapor-phase chromatography was performed on an F & M Scientific Model 700 laboratory chromatograph (thermal conductivity detector) with a temperature programming unit and a disk integrator. Preparative GLPC was carried out with a Varian Aerograph Model 90P gas chromatograph.

The kinetic data were processed on a Digital PDP 11/45 (Digital Computer Corp.) by using a magnetic dectape reader, a card reader, and a line printer, with a Fortran IV program for determining the kineic parameters.

Pyridine (Fisher reagent grade) was dried by stirring with barium oxide or refluxing with calcium hydride, and distilled, bp 116 °C. It was stored over 4-Å molecular sieves and transferred by syringe under argon.

Methanol used was Fisher or Mallinckrodt analytical grade. Glacial acetic acid was Baker reagent grade (99.9%). Triethylamine was refluxed over BaO powder for several hours, fractionally distilled, and stored over 4-Å molecular sieves. Acetonitrile (Mallinckrodt analytical reagent grade) was refluxed over P_2O_5 for 1 h and fractionally distilled under nitrogen through a 30-cm Vigreux column.

Triphenyl phosphite was purchased from the Aldrich Chemical Co. Older samples were purified by washing a dichloromethane solution with 0.1 N NaOH and then with brine. The organic layer was dried and filtered. The solvent was removed by evaporation and the triphenyl phosphite vacuum distilled at 160–161 °C under 0.03–0.05 mm pressure; n^{18}_D 1.5925. Infrared showed the absence of phenol.

Triphenyl phosphate from the decomposition of the ozonide was recrystallized from ether–ligroin and had mp 46–47 °C.

Trimethyl phosphate was fractionally distilled under nitrogen. The fraction collected at 196–198 °C appeared more than 97% pure by vapor chromatography.

Methyl phosphorodichloridate (Aldrich, 97%) was fractionally distilled, bp 44–45 °C (3 mm). Phenyl phosphorodichloridate (Aldrich, 97%) was purified by short-path vacuum distillation, bp 61–67 °C (0.04 mm).

Preparation of Diphenyl Methyl Phosphate. Sodium phenoxide (0.42 mol) was added to dry acetonitrile (300 mL) in a flame-dried three-neck 500-mL flask, equipped with a dropping funnel and a water-cooled condenser attached to a nitrogen bubbler. While the cooled slurry (15 °C) was vigorously stirred, freshly distilled methyl phosphorodichloridate (0.2 mol) was added dropwise over a 30-min period. The reactants were then warmed to 50 °C where the slurry became homogeneous, and stirred. After 2 h, the NMR signals of the methoxy protons indicated complete reaction. After the reaction mixture was dissolved in dichloromethane and washed with a 10-fold excess of water, the yellow organic extract was dried over $MgSO_4$, filtered, the solvent evaporated and the residue was vacuum distilled to give, in 50% yield, the diphenyl methyl phosphate, bp 143–146 °C at 0.04 mm.[17] The product was shown to be more than 99% pure by vapor chromatography, and its structure confirmed by the IR, NMR, and mass spectra of the distillate: IR (cm^{-1}) 3050 (w), 1600 (m), 1490 (vs), 1450 (w), 1290 (s), 1220 (m), 1195 (vs), 1165 (m), 1050 (m), 1025 (m), 1010 (m), 950 (vs), 910 (w), 825 (m), 770 (m), 690 (m); NMR ($CDCl_3$, Me_4Si) τ 2.73 (10 H), 5.99, 6.18 (CH_3O doublet, J_{POCH} = 11.5 Hz); mass spectrum (70 eV), *m/e* (rel intensity) 265 (14.5), 264 (100), 263 (53), 232 (15), 171 (8), 170 (40), 169 (17), 168 (6), 166 (9), 165 (13), 152 (4), 140 (4), 94 (37), 91 (39), 90 (20), 77 (65), 65 (25); parent peak, 264.

Preparation of Dimethyl Phenyl Phosphate. In the method of choice, phenyl phosphorodichloridite (0.07 mol) in anhydrous diethyl ether (150 mL) was placed in a 500-mL three-neck flask equipped with a mechanical stirrer, a dropping funnel, and a drying tube. While the cooled ether solution (0–5 °C) was vigorously stirred, a mixture of equivalent amounts of anhydrous methanol (0.14 mol) and dried triethylamine was added dropwise over a period of 15 min. The reaction mixture was stirred at room temperature for 2 h and then worked up by extraction of the triethylamine hydrochloride into 100 mL of water; the organic layer was dried over 4-Å molecular sieves and the ether was removed by rotary evaporation. The yellow oily residue was vacuum distilled through a short-path apparatus, giving a 47% yield of the dimethyl phenyl phosphate, bp 96–99 °C (0.06 mm). The product was shown to be at least 99% pure by GLPC analysis, and its structure was confirmed by its IR, NMR, and mass spectra: IR 2990 (w), 1600 (m), 1485 (s), 1450 (m), 1280 (s), 1210 (s), 1185 (s), 1165 (m), 1050 (s), 1010 (w), 950 (s), 908 (w), 855 (s), 795 (m), 765 (m), 690 (m); NMR ($CDCl_3$, Me_4Si) τ 2.73, (aromatic, 5 H), 6.09, 6.29 (CH_3O doublet, J_{POCH} = 11.5 Hz, 6 H); mass spectrum (70 eV), *m/e* (rel intensity) 203 (11), 202 (92), 201 (10), 187 (5), 171 (3), 170 (3), 143 (2), 141 (2), 140 (2), 121 (3), 109 (57), 108 (22), 107 (77), 104 (18), 97 (8), 96 (39), 94 (62), 93 (7), 91 (24), 90 (100), 79 (20), 77 (25), 65 (22).

Preparation of Diphenyl Methyl Phosphite. This ester was prepared by the known method[18] from phenol and methyl phosphorodichloridite and 2 equiv of phenol at 0–5 °C in the presence of triethylamine equivalent in amount to the phenol. After the mixture was stirred at room temperature for 30 min, the product was worked up; two preparations yielded 51% and 62% of a product shown to be at least 98% pure by vapor chromatography: IR (neat, cm^{-1}) 3050 (w), 2960 (w), 1590 (s), 1485 (s), 1450 (m), 1280 (w), 1225 (s), 1200 (s), 1160 (s), 1105 (w), 1070 (m), 1020 (s), 903 (s), 880 (s), 855 (s), 825 (m), 775 (s), 760 (s), 735 (s), 713 (s), 688 (s); NMR (CH_2Cl_2, 4.72 τ ref) τ 2.7 (aromatic multiplet, 10 protons), 6.08, 6.23 (CH_3O doublet, J_{POCH} = 9.5 Hz); mass spectrum (70 eV), *m/e* (rel intensity) 249 (6.8), 248 (48.3), 247 (7.8), 217 (4.2), 170 (3.4), 157 (1.7), 156 (13.6), 155 (100), 153 (1.7), 152 (1.7), 140 (4.2), 125 (2.8), 108 (5.1), 94 (5.9), 93 (2.5), 92 (2.5), 91 (15.3), 78 (9.4), 77 (9.5), 76 (3.8), 75 (1.7), 74 (1.7), 66 (2.5), 65 (11.8), 51 (21.2), 50 (5.1), 47 (7.6), 39 (11.8).

Preparation of Dimethyl Phenyl Phosphite. Dimethyl phenyl phosphite was similarly prepared from methanol and phenyl phosphorodichloridite in a total yield of about 33%. Its structure was confirmed by the infrared, NMR, and mass spectra of the GLPC purified sample: IR (neat, ν, cm^{-1}) 3000 (w), 2830 (w), 1590 (s), 1485 (s), 1450 (w), 1220 (s), 1180 (m), 1165 (m), 1070 (m), 1040 (s), 1015 (s), 902 (w), 865 (s), 827 (w), 778

(17) Cramer, F. *Chem. Ber.* **1968**, *91*, 1555: bp 125 °C (203 mm).
(18) Oae, S.; Nakanishi, A.; Kozuka, S. *Tetrahedron* **1972**, *28*, 549.

(s), 755 (s), 720 (s), 690 (s); NMR (CH_2Cl_2, 4.72 τ ref) τ 2.8 (aromatic multiplet, 5 protons), 6.27, 6.44 (CH_3O doublet, J_{POCH} = 10 Hz, 6 protons); mass spectrum (70 eV), *m/e* (rel intensity) 248 (2), 187 (1.5), 186 (17.3), 185 (2.5), 156 (1.2), 155 (23.5), 140 (1.5), 108 (3.2), 107 (2.0), 94 (9.5), 93 (100), 91 (6.5), 90 (2.2), 79 (2.1), 78 (5.5), 77 (27), 66 (3.5), 65 (11.5), 64 (2.5), 63 (16.5), 51 (11), 50 (4.5), 47 (8), 45 (10), 39 (13).

Preparation of Phosphite Ozonides. Dry ozonized oxygen was bubbled through anhydrous dichloromethane in a three-necked flask refrigerated at -78 °C for triphenyl phosphite or methyl diphenyl phosphite, or at -88 °C for phenyl dimethyl phosphite. The appropriate phosphite was dissolved in methylene chloride and added from a dropping funnel at such a rate that the blue color of the solution in the flask persisted throughout the addition. After the phosphite addition was complete, the ozone was bubbled through the solution for another 5-15 min, and the solution was then purged with oxygen prior to its use in a decomposition run. The yield of ozonide obtained determined the yield of oxygen from decomposition of the sample. In the case of triphenyl phosphite, yields of the ozonide were from 70 to 100% and the sample could be kept at -78 °C for 7 days; with methyl diphenyl phosphite the yields were only 25-35% under the same conditions, and the storage lifetime at -78 °C was limited to 6 h. The ozonide of phenyl dimethyl phosphite, prepared in 45-50% yielded at -88 °C, had to be used immediately.

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Registry No. 1, 29833-83-8; **2**, 84812-10-2; **3**, 84812-11-3; methanol, 67-56-1; pyridine, 110-86-1; diphenyl methyl phosphate, 115-89-9; sodium phenoxide, 139-02-6; methyl phosphorodichloridate, 677-24-7; dimethyl phenyl phosphate, 10113-28-7; phenyl phosphorodichloride, 770-12-7; diphenyl methyl phosphite, 3577-87-5; phenol, 108-95-2; dimethyl phenyl phosphite, 18351-42-3; phenyl phosphorodichloridite, 3426-89-9; triphenyl phosphite, 101-02-0.

The Total Synthesis of Ionophore Antibiotics. A Convergent Synthesis of Lasalocid A (X537A)[1]

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Abstract: The construction of both the left-side aldehyde **2** and the right-side ketone **3** available from the reverse aldol reaction with lasalocid A (X537A) is described. For each synthesis chiral starting materials are used. For the aldehyde **2**, (*R*)-(-)-citronellene is the source of the lone asymmetric center and the aromatic ring is prepared by a Diels-Alder reaction between the pyrone **22** and 1-(dibenzylamino)-1-propyne. For the ketone **3**, carbohydrate precursors serve as the source of the furanoid and pyranoid subunits. These subunits are then joined through the use of the ester enolate Claisen rearrangement. Details for the aldol condensation between the aldehyde **2** and the zinc enolate of the ketone **3** are presented, and the formation of the natural ionophore from this process completes the highly convergent total synthesis.

The recently characterized[7] polyether ionophore antibiotics[8] represent a broad new class of biologically potent compounds that have rapidly found commercial value as coccidiostats[9] and anabolic agents[10] in animal medicine. In addition, the demonstration of their powerful cardiotonic activity[11] and apparent tissue selectivity[11] in mammalian systems holds promise for their use in human pharmacology. In light of these results, it is not surprising that the synthesis of these molecules has attracted the concern of numerous research groups, and several representatives of this class have yielded to total synthesis.[12] One such effort resulting in the total synthesis of lasalocid A (X537A) (**1**) is described herein.[13]

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(6) Upjohn Co. Predoctoral Fellow, 1978-1980. For further details of this work, see: Thaisrivongs, S. Ph.D. Thesis, California Institute of Technology, 1980.

(7) Lasalocid A: Isolation—Berger, J.; Rochlin, A. I.; Scott, W. E.; Steinbach, L. H.; Goldberg, M. W. *J. Am. Chem. Soc.* **1951**, *73*, 5295-5298. Structure—Westley, J. W.; Evans, R. H., Jr.; Pruess, D. L.; Stempel, A. *Chem. Commun.* **1970**, 1467-1468. Johnson, S. M.; Herrin, J.; Liu, S. J.; Paul, I. C. *J. Am. Chem. Soc.* **1970**, *92*, 4428-4435.

(8) Moore, C.; Pressman, B. *Biochem. Biophys. Res. Commun.* **1964**, *15*, 562.

(9) Mitrovic, M.; Schildknecht, E. G. *Pult. Sci.* **1974**, *53*, 1448.

(10) Westley, J. W. *Annu. Rep. Med. Chem.* **1975**, *10*, 246. Raun, A. P. *U.S. Patent* 3 937 836.

(11) Pressman, B. C. "The Role of Membranes in Metabolic Regulation"; Mehlman, M. A., Hanson, R. W., Eds.; Academic Press: New York, 1972; p 149. Levy, J. V.; Cohen, J. A.; Inesi, G. *Nature (London)* **1973**, *242*, 461. Gillette, P. C.; Munson, R.; Lewis, R. M.; Schwartz, A. *Fed. Proc., Fed. Am. Soc. Exp. Biol.* **1974**, *33*, 397. Murray, J. J.; Reed, P. W.; Fay, F. S. *Proc. Natl. Acad. Sci. U.S.A.* **1975**, *72*, 4459. deGuzman, N. T.; Pressman, B. C.; Lasseter, K.; Palmer, P. *Clin. Res.* **1973**, *21*, 413. Schwartz, A.; Lewis, R. M.; Hanley, H. G.; Munson, R. G.; Dial, F. D.; Ray, M. Y. *Circ. Res.* **1974**, *34*, 102.

(12) (a) Calcimycin: Evans, D. A.; Sacks, C. E.; Kleschick, W. A.; Tabor, T. R. *J. Am. Chem. Soc.* **1979**, *101*, 6789-6791. Grieco, P. A.; Williams, E.; Tanaka, H.; Gilman, S. *J. Org. Chem.* **1980**, *45*, 3537-3539. (b) Lasalocid A: Nakata, T.; Schmid, G.; Vranesic, B.; Okigawa, M.; Smith-Palmer, T.; Kishi, Y. *J. Am. Chem. Soc.* **1978**, *100*, 2933-2935. (c) Monensin: Fukuyama, T.; Akasaka, K.; Karanewsky, D. S.; Wang, C.-L. J.; Schmid, G.; Kishi, Y. *Ibid.* **1979**, *101*, 259-263. Still, W. C.; McDonald, J.; Collum, D. *Ibid.* **1980**, *102*, 2117-2121.

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