Bondapak, triethylamine–phosphate buffer, iso 24% CH_3CN). Three peaks in the ratio 60:17:23 were observed (elution times 8.5, 10.2, and 11.5 min), the first peak corresponding to SP.

With Methyl *p*-Nitrobenzenesulfonate.[17] To [Hcy^{11}]-SP (2 μmol) in 1 mL of 0.1 M Tris buffer (pH 8.6) was added dropwise under N_2 stream 300 μmol of methyl *p*-nitrobenzenesulfonate in 300 μL of CH_3CN. The mixture was then analyzed by HPLC (C-18, μ-Bondapak, triethylamine–phosphate buffer, iso 24% CH_3CN). SP and [Hcy^{11}]-SP in the ratio 20:80 were observed.

With Chloromethane.[12] To a stirred solution of [Hcy^{11}]-SP (2 μmol) in 10 mL of dry liquid ammonia, protected from moisture and CO_2, was introduced a large excess of CH_3Cl gas, and the mixture was stirred for 10 min. After evaporation of the liquid ammonia and lyophilization the product was purified by preparative high-pressure liquid chromatography (RP-18 Lichrosorb column, 50:50:0.3 methanol–water–trifluoroacetic acid). Only one peak, corresponding to SP, was observed, the recuperation yield being 50%.

[*S*-[2-(Dansylamino)ethyl]-Hcy^{11}]-SP (10) as Described by Scouten.[19] [Hcy^{11}]-SP (2 μmol) and *N*-dansylaziridine (20 μmol) in 200 μL of 0.1 M phosphate buffer (pH 7.5) were stirred at room temperature. The evolution of the reaction was monitored by TLC (solvent system A). This method gave a complex mixture which was not further analyzed.

In Dry Liquid Ammonia. This procedure was done according to the previously described procedure for the alkylation of **7** with chloromethane, 5 μmol of **7** in 10 mL of dry liquid ammonia, and 20 μmol of *N*-dansylaziridine. After dissolution of the residue in 10% acetic acid and lyophilization, the product was purified by preparative HPLC (RP-18 Lichrosorb column, 50:50:0.3 methanol–water–trifluoroacetic acid) to yield **10**: 5 mg (56%); TLC R_f 0.19 (A); HPLC (iso, 30% CH_3CN) 13-min retention time (97% minimum purity); ^1H NMR (D_2O, dioxane, pH 4.5) from the dansyl group δ 8.66 (d), 8.18 (d) 8.12 (d), 7.53 (t), 7.52 (t), 7.30 (d), 2.92 ($SCH_2CH_2NHSO_2$), 2.75 ($(CH_3)_2N$), 2.27 ($SCH_2CH_2NHSO_2$). The other resonances are identical with those of SP.

Acknowledgment. This work was supported in part by grants from Pirmed (ASP No. 15) and CNRS (ATP No. 70823). We thank N. Ling (The Salk Institute, San Diego) for a generous gift of substance P, as well as J. L. Morgat for amino acid analyses.

Registry No. **1**, 85097-56-9; **2**, 85097-57-0; **3**, 85097-58-1; **4**, 85097-59-2; **5**, 85097-60-5; **6**, 33507-63-0; **7**, 85115-64-6; **8**, 85115-65-7; **9**, 85115-66-8; **10**, 85115-67-9; *N*-α-(*tert*-butoxycarbonyl)methionine, 2488-15-5; di-*tert*-butyl dicarbonate, 24424-99-5; *N*-α-Boc-Leu-OSucc, 3392-09-4; L-(*S*-*t*-Bu)Hcy-NH_2, 85097-61-6; DL-(*S*-*t*-Bu)Hcy, 85097-62-7; L-methionine, 63-68-3; *S*-*tert*-butylhomocysteine, 62965-24-6.

Supplementary Material Available: Figure 1, containing HPLC traces of [Hcy^{11}]-SP (1 page). Ordering information is given on any current masthead page.

Notes

Oxidation of Tertiary Phosphines and Arsines with Sulfur Trioxide and Sulfuryl Chloride Fluoride: Demonstration of Ambident Reactivity[1]

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The ambident reactivity of certain nucleophiles is well established. Nitrite ion (NO_2^-), cyanide ion (CN^-), and enolates of carbonyl compounds are well-known ambident nucleophiles.[4] However, the ambident behavior of electrophiles is in general limited to allyl cations and other resonance-stabilized cations.[4] Recently, we reported[5] the ambident reactivity of the nitronium ion (NO_2^+) toward sulfides, selenides, and phosphines, resulting in the oxidation of these substrates. Considering similarities in reactivity between the nitronium ion and sulfur trioxide in electrophilic aromatic substitution reactions, we thought it of interest to extend our studies to the possible ambident reactivity of sulfur trioxide.

Although sulfur trioxide is known as a strong oxidant, the mechanism of such reactions is not yet fully understood and generally is considered to be due to radical processes. It has been, for example, reported that SO_3 when reacted with methane at elevated temperatures (100–450 °C) and pressure (70 atm) gives a mixture of sulfonated and oxygenated products.[6-8] Other hydrocarbons also show similar behavior. The mechanism of the reaction was not established, but the forcing reaction conditions could indicate free-radical oxidation. Representative example of oxidation of halohydrocarbons with SO_3 are that of pentachlorotoluene to pentachlorobenzyl alcohol and pentachlorobenzaldehyde[9] and of trichlorofluoromethane and tribromofluoromethane to carbonyl chloride fluoride and carbonyl bromide fluoride,[10] respectively.

Scheme I

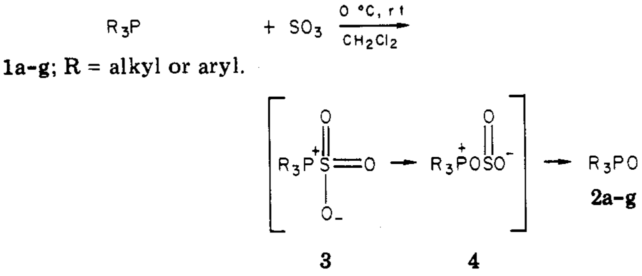

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Table I. Oxidation of Phosphines and Arsines Using Sulfur Trioxide

			yield by method,[a] %		mp or bp (mm), °C		
					obsd		
	substrate (1)	oxidation product (2)	A	B	A	B	lit.
a	Ph_3P	Ph_3PO	95	96	154.5	156.6	156[b]
b	$(p\text{-}CH_3C_6H_4)_3P$	$(p\text{-}CH_3C_6H_4)_3PO$	96	93	147.3	146.0	143-4[c]
c	$(m\text{-}CH_3C_6H_4)_3P$	$(m\text{-}CH_3C_6H_4)_3PO$	95	91	111.5	109.1	111[d]
d	$(o\text{-}CH_3C_6H_4)_3P$	$(o\text{-}CH_3C_6H_4)_3PO$	90	98	155.5	153.2	153[d]
e	$(p\text{-}ClC_6H_4)_3P$	$(p\text{-}ClC_6H_4)_3PO$	98	96	177.6	175.0	178[d]
f	$(n\text{-}Oct)_3P$	$(n\text{-}octyl)_3PO$	98	99	50.2	50.7	51.5[e]
g	$(n\text{-}Bu)_3P$	$(n\text{-}butyl)_3PO$	95		125-6/0.2-0.4		104/0.04[f]
h	$CH_3(C_6H_5)_2P$	$CH_3(C_6H_5)_2PO$		93		111.0	110-1[g]
i	Ph_3As	Ph_3AsO	70		195.1		190-2[h]

[a] Yield of the isolated product, also identified by IR and NMR; (A) SO_3; (B) SO_2ClF. [b] "Dictionary of Organic Compounds, 5th Supplement", 4th Ed.; Oxford University Press: New York, 1968. [c] Burger, A.; Dawson, M. D. *J. Org. Chem.* **1951**, *16*, 1250. [d] Mann, F. G.; Chaplin, E. J. *J. Chem. Soc.* **1937**, 527. [e] White, J. C. AEC Report ORNL-2161, **1956**, 24; *Chem. Abstr.* **1957**, *51*, 4205c. [f] Speciale, A. J.; Freeman, R. C. *J. Am. Chem. Soc.* **1960**, *82*, 903. [g] Davidson, R. S. *Tetrahedron* **1969**, *25*, 3383. [h] "The Aldrich Library of Infrared Spectra", 1970; no. 1105A.

Results and Discussion

We have now found that trialkyl- and triarylphosphines, when treated in methylene chloride solution with SO_3 at 0–25 °C are readily oxidized to give the corresponding phosphine oxides in excellent yield. The mechanism of the reaction is envisaged as outlined in Scheme I.

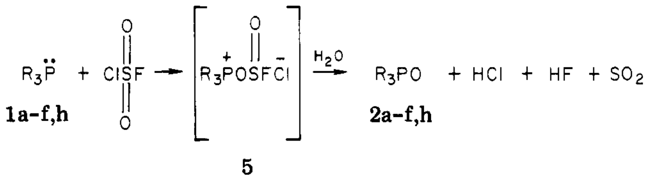
It is possible that the reaction of SO_3 with triphenylphosphine involves initial one-electron transfer from the phosphine to SO_3 followed by collapse of the radical cation–radical anion ion pair. Such an initial electron transfer, however, would still result in the formation of the phosphonium zwitterions **3** and **4** and the overall nature of the reaction is not effected.

The reaction proceeds equally readily with trialkyl- as well as arylphosphines. Aliphatic phosphines react more vigorously than their aromatic analogues, thus requiring carefully controlled reaction conditions. Also during prolonged reaction times, aliphatic phosphines can undergo fragmentation to give a complicated mixture of products.[5] In all the cases studied the reaction, however, could be carried out conveniently in methylene chloride at 0–25 °C with nearly quantitative conversion (90–98%) to the phosphine oxides. Triphenylarsine (**1i**) also reacted similarly with SO_3 to give triphenylarsine oxide (**2i**) in 70% yield (Table I). The results are summarized in Table I.

It is interesting to note that the interaction of sulfur trioxide with amines is quite different. Tertiary amines generally form N → S coordination complexes with sulfur trioxide. It has also been reported[11] that quinuclidine oxide when treated with sulfur dioxide produces the $QN\text{-}SO_3$ adduct. This product probably arises from the isomerization of the initially formed sulfitoamine, $QN\text{-}OSO_2$. Similar results have been reported previously with trimethylamine[12] and triethylamine[13] oxides. A possible explanation for this reverse trend is that the $N\text{-}OSO_2$ bond is weaker than the $N\text{-}SO_3$ bond. Therefore, the reaction is more favorable in the reverse direction. On the other hand, in the case of phosphines (and arsines), strong affinity of phosphorous to oxygen drives the reaction toward oxygenated products.

In the course of our studies we also found that sulfuryl chloride fluoride[14] used frequently as a solvent of low nucleophilicity in the spectroscopic investigations of carbocations[15] also reacts very readily with tertiary phosphines and arsines in a similar fashion to afford the corresponding phosphine oxides and arsine oxides, respectively, at room temperature. The reaction is instantaneous because of the excellent leaving-group ability of fluorosulfinate group. The reaction is general for alkyl- and arylphosphines. In contrast the corresponding reaction with sulfuryl chloride is very slow.

Scheme II



NMR (including ^{31}P NMR) studies indicate that phosphines preferentially attack on the oxygen atom of sulfuryl chloride fluoride to yield the corresponding phosphonium salts **5**. Consequently the suggested mechanism of the oxidation of tertiary phosphines (and arsines) is as shown in Scheme II.

In conclusion, our studies indicate the ambident reactivity of sulfur trioxide and sulfuryl chloride fluoride in their reactions with phosphines and arsines, allowing their use in extremely convenient and mild methods for the oxidation of tertiary phosphines (arsines) to the corresponding phosphine (arsine) oxides.

Experimental Section

General Procedure of Oxidation of Phosphines and Arsines with Sulfur Trioxide. To a well-stirred solution of sulfur trioxide[16] (0.72 g, 12 mmol) in dry methylene chloride (20 mL) at 0 °C was added a solution of phosphine (10 mmol) in dry methylene chloride (20 mL) dropwise through a dropping funnel while maintaining the temperature of the bath at 0 °C. The reaction mixture was allowed to stir at 0 °C[17] until the completion of the reaction (usually 1–2 h) while monitoring the reaction by TLC [hexane/chloroform (1:1)]. Soon after the completion of the reaction the reaction mixture was poured into ice-cold water and extracted with ether. The ethereal extract was washed twice with water (100 mL) and dried over anhydrous sodium sulfate. Evaporation of ethereal layer gave practically pure phosphine

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(16) SO_3 used was commercial "Stabilized SO_3". All operations with SO_3 were performed in a well-ventilated fume hood with extreme precautions.

(17) In case of arylphosphines, the reaction mixture was allowed to warm to room temperature.

oxides in quantitative yields (Table I).

General Procedure for Oxidation of Phosphines and Arsines with Sulfuryl Chloride Fluoride. A slight excess of sulfuryl chloride fluoride (11 mmol) is added to a stirred solution of the phosphine or arsine (10 mmol) in dichloromethane (25 mL) at room temperature. The reaction mixture was stirred for 1 h, and then it was quenched with 10% aqueous sodium bicarbonate solution (25 mL) and extracted with dichloromethane (2 × 20 mL). The organic extract was dried over anhydrous sodium sulfate and the solvent evaporated. The crude products were purified by crystallization.

Acknowledgment. Support of our work by the National Institutes of Health and the National Science Foundation is gratefully acknowledged.

Registry No. **1a**, 603-35-0; **1b**, 1038-95-5; **1c**, 6224-63-1; **1d**, 6163-58-2; **1e**, 1159-54-2; **1f**, 4731-53-7; **1g**, 998-40-3; **1h**, 1486-28-8; **1i**, 603-32-7; **2a**, 791-28-6; **2b**, 797-70-6; **2c**, 6151-88-8; **2d**, 6163-63-9; **2e**, 4576-56-1; **2f**, 78-50-2; **2g**, 814-29-9; **2h**, 2129-89-7; **2i**, 1153-05-5; SO_3, 7446-11-9; $ClSO_2F$, 13637-84-8.

Electrochemistry of Cyclopentadienones

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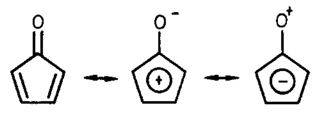
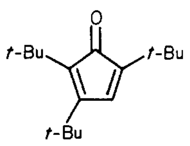
Although electrochemical techniques have been used occasionally for the demonstration of interesting properties of molecules (for example, in Breslow's classic demonstration of the relative antiaromaticity of cyclobutadiene derivatives[1]), there has evolved only little general appreciation of the power of cyclic voltammetry for the solution of problems in physical organic chemistry. We report in this note an electrochemical study of some cyclopentadienone derivatives that demonstrates how a simple electrochemical experiment can provide a rapid characterization of the molecular orbitals relevant to the chemical behavior of these compounds.

The extent of delocalization in annulenones is an important test for theories of aromaticity. Whether [5]-annulenone, cyclopentadienone 1, behaves as a normal enone or as a significantly polarized species (as in resonance contributor **1a**, where normal carbonyl polarization generates a potentially antiaromatic cyclopentadienyl cation, or as in contributor **1b**, where a cyclopentadienyl anionic delocalized systems ensues) is a question of theoretical interest.



1 1a 1b



2

Although electrochemical characterization of 1 would provide valuable information regarding the energies of the relevant frontier orbitals, the well-established proclivity of the parent cyclopentadienone to dimerization[2,3a] precludes its direct study. Alkylation with bulky substituents provides a steric barrier to such cycloaddition reactions, however, and permits study of the monomeric derivatives. We report here our investigation of the redox potentials of 2,3,5-tri-*tert*-butylcyclopentadienone (2)[3b] and several of its simple derivatives.[3c] In this series, we find an irreversible oxidation (E_{pa} = +1.68 V vs. SCE for 2) and two quasi-reversible one-electron reductions (−1.48 and −2.41 V vs. SCE for 2), the first of which occurs at a potential much less negative than one would expect from localized models (Figure 1).[4]

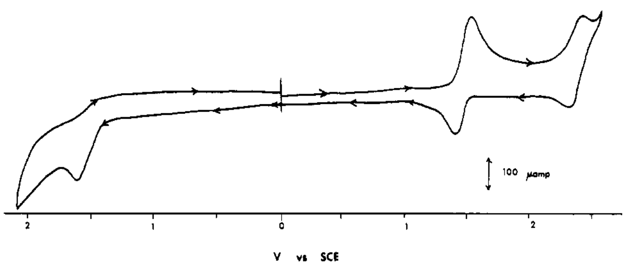


Figure 1. Cyclic voltammogram of 2: 5×10^{-3} M in acetonitrile containing 0.1 M tetrabutylammonium perchlorate; room temperature; scan rate 500 mV/s; glassy carbon working electrode; platinum coil counterelectrode.

Some information about the molecular orbitals of substituted cyclopentadienones is available. For example, Garbisch and co-workers had earlier studied the absorption spectra, and hence the HOMO–LUMO gaps, of alkylated derivatives of 1.[5] In a more definitive study, Schweig, Maier, and co-workers found photoelectron spectroscopic evidence for a strong inductive effect of the carbonyl group (which is probably partially compensated by the effect of the alkyl groups) on the lowest energy ionization ($\pi(a_2)$ MO with a node along the C=O bond).[6] Since cyclic voltammetry can, in principle, provide valuable information regarding the energies of both the HOMO and LUMO, we wished to compare the electrochemical descriptions of these orbitals with those obtained by these other techniques. It is clear, however, from both absorption data and from ionization potentials, that substituent effects must be quantitatively examined before conclusions can be made regarding the energy of the LUMO of 1.

The reduction potentials of compound 2 and some related model systems are listed in Table I.

These values allow for an evaluation of the LUMO energy of 1, a value not previously available for this family of compounds. The quasi-reversible reduction of 2 occurs at potentials much less negative than might be expected from model compounds. We can estimate a reasonable value for a localized (resonance contributor 1) model for the electronic properties of 1 in the following way. To a first approximation, a localized 1 might be expected to exhibit redox behavior analogous to that observed in a

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[†] Department of Chemistry.

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