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Reaction of Organo-Group 5A Compounds with *tert*-Butyl Hydroperoxide

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The rapid reduction of hydroperoxides by trivalent phosphorus compounds (eq 1) provides a useful qualitative[1] and quantitative[2] analytical tool. Yet little is known about the kinetics of this reaction. The early observation that the reduction occurs "essentially instantaneously" at −40 °C[3] has more recently been quantitated for some phosphites[4] and for triphenylphosphine.[5] But rate data are available only for those compounds which react slowly enough to permit quenching of aliquots and titration of unreacted peroxide[4] or for compounds which contain chromophores to provide for analysis by UV spectroscopy.[5]

$$\mathrm{ROOH} + \mathrm{R_3'P} \rightarrow \mathrm{ROH} + \mathrm{R_3'P{=}O} \qquad (1)$$

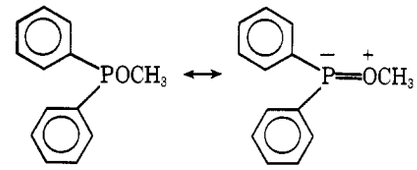
To circumvent these restrictions, we have used an in situ polarographic technique which allows the ready determination of the kinetics of hydroperoxide reactions with second-order rate constants ranging from 0.005 to >10 M^{-1} s^{-1}. This convenient kinetic technique has been used to study the reaction of *tert*-butyl hydroperoxide with a cross section of trivalent organo-group 5A compounds. We report herein our results in this area, including the first rate study of the trialkylphosphine–hydroperoxide reaction.

Results and Discussion

Polarography can be used to follow chemical reactions from the change of limiting currents with time as long as one component of the reaction mixture is electroactive.[6] Hydroperoxides possess such an electroactive handle.[7] We have found that the chemical reactivity of hydroperoxides with organo-group 5A compounds is sufficiently high that the electrochemical reaction at the dropping mercury electrode does not significantly perturb the concentration of the reactants. Thus, a chemical reaction and its electrochemical analysis can be run in the polarographic cell simultaneously.

As shown in Table I, the reactivity of trivalent phosphorus compounds with *tert*-butyl hydroperoxide decreases as the substituents on phosphorus become increasingly electron withdrawing, i.e., in the order: trialkylphosphines (entries 1 and 2) > triarylphosphines (entries 6–10) > trialkyl phosphites (entries 11–14) > triphenyl phosphite (entry 15). This is as expected, since by far the predominant pathway of the reaction for both phosphites[8] and triphenylphosphine[3,5] is nucleophilically induced cleavage of the peroxide linkage. Approximately one order of magnitude separates the contiguous classes in the above reactivity series.

Diphenylmethoxyphosphine (entry 3) represents an anomaly in the above series in that inductive effects alone do not explain its reactivity toward *tert*-butyl hydroperoxide. Whereas the replacement of a phenyl group of triphenylphosphine by an electron-withdrawing methoxyl would be expected to decrease the oxophilicity of the resulting compound, the opposite effect is observed. A similar observation was made by Denney et al.,[9] who found that in competitive reactions triphenylphosphine and diphenylethoxyphosphine possess approximately equal oxophilicities toward benzoyl peroxide. These results can be attributed to the resonance effect of a methoxyl group more than counterbalancing its inductive effect, thereby enhancing the oxophilicity of phosphorus. Such a process is possible because of the well-known



ability of phosphorus to expand the octet in its outer electron shell. Alternatively, the increased reactivity of phosphinite esters may be a manifestation of the α effect.[10] In any case, replacing a second phenyl group in triphenylphosphine by methoxyl causes a balancing of inductive and resonance/α effects, so that dimethoxyphenylphosphine (entry 5) is essentially equal to triphenylphosphine in oxophilicity.

Our results with trialkyl phosphites (entries 11–14) show the expected[11] dependence of oxophilicity on inductive effects (e.g., triethyl phosphite > trimethyl phosphite) as long as steric factors do not interfere. However, triisopropyl (entry 13) and tri-2-ethylhexyl (entry 14) phosphites react with *tert*-butyl hydroperoxide more slowly than would be predicted by inductive effects alone, which suggests that steric factors do play a part in this reaction. Interestingly, the relative reactivity of trimethyl and triethyl phosphites toward *tert*-butyl hydroperoxide (0.65) is the same as that toward singlet oxygen.[12]

A Hammett plot (Figure 1) for para-substituted triarylphosphines (entries 6–10) shows a reasonable correlation of rate with σ constants (r = 0.967). Using the Yukawa–Tsuno[13] treatment to blend fractional amounts of σ^+ into the relationship does not improve the straight-line fit. This is consistent with the hypothesis[5] that little positive charge is present on phosphorus in the transition state of the phosphine–hydroperoxide reaction. However, the lack of σ^+ con-

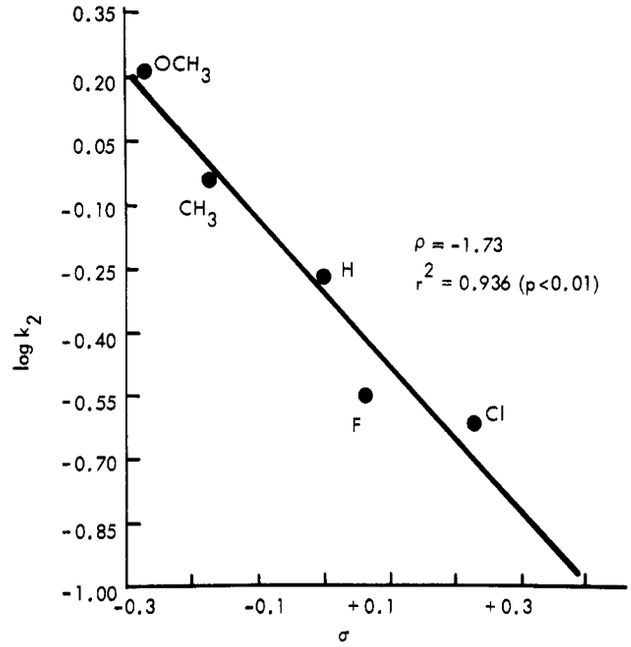


Figure 1. Relationship between Hammett σ and log k_2 for the reaction of triarylphosphines with *tert*-butyl hydroperoxide.

Table I. Reaction of *tert*-Butyl Hydroperoxide with Trivalent Organo–Group 5 Compounds[a]

Registry no.	Entry	Hydroperoxide decomposer	10^3 [decomposer]$_0$, M	10^3 [*t*-BuOOH]$_0$, M	10^2k_2,[b] M^{-1} s^{-1}
		R_3P			
554-70-1	1	R = CH_3CH_2	0.778	0.388	585
998-40-3	2	R = $CH_3CH_2CH_2CH_2$	1.024	0.188	620
		$(C_6H_5)_2PR$			
4020-99-9	3	R = CH_3O	2.47	0.369	128
5525-95-1	4	R = C_6F_5	40.9	9.26	2.53
2946-61-4	5	$C_6H_5P(OCH_3)_2$	9.65	4.87	43.6
		$(p\text{-}XC_6H_4)_3P$			
855-38-9	6	X = CH_3O	2.04	0.995	163
1038-95-5	7	X = CH_3	9.99	2.00	91.0
603-35-0	8	X = H	19.2	9.25	53.7
18437-78-0	9	X = F	5.10	2.51	28.1
1159-54-2	10	X = Cl	16.0	7.41	23.9
		$(RO)_3P$			
121-45-9	11	R = CH_3	51.7	9.50	6.64
122-52-1	12	R = CH_3CH_2	49.5	9.60	10.2
116-17-6	13	R = $(CH_3)_2CH$	51.4	9.73	7.90
301-13-3	14	R = $CH_3(CH_2)_3CH(C_2H_5)CH_2$	31.5	6.09	5.88
101-02-0	15	R = C_6H_5	105.7	9.22	0.66
		R_3As			
617-75-4	16	R = CH_3CH_2	26.8	4.89	24.0
603-32-7	17	R = C_6H_5	104.8	9.70	0.97
603-36-1	18	$(C_6H_5)_3Sb$	5.11	1.01	43.0

[a] At 25.0 ± 0.1 °C in 1:1 methanol–benzene containing 0.3 M LiCl. [b] All rates are averages of at least two runs; reactions exhibited excellent second-order kinetics over at least 3 half-lives.

tribution may simply reflect a lack of significant bonding effects between the π-electron cloud of aromatic rings and the empty 3d orbitals of phosphorus.[14]

For the series of Ph_3M compounds (M = P, As, Sb), we have observed that the reactivity with *tert*-butyl hydroperoxide decreases in the order triphenylphosphine (entry 8) ≥ triphenylstibine (entry 18) > triphenylarsine (entry 17). During the course of our work, Hiatt et al.[15] published similar rate constants for this series and also noted the anomaly of triphenylstibine reactivity. If one considers the reaction with *tert*-butyl hydroperoxide as a series of nucleophilic attacks on a soft electrophile, the antimony derivative is out of line, i.e., the reactivity order should be P > As > Sb. The same order is predicted from a consideration of heteroatom-to-oxygen bond strengths. Hiatt attributes the anomaly of triphenylstibine reactivity to increased availability of d orbitals in this compound for π bonding with peroxidic oxygen.[16]

Our results can neither confirm nor deny Hiatt's argument. We have noted, however, that during the reaction of triphenylstibine with *tert*-butyl hydroperoxide a new electroactive species is produced ($E_{1/2}$ = −1.65 V). While this wave could simply correspond to the reduction of the Sb–O bond of triphenylstibine oxide, it is also consistent with a peroxidic linkage in the product. Indeed, the polymeric triphenylstibine oxide prepared by the oxidation of triphenylstibine with hydrogen peroxide produces free iodine from potassium iodide in glacial acetic acid,[17] even though the material is free of hydrogen peroxide.[18] If triphenylstibine oxide contains a peroxidic bond, then the anomaly of triphenylstibine reactivity could indicate a dichotomy of mechanism in the reaction of Ph_3M compounds with *tert*-butyl hydroperoxide. Elucidation of this point awaits further work.

Experimental Section

Materials and Instrumentation. *tert*-Butyl hydroperoxide (MC/B Manufacturing Chemists), 83% pure by iodometric titration, was used without purification. Stock solutions (ca. 5×10^{-2} M) were prepared in electrolyte solution (vide infra), aliquots of which were used in kinetic runs. All hydroperoxide decomposers were used as received from commercial suppliers (Strem Chemicals, Alfa Products, Aldrich Chemical Co., MC/B), except as follows: triphenylphosphine (mp 80.5 °C) and tris(*p*-methoxyphenyl)phosphine (mp 130.5–131.5 °C) were recrystallized from ethanol–water; tributylphosphine (bp 124.5 °C (12 mm)), trimethyl phosphite (bp 110.5 °C (760 mm)), triisopropyl phosphite (bp 76 °C (14 mm)), tri-2-ethylhexyl phosphite (bp 154 °C (0.5 mm)), and triphenyl phosphite (bp 152 °C (0.5 mm)) were distilled under an inert atmosphere.

Polarograms were run on a Sargent Model 21 polarograph at 25.0 ± 0.1 °C, using a standard calomel electrode as reference. The electrolyte solution for all runs was 0.3 M lithium chloride in 1:1 (v/v) benzene–methanol containing 0.001% triton X-100 to suppress maxima. A three-compartment cell was used: a reaction (test) cell, a reference cell, and a cell containing a saturated aqueous solution of potassium chloride separating the two. Appropriate control experiments established that, for *tert*-butyl hydroperoxide, diffusion current varied linearly with concentration from 10^{-2} to 10^{-5} M.

Method. Five milliliters of a known concentration of *tert*-butyl hydroperoxide (10^{-2} to 10^{-4} M) in deaerated electrolyte solution was placed into the test cell, which was thermostated at 25.0 ± 0.1 °C. The solution was purged with nitrogen (saturated with benzene–methanol) for 5 min, the dropping mercury electrode was put into place, and the polarogram of the hydroperoxide was recorded from −0.1 to −2.1 V, operating under nitrogen. A half-wave potential of −1.15 V was observed for the hydroperoxide. The polarograph was then switched to constant voltage operation, the voltage (generally −1.5 to −1.7 V) being chosen so as to allow recording of the limiting current. A concentrated solution of the hydroperoxide decomposer was then added to the test cell by microliter syringe, nitrogen was bubbled through the solution for 5 s to provide mixing, and the recorder was started. Hydroperoxide decomposition (as measured by decreasing limiting current) was followed under a nitrogen blanket for at least 3 half-lives, and an infinity point was measured after 10 half-lives by recording a complete polarogram from −0.1 to −2.1 V. Since the frit which separated the test and the potassium chloride cells became clogged by mercury after 50 min of operation, slow reactions were followed by direct recording for only 20–30 min. The dropping mercury electrode was then removed. Subsequent points were measured by repositioning the electrode, recording the diffusion current, and again removing the dropping mercury electrode from the cell.

Rate constants were calculated from rate data using the integrated forms of the second-order rate laws. In all cases, plots of $(b - a)^{-1} \ln (b - x/a - x)$ vs. time were linear throughout the reaction (at least 3 half-lives). No deviations from second-order kinetics were observed.

Acknowledgment. The author thanks William F. Boller for invaluable technical assistance.

Registry No.—*tert*-Butyl hydroperoxide, 75-91-2.

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Synthesis of Substituted β-Lactams by Addition of Nitromethane to 6-Oxopenicillanates and 7-Oxocephalosporanates[1]

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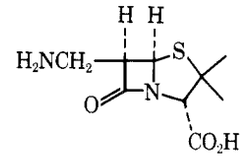
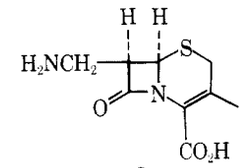
As part of our program of investigation of modified β-lactams we decided to explore the synthesis of 6-aminomethylpenicillin (**1**) and 7-aminomethyldeacetoxycephalosporin (**2**). These compounds represent an interesting hypothetical basis for the preparation of a family of homologous penicillins and cephalosporins.

Our synthetic plan was conditioned by the requirement that we needed to have starting materials which could be prepared in gram quantities and in relatively few steps. In a manner consistent with these objectives, we chose a scheme which utilized 6-oxopenicillanate **3** since it was known to undergo ready reaction with nucleophiles[3-6] and it was conveniently available from 6-hydroxypenicillanate **4**.[7]

The preparation of 6-oxopenicillanate **3** was not as straightforward as one was led to believe from literature reports. Sheehan's original report of the synthesis of **3** by the Pfitzner–Moffatt oxidation of **4** did not include a mention of the yield.[3] Vanderhaeghe[8] has published experimental details of a comparison of oxidative methods which have been applied to the synthesis of **3**. He found that oxidation with Me_2SO–acetic anhydride gave **3** in 92% yield, whereas the Pfitzner–Moffatt oxidation using as catalyst either orthophosphoric acid or pyridinium trifluoroacetate afforded **3** in only 50% yield. Our initial attempts at reproducing the Me_2SO–acetic anhydride oxidation of **4** were rewarded with the preparation of the trivial benzyl 6α-acetoxypenicillanate. We did manage to reproduce the literature report[8] by using acetic anhydride which had been purified by distillation from either aluminum chloride or calcium carbide.[9] We also found that the Pfitzner–Moffatt oxidation of **4** using dichloroacetic acid[10] gave **3** in 78–83% yield. Our attempts at converting **4** to **3** using *N*-chlorosuccinimide–dimethyl sulfide,[11] Jones reagent,[12] or silver carbonate on Celite[13] all met with failure.



1



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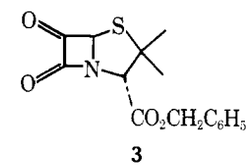

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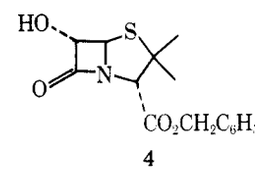

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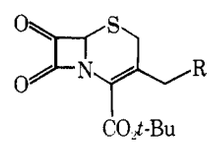
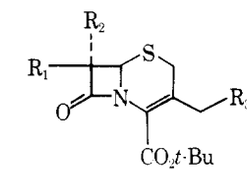
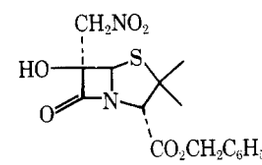


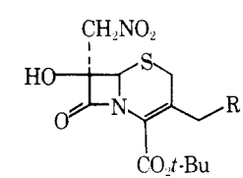
5, R = H
9, R = OAc



6, $R_1 = R_3 = H$, $R_2 = OH$
7, $R_1 = OH$, $R_2 = R_3 = H$
8, $R_1 = NH_2$, $R_2 = R_3 = H$
10, $R_1 = H$, $R_2 = OH$, $R_3 = OAc$
11, $R_1 = OH$, $R_2 = H$, $R_3 = OAc$



12



13, R = H
14, R = OAc

The route to the deacetoxycephalosporin **2** utilized the 7-oxo-3-deacetoxycephalosporanate **5**, which was prepared by the oxidation of the epimer mixture **6**:**7**. The alcohols **6**:**7** (3:1) were prepared in 37% yield by treatment of amine **8**[14] with nitrous acid. We were unable to find satisfactory conditions for the oxidation of **6**:**7** using either Me_2SO–acetic anhydride[8] or Me_2SO–trifluoroacetic anhydride.[15] Oxidation of **6**:**7** with Me_2SO–dicyclohexylcarbodiimide–dichloroacetic acid proceeded smoothly to give **5** in 70% yield.

The 7-oxocephalosporanate **9** was prepared by Me_2SO–dicyclohexylcarbodiimide oxidation of the epimer mixture **10**:**11**. In this instance the Pfitzner–Moffatt oxidation was not as clean as with **6**:**7**.

The scheme chosen for the conversion of the keto compounds into the aminomethyl compounds involved the addition of nitromethane, followed by elimination of water and reduction. Reaction of the keto compounds **3**, **5**, and **9** with nitromethane and potassium *tert*-butoxide in THF at 0 °C gave the α-nitromethyl compounds **12** (51%), **13** (39%), and **14** (21%).[16] The assignment of stereochemistry in **12**–**14** is based on the known course of nucleophilic addition in this series.[3-6] Compounds **12** and **13** were converted into nitroolefins **15** (47%) and **16** (55%) by reaction with mesyl chloride–triethylamine in CH_2Cl_2 at −40 °C. Catalytic hydrogenation using tris(triphenylphosphine)rhodium chloride[17] afforded the reduced compounds **17** (64%), **18** (11%), and **19** (46%). Compounds **18** and **19** were also obtained by $NaBH_4$