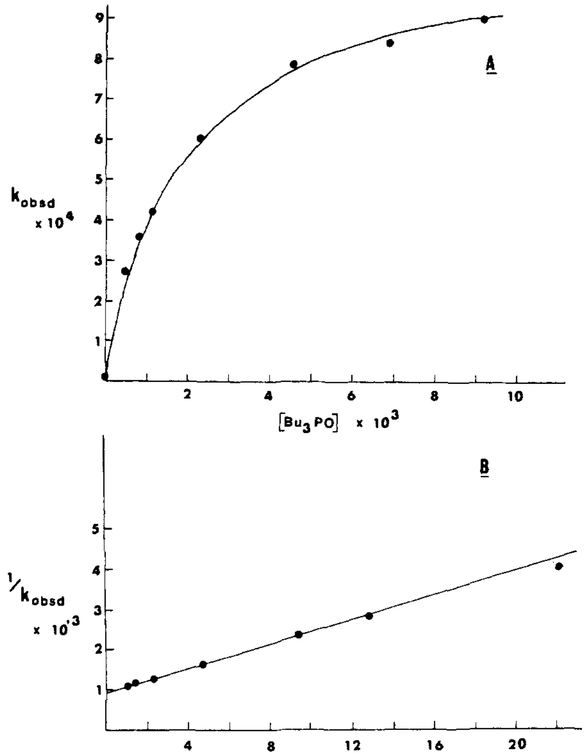

Figure 3. (A) Observed rate constant vs. $[(n\text{-}C_4H_9)_3PO]$ for the reaction of $Mo(CO)_5NHC_5H_{10}$ with $(C_6H_5)_3P$ in the presence of $(n\text{-}C_4H_9)_3PO$. (B) Reciprocal plot for the reaction of $Mo(CO)_5NHC_5H_{10}$ with $(C_6H_5)_3P$ in the presence of $(n\text{-}C_4H_9)_3PO$ (intercept equals $1/k_3$ and slope equals $1/k_3K_{eq}$).

$R''_3P{=}O$ making this fairly unlikely. In any case this would not affect the kinetic analysis given here.[9] For tertiary amines where no hydrogen-bonding can occur or for substitution reactions in the absence of hydrogen-bonding ligands or solvents, the rate law follows the familiar form,[10]

$$\text{rate} = (k_1 + k_2[PR_3])[M(CO)_5(\text{amine})]$$

In the presence of hydrogen-bonding ligands or solvents the substitution product $M(CO)_5PR_3$ is obtained in 100% yield which results from the rapid equilibrium (K_{eq}) followed by the rate-determining k_3 term, i.e., rate = $k_3[M(CO)_5R'_2NH{:}OPR''_3]$. For reactions proceeding through the hydrogen-bonded intermediate the observed rate constants obey the expressions

$$k_{obsd} = \frac{k_3K_{eq}[OPR''_3]}{1 + K_{eq}[OPR''_3]}$$

or

$$\frac{1}{k_{obsd}} = \frac{1}{K_{eq}k_3[OPR''_3]} + \frac{1}{k_3}$$

as illustrated in Figure 3 for the reaction of $Mo(CO)_5NHC_5H_{10}$ with $(C_6H_5)_3P$ in the presence of $(n\text{-}C_4H_9)_3P{=}O$.[11,12] The equilibrium constant, K_{eq}, for this reaction was found to be 600 M^{-1} at 34.5°. Spectroscopic determination of K_{eq} for the reaction between $Mo(CO)_5NHC_5H_{10}$ and $(n\text{-}C_4H_9)_3P{=}O$ was in good agreement with that found by kinetic analysis.

This and related systems provide excellent opportunities to carefully investigate the heat of formation of $M\text{-}NR_2\text{-}H\cdots OPR'_3$ bonds since K_{eq} for adduct formation (which is measured kinetically) can be obtained quite accurately as a function of temperature. Work along these lines is in progress in our laboratory.

Acknowledgment. We thank the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research. We also thank the Research Corporation for a grant used to purchase the Perkin-Elmer 521 infrared spectrophotometer used in this study.

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(5) This ν(CO) shift has also been observed upon addition of $(n\text{-}C_4H_9)_3P$, $(c\text{-}C_6H_{11})_3P$, and $(CH_3O)_3P$ to $Mo(CO)_5NHC_5H_{10}$. However, in these phosphorus ligands it is extremely difficult to eliminate trace quantities of the corresponding oxide species which have been shown to be good hydrogen-bonding ligands. We therefore feel that in these cases the observed shifts are primarily due to the ubiquitous impurities, phosphine oxides, in these phosphorus ligands. This has been verified for the reaction of $Mo(CO)_5NHC_5H_{10}$ with $(n\text{-}C_4H_9)_3P$.
(6) The ratio, ν(NH)ν(ND), as calculated by the Teller–Redlich product rule is 1.369.
(7) Since the two species are related via a rapid equilibrium step, monitoring the disappearance of $M(CO)_5NHR_2$ or $M(CO)_5NHR_2{\cdot}PR'_3$ yields the same rate constant.
(8) Similar rate data were observed for the reaction of $(n\text{-}C_4H_9)_3P$ with $Mo(CO)_5NHC_5H_{10}$ in the presence of $(n\text{-}C_4H_9)_3P{=}O$.
(9) There is ir spectral evidence that some $M(CO)_5(R''_3PO)$ forms in solutions where no PR_3 is added. However, these species are very unstable and therefore difficult to isolate and characterize.
(10) It should be noted that specific interactions of the type discussed in this communication account for the large deviation in the extrapolated k_1 value for $(n\text{-}C_4H_9)_3P$ substitution reactions of $W(CO)_5$(amine) derivative,[2] as well as some of the solvent effects previously reported.[4] We have also observed similar kinetic and spectral behavior to that reported here for the reaction of $Mo(CO)_5NHC_5H_{10}$ with $(C_6H_5)_3P$ in hexane where small quantities of the hydrogen-bonding solvent, THF, has been added.
(11) It has been brought to our attention by a reviewer that the reaction could be proceeding through the normal rate law, rate = $(k_1 + k_2[PR_3])[M(CO)_5(\text{amine})]$, with the hydrogen-bonded adduct being an inert species and not on the reaction coordinate. Kinetically similar behavior would be expected.[12] This should not, however, be the case here since the rates of substitution are much faster than that anticipated on the basis of the normal rate law. In addition, the effect of prior adduct formation on substitution reactions of tungsten is significantly less than that observed for the molybdenum analogue (enhanced by <10 as opposed to 100) which reflects a reduction in steric crowding in the case of tungsten. On the other hand, we would expect an enhanced effect in going from molybdenum to tungsten via the normal mechanism.
(12) See, for example, J. Halpern, *J. Chem. Educ.*, **45**, 372 (1968), and references therein.

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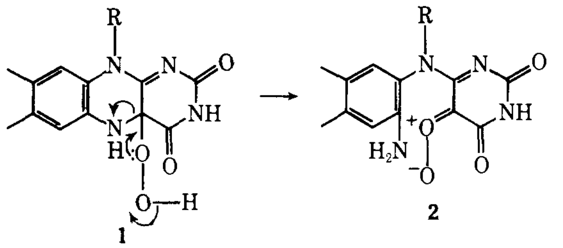
Received May 16, 1975

The Epoxidation of Alkenes and the Hydroxylation of Phenols by an Intermediate in the Reaction of Ozone with Alkynes. Possible Model Reactions for Some Flavin-Containing Monooxygenases[1]

Sir:

Although it is now widely believed that the oxygen atom transfer or oxenoid mechanism[2] is involved in many monooxygenase-catalyzed reactions,[3-8] the structures of the various oxenoid reagents have not been elucidated. Recently one of us proposed[4-6] that the oxenoid reagent in flavoenzyme-catalyzed hydroxylations of phenols is a flavin-derived α-carbonyl carbonyl oxide (or vinylogous ozone), **2**, formed from a flavin hydroperoxide, **1**, as shown in eq 1. By comparison[4-6] with known chemical reactions, including oxidations performed by some unsubstituted carbonyl oxides,[25] it appeared that compounds like **2** should be capable of transferring oxygen atoms to various acceptors but direct evidence for this was not available. In this communication we report experimental results indicating that α-carbonyl carbonyl oxides, probably in their cyclized trioxide form, are potent oxenoid reagents.

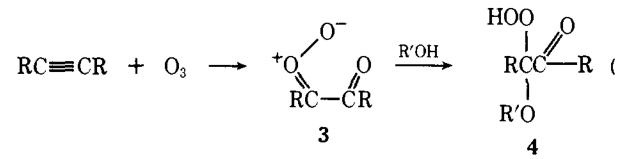


(1)

1

2

The ozonation of alkynes frequently yields a complex product mixture[9-11] but considerable evidence indicates that at least part of the reaction proceeds through **3** (eq 2). For example, compounds of structure **4** are formed when the ozonation is carried out in the presence of alcohols or acids. This prompted us to investigate the possibility that intermediates in the ozonation of alkynes might possess oxenoid properties. The alkene epoxidation results reported in this communication were obtained using the following protocol: (1) to a 0.02 *M* (1 equiv) solution of alkyne (2-butyne usually but other alkynes give similar results) in CH_2Cl_2 at −70° was added over a period of 10–15 min ca. 0.8 equiv of O_3 in a 5% O_3/O_2 stream, (2) the −70° solution was then flushed with N_2 for 2–3 min, (3) alkene (final concentration 0.2 *M*) was added at −70°, (4) after about 1 min, excess diethyl sulfide or $NaBH_4$ was added at −70°, (5) the solution was warmed to room temperature and analyzed for epoxides by standard gas chromatographic methods. With a variety of alkene reactants, epoxide yields of 10–12% (based on the amount of alkyne which reacts) are obtained. Epoxides are the only significant products formed from the alkenes; no ketones or alcohols are observed. Control experiments showed that flushing with N_2 (step 2) for longer (up to 30 min) times had no effect on the results. Other controls showed that no epoxide is formed if alkyne is omitted from the above protocol or if alkene is present during the addition of O_3 (in the presence or absence of alkyne). Thus, the formation of epoxides cannot be due to dissolved O_3 but is completely dependent on the prior reaction of O_3 with the alkyne. If step 4 of the above protocol is omitted, up to a 35% yield of epoxide is obtained. Various trapping experiments[11] indicate that the additional epoxide is formed during warm-up and is caused by other oxidants (one being peroxy acid) formed during the ozonation of alkynes. These oxidants do not epoxidize alkenes at temperatures below −30° and are removed by the diethyl sulfide or $NaBH_4$ treatment.



(2)

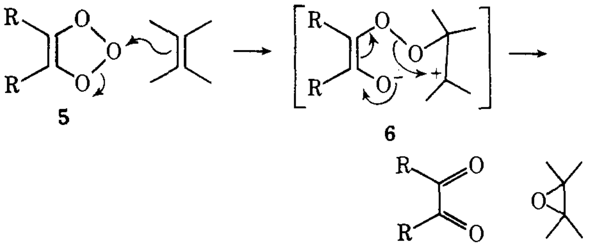
3

4

From competition experiments the relative reactivities of several alkenes for the 2-butyne plus O_3 oxidant at −70° were found to be: cyclohexene, 1.0; 1-octene, 0.026; methylenecyclohexane, 0.4; 1-methylcyclohexene, 3.8; *cis*-3-hexene, 0.51; and *trans*-3-hexene, 0.05. The effects of increased alkyl substitution on the double bond are similar to those observed in peroxy acid epoxidations,[12] and thus indicate an electrophilic mechanism for the epoxidation step. However, the 10–20-fold greater reactivity of cis alkenes relative to trans alkenes is in marked contrast to that observed in peroxy acid epoxidations in which the difference is usually less than 30%. The result implies a large steric requirement for the alkyne plus ozone epoxidation. Epoxidations by the 2-butyne plus O_3 oxidant at −70° are almost, but not completely stereospecific. Thus, *cis*-3-hexene gives a mixture consisting of 95% *cis*- and 5% *trans*-epoxide, and *trans*-3-hexene gives a mixture of 1% *cis*- and 99% *trans*-epoxide.

In direct analogy to the enzymic phenol hydroxylations, the 2-butyne plus O_3 oxidant at −70° to −50° converts 4-*tert*-butylphenol to 4-*tert*-butylcatechol[13] in 4% yield.[15] These experiments were performed in the same way as the alkene epoxidations except that the phenol (0.02 *M*) replaced alkene in step 3 and was allowed to react for 20 min at −70° to −50° before the addition of $NaBH_4$ (step 4). The lower yields observed, and the longer reaction times required, are presumably due to the decreased reactivity of the phenol relative to an alkene.

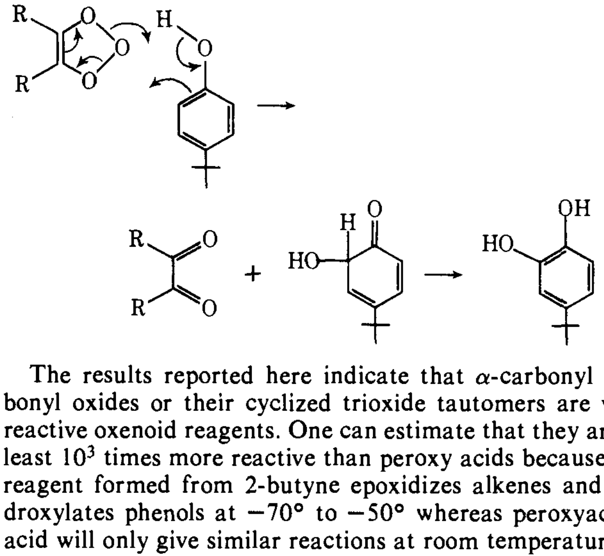
Some information relevant to the structure of the −70° oxidant is the following: (1) lower yields of epoxide are formed if the usual protocol is followed but with increasing amounts of methanol in the solvent (presumably the methanol traps the oxidant as shown in eq 2), (2) treatment of the oxidant with diethyl sulfide converts it to 2,3-butanedione, (3) in the absence of an oxygen atom acceptor the oxidant is relatively stable in CH_2Cl_2 at −70° but decomposes (determined by loss of alkene epoxidizing activity) in minutes at −50° to unidentified products. All of these and other[11] results are consistent with the oxidant being **3** or more probably its cyclized trioxide tautomer **5**.[26] Bond energy considerations[16] indicate that **5** is probably slightly favored thermodynamically, and the stability of the oxidant in CH_2Cl_2 at −70° favors **5** (**3** would be expected to dimerize). In any event **3** is probably an intermediate in many of the reactions of **5**. Mechanisms for the epoxidation and phenol hydroxylation with **5** as the oxidant are shown in eq 3 and 4; if **3** is the oxidant very similar mechanisms would apply. The lack of complete stereochemical retention indicates that the epoxidation is not concerted. With **6** as an intermediate some equilibration would result.[17] The conversion of the phenol to the dienone may or may not be concerted as shown in eq 4, and may involve an arene oxide[8] intermediate.



5

6

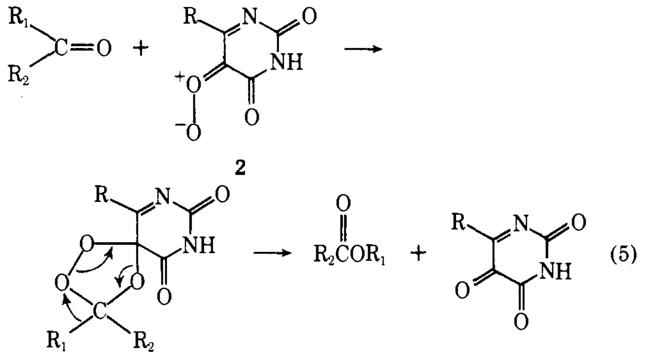
(3)



(4)

The results reported here indicate that α-carbonyl carbonyl oxides or their cyclized trioxide tautomers are very reactive oxenoid reagents. One can estimate that they are at least 10^3 times more reactive than peroxy acids because the reagent formed from 2-butyne epoxidizes alkenes and hydroxylates phenols at −70° to −50° whereas peroxyacetic acid will only give similar reactions at room temperature or above. Thus, the suggestion that **2** or its cyclized tautomer is the oxenoid reagent in the enzymic phenol hydroxylations[4-6] seems reasonable.[18,19] Recently Ono and Bloch[20] reported evidence that squalene epoxidase is also a flavoenzyme. The present results thus indicate that the same intermediate is a reasonable possibility for the oxenoid reagent in biological epoxidations as well.

Two other types of flavin-containing monooxygenase reactions which can readily be rationalized if **2** is the oxidant are: (1) the conversion of a ketone to a lactone or ester (for example, camphor to camphor lactone[21]), and (2) the conversion of an aldehyde to an acid in a bioluminescent reaction.[22] It is suggested here that each of these proceeds through the intermediacy of an ozonide formed from the aldehyde or ketone reactant and the carbonyl oxide **2** (eq 5).



A rearrangement as shown would give the observed products; numerous chemical analogies[9,23] (including a very close analogy for the camphor conversion[24]) to these reactions can be found in the ozonide literature. In the bioluminescent reaction, one of the products, presumably the flavin fragment, would have to be formed in an electronically excited state. There is sufficient energy in the ozonide intermediate for this to occur, but the details of how the energy might be channeled into an excited state must await further study.

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(13) The catechol product was analyzed by gas chromatography after conversion to the dimethyl ether as previously described.[14]
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(15) The *direct* reaction of ozone with phenol gives some catechol but in the usual protocol this is not occurring because all the *free* ozone is removed by the N_2 flush (step 2).
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(17) The difference in the reactivities of the cis and trans alkenes is presumably because **5** must approach in a plane approximately parallel to the alkene plane but above or below it. With cis alkenes the transition state can thus be reached with no steric interaction between the alkene substituents and **5**, whereas this is not possible with the trans alkenes.
(18) An elaboration[6] of the original suggestion[4] for the enzymic reactions, involving an intermediate α-hydroperoxy ether which undergoes a Cope-type rearrangement to ultimately give the catechol, has recently been shown to be unlikely (R. E. Keay and G. A. Hamilton, *J. Org. Chem.*, **39**, 3604 (1974)).
(19) The recent suggestion (H. W. Orf and D. Dolphin, *Proc. Nat. Acad. Sci. U.S.A.*, **71**, 2646 (1974)), that the oxenoid reagent in flavin-containing monooxygenases is an oxaziridine, is unlikely for the following reasons among others: (1) H_2O_2 is a product of the enzymic reactions when a poor substrate is used, and there is no reasonable mechanism for the formation of H_2O_2 from the proposed oxaziridine reagent, and (2) oxaziridines are well-defined chemical compounds; there is no indication that they will transfer oxygen atoms to alkenes or phenols. The conclusions, derived from molecular orbital calculations by Orf and Dolphin, on the reactivity of the suggested carbonyl oxide intermediate **2** are negated by the present results, but in any event the calculations are irrelevant to the reactivity of the species because they are ground state calculations whereas reactivity depends on differences between ground and transition states.
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(26) Very recent theoretical calculations (W. R. Wadt and W. A. Goddard III, *J. Am. Chem. Soc.*, **97**, 3004 (1975)) indicate that a simple carbonyl oxide may exist primarily in a three-membered ring cyclized form or as a diradical. Whether this is also true for α-carbonyl carbonyl oxides is not clear but in any event mechanisms very similar to those of eq 3 and 4 would still apply.
(27) NIH Special Research Fellow (GM 57203), 1975, in the laboratory of O. Hayaishi, Department of Medical Chemistry, Kyoto University, Kyoto, Japan.

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Macrocycle Synthesis by Repeatable 2,3-Sigmatropic Shifts. Ring-Growing Reactions

Sir:

Multicarbon ring expansion can be achieved by fragmentation of a bicyclic intermediate derived from a monocyclic precursor[1,2] or by central bond cleavage in a bicyclic transition state for thermal,[1,3] photochemical,[4] or solvolytic rearrangement.[5] These reactions could be used to prepare macrocycles from readily available five- or six-membered rings if two or more ring expansions could be performed in succession. However, none of the methods reported previously can be repeated easily because the necessary functionality is lost during the fragmentation or rearrangement step.

We wish to describe an approach to macrocyclic compounds by a series of 2,3-sigmatropic shifts.[6] We refer to this process as a ring-growing sequence to denote an easily repeatable reaction scheme which allows systematic ring enlargement. In the first step, an α-vinyl heterocycle such as **1** is converted into a carbonyl-stabilized ylid **3** (Scheme I). Rearrangement of **3** under the conditions of ylid generation (toluene solution, 90°)[7] gives a mixture of ring expansion products **4** (67%)[8] and **5** (7%).[9,10] On the basis of extensive NMR decoupling studies in the presence of $Eu(fod)_3$, **4** is conclusively shown to be the desired eight-membered ring having a cis double bond ($J_{4,5}$ = 11 Hz) while **5** can only be the corresponding trans isomer ($J_{4,5}$ = 16 Hz).

Wittig reaction of **4** and methylidenetriphenylphosphorane affords a new α-vinyl heterocycle **6** which is ready for further ring expansion. Copper bronze catalyzed decomposition of dimethyl diazomalonate in the presence of **6** at 100° results in a single major product **8**. Spectral and analytical evidence supports the 11-membered ring structure.[11] In particular, the methyl ester and C_3 methylene hydrogens are observed as singlets at room temperature, indicating a large, conformationally flexible ring having no centers of asymmetry.

Interesting conformational questions arise in connection