icant by control experiments. Increasing the *p*-nitrophenol concentration sevenfold did not cause a decrease in observed proton release, nor did the substitution of indole for the substrate. We have previously shown that between pH 6.1 and 6.4 the fraction of α-chymotrypsin in the active conformation is pH independent at 83–84% so that the substrate-induced perturbation of the conformational equilibrium does not lead to pH changes.[6]

This is consistent with case c, and rules out a and b, as previously postulated from indirect evidence.[1] An additional intermediate occurs after the Michaelis complex and does not accumulate.

By analogy with nonenzymatic acyl transfer reactions[7] a reasonable interpretation[1] is that this intermediate is the tetrahedral adduct of Ser-195 with the carboxyl group of the amide. At low pH there is rate-determining formation of the intermediate, as this partitions favorably toward products by an acid-catalyzed route. At high pH its breakdown is rate determining; the intermediate reverts faster to the Michaelis complex than to the acyl–enzyme (see Figure 2).

(6) A. R. Fersht and Y. Requena, *J. Mol. Biol.*, **60**, 279 (1971).

(7) A. R. Fersht, *J. Amer. Chem. Soc.*, **93**, 3504 (1971).

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On the Mechanism of Epoxidation of Olefins by Covalent Peroxides of Molybdenum(VI)

Sir:

Mimoun, de Roch, and Sajus made the important discovery that molybdenum(VI) peroxo compounds such as I stoichiometrically epoxidize olefins under anhydrous conditions in organic solvents.[1a] These workers have also claimed[1b] that peroxo species of molybdenum, tungsten, and vanadium are regenerated *in situ* during epoxidations of olefins using organic hydroperoxides and catalytic quantities of salts of these metals,[2] strongly implicating these peroxo species as the key intermediates in this whole family of oxidation reactions. Mimoun and coworkers[1a] proposed the mechanism shown in Scheme I for reaction of olefins with complex I. We report here several new observations bearing on the mechanism of these unusual epoxidations.

Due to our interest in the mechanism of epoxidation of olefins by oxo transition metal compounds,[3] we felt it was important to exclude alternate mechanisms in which the oxo oxygen of I is transferred to the olefin. Complex I (L = hexamethylphosphoramide (HMPA), L′ = no ligand) was labeled with ^{18}O uniquely in the oxo oxygen by solution in dry methanol and exposure to 70 atom-% ^{18}O-enriched water for 3 hr at room temperature.[4] The ir spectrum of the exchanged substance (Figure 1)[5] clearly indicates approximately statistical incorporation of ^{18}O into the oxo oxygen and no incorporation into the peroxo oxygens.[6] Two reactions of labeled I (L = HMPA, L′ = no ligand) in dry methylene chloride with *trans*-cyclododecene, in mole ratios of

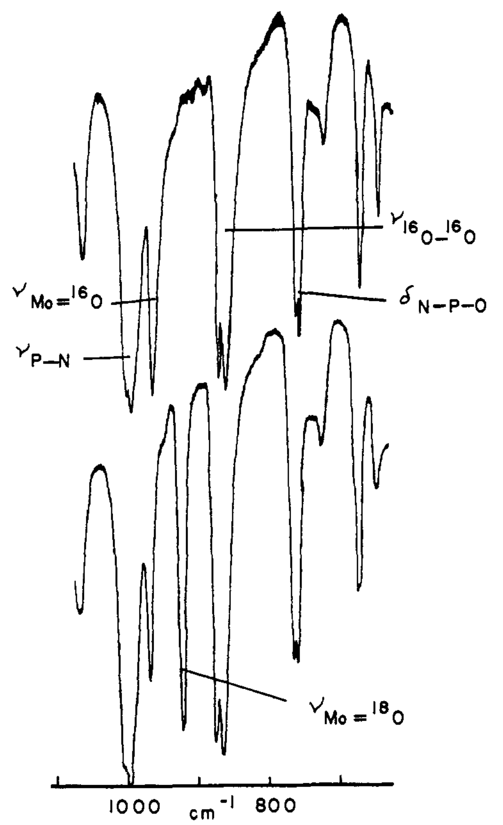
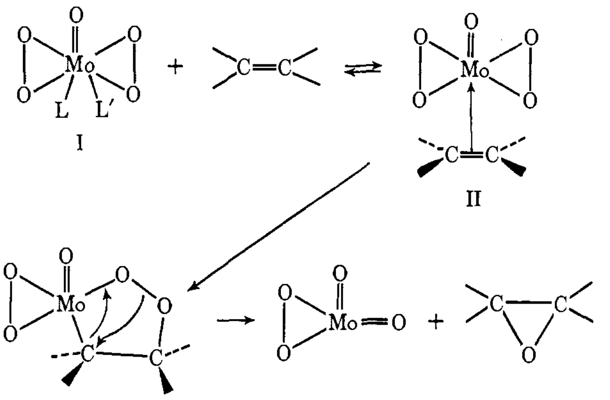


Figure 1. Infrared spectra (Nujol mulls) of $MoO_5 \cdot HMPA, H_2O$ before (upper curve) and after (lower curve) exchange with 70 atom % ^{18}O-enriched water. Assignments follow ref 1c.

Scheme I



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(1) (a) H. Mimoun, I. Seree de Roch, and L. Sajus, *Tetrahedron*, **26**, 37 (1970); (b) H. Mimoun, I. Seree de Roch, L. Sajus, and P. Menguy, French Patent 1549184 (1968); *Chem. Abstr.*, **72**, 3345*p* (1970); H. Mimoun, I. Seree de Roch, and L. Sajus, *Bull. Soc. Chim. Fr.*, 1481 (1969).

(2) For a leading reference to the numerous studies of these metal-catalyzed hydroperoxide oxidations, see G. R. Howe and R. R. Hiatt, *J. Org. Chem.*, **36**, 2493 (1971).

(3) K. B. Sharpless and T. C. Flood, *J. Amer. Chem. Soc.*, **93**, 2316 (1971).

(4) No attempt was made to determine the minimum time required for exchange.

(5) The spectra shown are of the hydrated complex I (L = HMPA, L′ = H_2O). The labeling procedure and the oxygen-transfer reactions were performed with the anhydrous complex obtained by dehydration of I over P_2O_5 *in vacuo*. The spectra of the anhydrous complexes (labeled and unlabeled) are almost identical with the spectra of the corresponding hydrates in the region shown. Based on the assignments provided for the isotopically normal complex, a simple Hooke's law calculation predicts the $\nu_{Mo=^{18}O}$ band to appear at 920 cm^{-1} and $\nu_{^{18}O-O}$ bands to appear in the 810–850-cm^{-1} region.

(6) Molybdenum-catalyzed decomposition of hydrogen peroxide in ^{18}O-enriched water gave only isotopically normal oxygen; unpublished results of H. Taube, Stanford University. For similar results with other metal catalysts, see A. E. Cahill and H. Taube, *J. Amer. Chem. Soc.*, **74**, 2312 (1952).

Table I. Relative Reactivities of Selected Olefins in Reactions with Cyclic Transition States

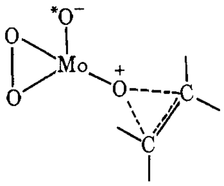
Reagent	Ref	Size of cyclic transition state	Reactivity ratio Norbornene : cyclohexene	Reactivity ratio *trans*-Cyclododecene : *cis*-cyclododecene
$MoO_5 \cdot$HMPA (I)[b]	*a*	?	1.94	0.90
Phenyl azide	*e, f, g*	5	6500	
Picryl azide	*e, f*	5	8000	
Benzonitrile oxide	*g*	5	1800	
Osmium tetroxide[c]	*a*	5	~320	30.5
Osmium tetroxide[d]	*h*	5	72.3	
Chromium(VI)	*i*	3	5.5	
Perlauric acid	*e*	3	1.2	
Peracetic acid[b]	*a*	3		1.63
m-Chloroperbenzoic acid[b]	*a*	3	2.39	1.63

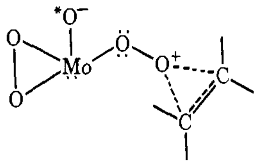
[a] This work. [b] Competitions were run in methylene chloride with mixtures of the appropriate olefin pair. The extent of reaction was always <5%; product ratios were determined by glc analysis. [c] Ether was the solvent. The osmate esters were decomposed by bubbling H_2S through the reaction mixtures and the liberated diols were converted to their corresponding acetonides for glc analysis. [d] Pyridine was the solvent. The relative rate difference between pyridine and ether for norbornene *vs.* cyclohexene suggests that the osmylating reagent is different in these two solvents. This interesting possibility is under further investigation. [e] K. D. Bingham, G. D. Meakins, and G. H. Whitham, *Chem. Commun.*, 445 (1966). [f] A. S. Bailey and J. E. White, *J. Chem. Soc. B*, 819 (1966). [g] R. Huisgen, R. Grashey, and J. Sauer in "The Chemistry of Alkenes," S. Patai, Ed., Interscience, London, 1964, Chapter 11. [h] R. E. Erickson and R. L. Clark, *Tetrahedron Lett.*, 3997 (1969). [i] Reference 10.

1:2 and 1:25, respectively, gave *trans*-cyclodecene oxide which by mass spectral analysis contained no ^{18}O above natural abundance. Similarly, reaction of labeled I with triphenylphosphine (1:1 mole ratio) yielded ^{18}O-free triphenylphosphine oxide.[7] These results prove that the epoxide oxygen arises exclusively from the peroxo ligands of I. Although this finding is in accord with the mechanism in Scheme I, the results of further experiments (Table I) do not favor the key features of this mechanism.

The five-membered peroxo structure III (Scheme I) resembles the intermediate in the 1,3-dipolar addition mechanism for peracid epoxidation proposed by Kwart.[8] Bingham, Meakins, and Whitham[9] offered strong evidence against the five-center reaction for epoxidation by developing a structure–relative rate correlation involving certain cyclic olefins. In particular, these workers observed that the perlauric acid epoxidation of norbornene proceeded only 1.2 times faster than epoxidation of cyclohexene, in distinct contrast to the relative reactivity of these two olefins toward typical 1,3-dipolar reagents (Table I). Roček has also used this correlation to implicate a three- rather than a five-membered cyclic transition state in the oxidation of olefins by chromium(VI).[10] Table I summarizes some of the data upon which this correlation is based, together with our own results relevant to the peroxomolybdenum epoxidation. The final column of Table I contains new data for another pair of olefins, *cis*- and *trans*-cyclododecene, whose relative reactivity in addition reactions also appears to be sensitive to the size of the cyclic transition state involved, although the effect is less pronounced than with the norbornene–cyclohexene pair.[11] The data in Table I reveal that for both pairs of olefins, the reactivity of the molybdenum complex closely parallels that of peracids.

Our new findings suggest that alternative mechanisms involving transfer of one of the peroxo oxygens to the olefin through a three-membered ring transition state should be considered. One can imagine transition states for the transfer ranging between extremes such IV and V (the asterisk in the structure indicates origin from the oxo oxygen of complex I).[12,13] However, the mechanism outlined in Scheme I might fit the new data if formation of the olefin complex II were the rate-determining step.


IV


V

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(7) A control experiment demonstrated that the labeled molybdenum complex used in the oxidation of the olefin and the phosphine could be dissolved in dry methylene chloride and recovered after 3 hr with only minor loss of ^{18}O content.

(8) H. Kwart and D. M. Hofmann, *J. Org. Chem.*, **31**, 419 (1966).

(9) See Table I, footnote *e*.

(10) A. K. Awasthy and J. Roček, *J. Amer. Chem. Soc.*, **91**, 991 (1969); this reference also contains a compilation of the relative rate data in the literature for reagents known to react with olefins through three-, four-, five-, or six-membered cyclic transition states. See also F. Freeman, P. D. McCart, and N. J. Yamachika, *ibid.*, **92**, 4621 (1970).

(11) M. Ohno and S. Torimitsu, *Tetrahedron Lett.*, 2259 (1964). These authors observed the high preference of both OsO_4 and $KMnO_4$ (reagents which add to olefins through a five-membered cyclic transition state) for trans olefins over cis olefins; they provide reasonable explanations for the selectivity.

(12) The arrangement of the molybdenum and the peroxo ligand in V resembles the active epoxidizing agent proposed by Hamilton for iron-based mixed function oxygenases: G. A. Hamilton, *J. Amer. Chem. Soc.*, **86**, 3391 (1964).

(13) Protic catalysis by traces of water or other impurities would permit one to invoke a mechanism analogous to that of epoxidation by peracids. Although this possibility cannot be completely discounted at the present time, we feel it is unlikely for the following reasons. Mimoun, *et al.*,[1a] observed that the presence of 1 equiv or more of water actually retarded the reaction, and we have observed the same effect when dry methanol was used as solvent.