Vanadium-Catalyzed Epoxidation of Cyclic Allylic Alcohols. Stereoselectivity and Stereocontrol Mechanism

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Abstract: The stereochemistry of vanadyl acetylacetonate catalyzed epoxidation of cyclic allylic alcohols with *tert*-butyl hydroperoxide is examined and compared with that of the *m*-chloroperoxybenzoic acid epoxidation. The opposite direction of stereoselectivity is found for medium-ring alcohols. Thus, the cis epoxides are preferentially obtained by the vanadium-catalyzed epoxidation of (*Z*)-cyclooct-2-en-1-ol (**1b**), (1*SR*,2*RS*)-(*E*)-cyclooct-2-en-1-ol (**1g**) (*Z*,*Z*)-2,6-cyclooctadien-1-ol (9), (*Z*,*Z*)-2,4-cyclooctadien-1-ol (**10**), (*E*)- and (*Z*)-cyclonon-2-en-1-ols (**1h, 1e**), and (*E*)-cyclododec-2-en-1-ol (li), whereas mainly the trans epoxides are produced by the peroxy acid epoxidation of them. (1*RS*,2*RS*)-(*E*)-cyclooct-2-en-1-ol (**1f**) is an exception, which on vanadium-catalyzed epoxidation gives the trans epoxide selectively. In the vanadium-catalyzed epoxidation of conformationally biased 5-*tert*-butylcyclohex-2-en-1-ols (**16, 17**), higher cis stereoselectivity is observed for the quasi-axial (**17**) than for the quasi-equatorial one (**16**). In the latter case, the vanadium-catalyzed oxidation of the alcohol function to give the conjugated enone becomes the main reaction pathway. From the results, a transition state geometry model involving a quasi-axial hydroxyl conformation can be proposed for the vanadium-catalyzed stereoselective epoxidation.

Selective epoxidation of olefinic compounds is one of the most important steps in organic synthesis. Organic peroxy acids[2] and hydroperoxide/group 5B or 6B transition metal (e.g., Mo, W, V) catalyst systems[3-5] have been known as the useful reagents for the epoxidation. The epoxidations with these reagents, generally, have characteristics of electrophilic addition of active oxygen to the less hindered side of the double bond. In the epoxidation of allylic alcohols, however, the hydroxyl group at the allylic position to the double bond exerts directing and promoting effects on the epoxidation rather than steric hindrance.[3c,4]

For example, in 1958, Henbest and Wilson[6] found that cyclohex-2-en-1-ol (**1a**) was stereoselectively epoxidized to *cis*-2,3-epoxycyclohexanol (**2a**) by peroxybenzoic acid. They suggested that the transition state might involve a hydrogen bonding between the alcoholic hydroxyl and the peroxy acid. Moreover, in 1973, Sharpless and Michaelson[4] recommended the *t*-BuOOH/$VO(acac)_2$ catalyst system as the more excellent reagent for the stereoselective epoxidation of **1a.** Since then, the selective epoxidation of allylic alcohols catalyzed by vanadium has been extensively employed as the key step in the synthetic sequences of naturally occurring substances.[7,8] However, the stereocontrol mechanism of this catalytic reaction has not yet been elucidated.[9]

In the previous communication,[10] we reported that *t*-BuOOH/vanadium catalyst system and *m*-chloroperoxybenzoic acid (MCPBA) epoxidized medium-ring cyclic allylic alcohols with mutually opposite direction of stereoselectivity, i.e., the vanadium system with high cis selectivity and the peroxy acid with high trans selectivity. The observation suggested that these two epoxidations proceeded via different geometries of the transition state, and opened a clue to the clarification of the stereocontrol mechanism.

Here, we describe our systematic investigations on the stereochemistry of these epoxidations from the following viewpoints: (1) the relationships between the ring size and stereoselectivity for cyclic allylic alcohols; (2) the structure-reactivity relationships for conformationally "fixed" allylic alcohols. Ultimately we wish to propose a reasonable model for the transition-state geometry of the vanadium-catalyzed epoxidation.

Results and Discussion

In the vanadium-catalyzed epoxidation of cyclooct-2-en-1-ol (**1b**), the effects of metal valency and ligands on the catalytic activity and the stereoselectivity were examined. The results are shown in Table I. Homogeneous systems showed higher catalytic activity than heterogeneous ones, but no significant differences in stereoselectivity were observed. $VO(acac)_2$ complex was used as a representative vanadium catalyst because of its stability, availability, and facility in handling as well as high activity. A molybdenum complex, $MoO_2(acac)_2$, was used in order to compare its catalytic activity for epoxidation with $VO(acac)_2$.

In the peroxy acid epoxidation of **1b,** there are little differences in stereoselectivity with varying the kind of peroxycarboxylic acids, at most within 5%.[11] Therefore, the general trend of stereoselectivity in peroxy acid epoxidations can be represented by that with MCPBA.

Ring-Size Effect on Stereoselectivity in Epoxidation of Cyclic Allylic Alcohols. The stereochemistry of epoxidation for a series of cyclic allylic alcohols was examined with the following three reagents: MCPBA, *t*-BuOOH/$MoO_2(acac)_2$ catalyst system, and *t*-BuOOH/$VO(acac)_2$ catalyst system. The total yield of epoxy alcohols and cis/trans epimer ratio of each reaction were determined by the quantitative GLC method. The results for five- to nine-membered ring *Z* allylic alcohols (**1a–e**) and for eight- to twelve-membered ring *E* allylic alcohols (**1f–i**) are summarized in Tables II and III, respectively. The structures of these epoxy alcohols were determined either by the agreement of spectral data with authentic specimens or by the lithium aluminum hydride ($LiAlH_4$) reduction to the structure-known cycloalkane 1,2- and 1,3-diols. The relative stereochemistry of epoxy alcohols was further confirmed on the basis of the empirical rules of NMR and IR spectral behavior as shown in the Appendix.

For **1a** and cyclopent-2-en-1-ol (**1c**), the peroxy acid reaction as well as the metal-catalyzed reactions proceeded with high cis selectivity. The highest selectivity was attained with the vanadium catalyst system. These results are compatible with those reported by earlier workers.

In going to medium-ring allylic alcohols, the direction of peroxy acid epoxidation drastically changes from cis to trans. The exclusively high trans selectivity for eight- and nine-membered rings (**1b, 1e**) is noted. In contrast, the vanadium-catalyzed epoxidation exhibited the high cis selectivity common to medium-ring *E* and *Z* allylic alcohols consistently.[10] Even for the twelve-membered ring (**1i**), the cis selectivity was conserved. Exceptional was (1*RS*,2*RS*)-(*E*)-cyclooct-2-en-1-ol (**1f**), one of the two diastereoisomers of highly strained cyclic *E* allylic alcohols, which on vanadium-catalyzed epoxidation afforded the trans epoxy alcohol (**3f**) predominantly.

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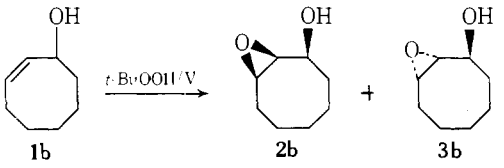
Table I. Effect of Metal Valency and Ligands on Catalytic Activity of Vanadium-Catalyzed Epoxidation of **1b**[a]

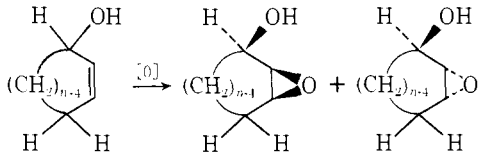


1b **2b** **3b**

ligand	metal valency	epoxy alcohol yield,[c] %	epimer ratio[c] cis, %	epimer ratio[c] trans, %	system
$VO(acac)_2$	+4	83	97	3	homogeneous
VCl_4	+4	86	96	4	homogeneous
$VO(SO_4)\cdot 3H_2O$	+4	65	97	3	homogeneous
$V(acac)_3$	+3	79	97	3	homogeneous
V_2O_5	+5	29	95	5	heterogeneous[b]
$C_5H_5V(CO)_4$	+1	75	94	6	homogeneous

[a] Reaction conditions: **1b** (5.0 mmol), *t*-BuOOH (6.0 mmol), $VO(acac)_2$ (0.025 mmol), dry benzene (10 mL), 40 °C, 24 h, stirred. [b] Unreacted *t*-BuOOH was recovered in 56%. [c] Determined by GLC.

Table II. Ring Size and Stereoselectivity in Epoxidation of Cyclic *Z* Allylic Alcohols

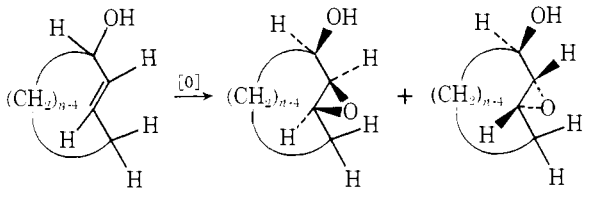


1 **2** **3** **a, b, c, d, e** n = 6, 8, 5, 7, 9

reactant	*t*-BuOOH/$VO(acac)_2$[a] yield, %	epimer ratio cis, %	epimer ratio trans, %	*t*-BuOOH/$MoO_2(acac)_2$[b] yield, %	epimer ratio cis, %	epimer ratio trans, %	MCPBA[c] yield, %	epimer ratio cis, %	epimer ratio trans, %
1c, n = 5	71	99.2	0.8				80	84	16
1a, n = 6	86	99.7	0.3	67	98	2	83	95	5
		(98)[d]	(2)[d]					(92)[e]	(8)[e]
1d, n = 7	87	99.6	0.4	73	95	5	95	61	39
								(66)[f]	(34)[f]
1b, n = 8	83	97	3	78	42	58	81	0.2	99.8
								(≃0)[g]	(≥99)[g]
1e, n = 9	85	91	9	77	3	97	89	0.2	99.8

[a] Reaction conditions: alcohol (10.0 mmol), *t*-BuOOH (12.0 mmol), $VO(acac)_2$ (0.05 mmol), dry benzene (20 mL), 40 °C, 24 h, stirred. [b] $MoO_2(acac)_2$ (0.05 mmol) instead of $VO(acac)_2$, 80 °C, 5 h, other conditions are the same as *a*. [c] Alcohol (10.0 mmol), MCPBA (10.0 mmol), CH_2Cl_2 (40 mL), 0 °C, 24 h, stirred. [d] Cited from ref 4. [e] Cited from ref 6. [f] Cited from ref 12. [g] Cited from ref 11.

Table III. Ring Size and Stereoselectivity in Epoxidation of Cyclic *E* Allylic Alcohols

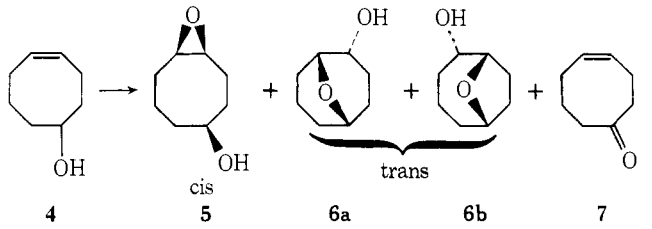


1 **2** **3** **f, g, h, i** n = 8, 9, 12

reactant	*t*-BuOOH/$VO(acac)_2$[a] yield, %	epimer ratio cis, %	epimer ratio trans, %	*t*-BuOOH/$MoO_2(acac)_2$[b] yield, %	epimer ratio cis, %	epimer ratio trans, %	MCPBA[c] yield, %	epimer ratio cis, %	epimer ratio trans, %
1f, n = 8 (1*RS*,2*RS*)	45	(3)[d]	97				57	(0.5)[d]	99.5
1g, n = 8 (1*SR*,2*RS*)	62	93	(7)[d]				58	84	(16)[d]
1h, n = 9	84	96	4	82	51	49	92	10	90
1i, n = 12	78	71	29	79	45	55	88	25	75

[a,b,c] Reaction conditions are the same as those in Table II. [d] The minor components were not fully identified. The GLC shoulders of main peaks were tentatively assigned to the minor epimers of epoxy alcohols. The structures of main components were assigned by the spectral evidences (see Experimental Section).

Table IV. Epoxidation of Cyclooct-4-en-1-ol



reagent	recovery of **4**, %	epoxy alcohol yield, %	epoxy alcohol epimer ratio **5**, %	epoxy alcohol epimer ratio **6a** + **6b**[d] %	enone yield, %
t-BuOOH/VO(acac)$_2$[a]	33	5	47	53	60
t-BuOOH/MoO$_2$(acac)$_2$[b]	3	91	52	48	4
MCPBA[c]	5	90	46	54	0.5

[a,b,c] Reaction conditions are the same as those in Table II. [d] Both derived from *trans*-4,5-epoxycyclooctanol. See note 13.

Scheme I. Epoxidation of Cyclooctadienols **9** and **10**

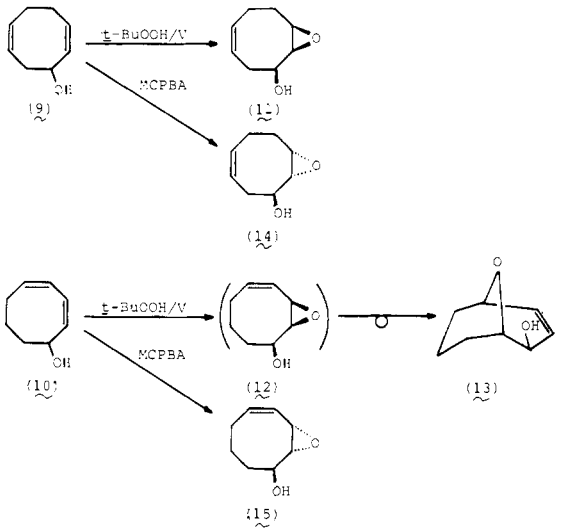
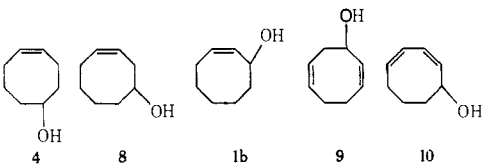


Table V. Relative Oxidation and Epoxidation Reactivity of Cyclooctenols and Cyclooctadienols for *t*-BuOOH/VO(acac)$_2$ Catalyst System[a]



	4	**8**	**1b**	**9**	**10**
relative[b] oxidation rate	1.4	7.1	100	42	23
relative[c] epoxidation rate	0.09	2.1	100	40	19

[a] Reaction conditions: alcohol A (1.0 mmol), alcohol B (1.0 mmol), *t*-BuOOH (0.20 mmol), VO(acac)$_2$ (0.02 mmol), dry benzene (2.0 mL), 40 °C, 24 h, stirred. [b] Calculated from the relative consumption of the two alcohols A and B. [c] Obtained by multiplying the value of relative oxidation rate with the selectivity for epoxidation (see Experimental Section).

This apparent anomaly will be precisely discussed later. The molybdenum-catalyzed epoxidation had a rather stereorandom character for the medium-ring allylic alcohols.

The three reagents were further attempted for epoxidation of a nonallylic alcohol, cyclooct-4-en-1-ol (**4**). In all three cases, the hydroxyl group remote from the double bond exerted no directing influence on its epoxidation; cis and trans epoxy alcohols (**5** and **6a** + **6b**)[13] were obtained in almost equal amounts, as shown in Table IV. In the vanadium-catalyzed reaction of **4**, moreover, the chemoselectivity for epoxidation itself was almost lost. Alternatively the dehydrogenation of secondary alcohol to the unsaturated ketone (**7**) became a main oxidation pathway.

The relative reactivity for epoxidation of various unsaturated alcohols, **1b**, **4**, **8**, **9**, and **10**, with the *t*-BuOOH/VO(acac)$_2$ system was examined. The results are summarized in Table V. It is evident that an allylic hydroxyl group remarkably enhances the rate of the epoxidation. For example, **1b** was epoxidized 10^3 times faster than **4**. Such a rate enhancement by allylic hydroxyl may reveal itself as the regioselectivity on the epoxidation of polyene alcohols. In fact, vanadium-catalyzed epoxidations of 2,6-cyclooctadien-1-ol (**9**) and 2,4-cyclooctadien-1-ol (**10**) with 1 equiv of *t*-BuOOH gave exclusively *cis*-2,3-epoxycycloocten-1-ols (**11** and **12**), respectively, as shown in Scheme I. In each case, the regioselectivity of initial attack on the β,γ double bond was higher than 99%. In the latter case, however, the initial product, *cis*-2,3-epoxycyclooct-4-en-1-ol (**12**), was not isolated exactly because **12** underwent the successive rearrangement to 9-oxabicyclo[3.3.1]-non-3-en-*exo*-2-ol (**13**) under the reaction conditions, as reported previously.[14] The detailed mechanistic investigations on this rearrangement will be published elsewhere. MCPBA epoxidations of **9** and **10** gave *trans*-2,3-epoxycycloocten-1-ols, **14** and **15**, respectively, as the major products.

Thus, it has become evident that the rate enhancement and directing control by the allylic hydroxyl are the essential features of the vanadium-catalyzed epoxidation. On the other hand, the peroxy acid reaction is also under the directive influence of allylic hydroxyl, but the rate enhancement seems not to be inherent in it. In fact, it is known that the introduction of a hydroxyl group into the allylic position reduces the rate of the peroxy acid epoxidation, compared with the parent olefins.[6]

The direction change from cis to trans, observed for the peroxy acid epoxidation with increasing the ring size from common to medium, can be rationalized in terms of Whitham's model[11] for the transition state geometries, I and II, as shown in Scheme II. There the partial geometries about the C_1-C_2 axis resemble the preferred conformations of the starting alcohols.

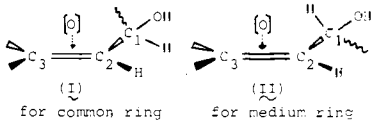
In contrast, the vanadium-catalyzed epoxidation of medium-ring alcohols gave cis epoxides selectively. The fact indicates that in the vanadium reaction the preferred transition state geometry of medium-ring alcohols might be far different

Table VI. Epoxidation of *cis*- and *trans*-5-*tert*-Butylcyclohex-2-en-1-ol **16**, **17**

	t-BuOOH/VO(acac)$_2$[a]				MCPBA[b]			
	enone	epoxy alcohol			enone	epoxy alcohol		
reactant	yield, %	yield, %	cis, %	trans, %	yield, %	yield, %	cis, %	trans, %
16	74	19	93	7	0.5	92	98 (96)[c]	2 (4)[c]
17	15	83	99.9	0.1	3	89	90 (84)[c]	10 (16)[c]

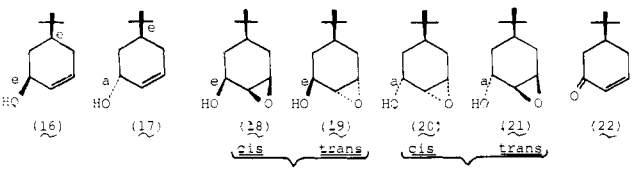
[a] 40 °C, 50 h; other reaction conditions are the same as *a* in Table II. [b] 50 h; other reaction conditions are the same as *c* in Table II. [c] Values cited from ref 11.

Scheme II. Whitham's Model for Transition State Geometry of Peroxy Acid Epoxidation

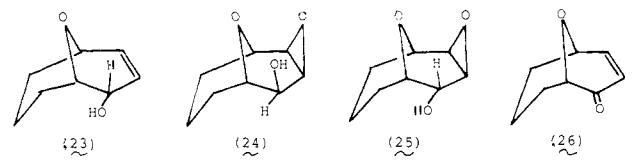


from II and strongly suggests that the reactant allylic alcohol might undergo a conformational change through its coordination to the metal on the way to the transition state. This concept can be tested by the epoxidation of conformationally "fixed" allylic alcohols.

Epoxidation of Conformationally "Fixed" Allylic Alcohols. The hydroxyl group of *cis*-5-*tert*-butylcyclohex-2-en-1-ol (**16**) occupies preferentially the quasi-equatorial position, whereas the trans hydroxyl of *trans*-5-*tert*-butylcyclohex-2-en-1-ol (**17**) occupies the quasi-axial one.[15] The conformations of **16** and **17** are rigid enough to be retained during the epoxidation. The



peroxy acid epoxidation of **16** yielded the cis,cis epoxy alcohol (**18**) and the trans,cis one (**19**) in the epimer ratio of 98:2, whereas **17** gave the cis,trans epoxy alcohol (**20**) and its trans,trans counterpart (**21**) in the ratio of 90:10 as shown in Table VI. The cis stereoselectivity was higher for the quasi-equatorial alcohol (**16**) than for the quasi-axial one (**17**). In the vanadium-catalyzed reaction, the dehydrogenation of secondary alcohol to the enone (**22**) competes with the epoxidation. Especially for **16**, the dehydrogenation became a main pathway. However, it is noted that the cis stereoselectivity of the vanadium-catalyzed epoxidation was higher for **17** than for **16**, which is the trend opposite to that of the peroxy acid epoxidation. This seems to imply that the peroxy acid epoxidation favors the quasi-equatorial hydroxyl in the transition state, while the vanadium epoxidation favors the quasi-axial one.

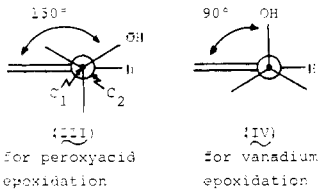


Another pair of conformationally "fixed" allylic alcohols is the bridged bicyclic system of 9-oxabicyclo[3.3.1]non-3-en-2-ols, **13** and **23**. The dihydropyran ring might adopt a quasi-chair conformation like that of a cyclohexene ring.[16] Thus, the exo alcohol (**13**) has a quasi-axial hydroxyl, while the endo alcohol (**23**) has a quasi-equatorial one.

The epoxidation of **13** with MCPBA as well as *t*-BuOOH/VO(acac)$_2$ system afforded the cis epoxy alcohol (**24**) stereoselectively in 65 and 73% yields, respectively. On the other hand, **23** was resistant to the peroxy acid epoxidation; after 2 days, the trans epoxy alcohol (**25**) was obtained as a main product in only 42% yield. The vanadium-catalyzed reaction of **23** gave the conjugated enone (**26**) in 95% yield. In both cases, the corresponding endo cis epoxy alcohol of **23** was not detected. The endo approach of active oxygen to C_3,C_4 double bonds might be sterically hindered by the C_7-endo methylene protons of double chair conformers[16] of **13** and **23**. Thus, the oxidation reactivities of **13** and **23** are complicated by the participation of two structural features, i.e., the directing effect by the hydroxyl and the steric hindrance by the C_7 bow methylene group. However, it is evident that the hydroperoxide/vanadium catalyst system acts as two types of oxidizing reagents: (1) as a stereoselective cis-epoxidation reagent for quasi-axial allylic alcohols and (2) as an oxidative dehydrogenation reagent for quasi-equatorial allylic alcohols and other olefinic alcohols. This double character of the vanadium system is reminiscent of the action of Jones oxidant (CrO_3/H^+) for the conformationally biased steroid allylic alcohols. Glotter et al.[17] reported that the Jones oxidation of 4α-hydroxycholest-5-ene, an equatorial alcohol, gave the corresponding enone, whereas 4β-hydroxycholest-5-ene, an axial alcohol, yielded 5β,6β-epoxycholestan-4-one.

This similarity between the two oxidizing reagents leads us to anticipate the intermediacy of oxo-metal bonds, M=O or O=M=O, as an actual oxidizing species in the vanadium system.

Scheme III. Preferred Transition State Geometries



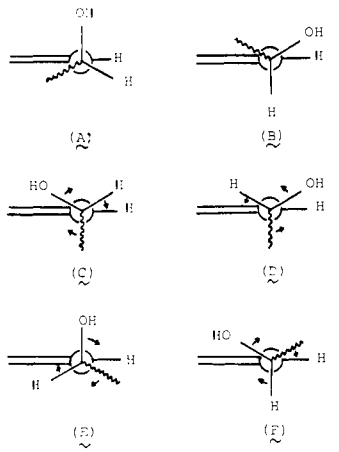
Stereocontrol Mechanism of Epoxidation. Before going into the mechanistic considerations, aforementioned experimental evidences are summarized: (1) for common-ring allylic alcohols, both the peroxy acid and vanadium-catalyzed epoxidations occur with high cis stereoselectivity; (2) for medium-ring allylic alcohols, the peroxy acid epoxidation exhibits high trans stereoselectivity, whereas the vanadium epoxidation shows high cis stereoselectivity; (3) among the conformationally "fixed" allylic alcohols, the peroxy acid epoxidation favors quasi-equatorial ones while the vanadium epoxidation favors quasi-axial ones; (4) the vanadium system oxidizes conformationally "fixed" quasi-equatorial allylic alcohols into the corresponding enones predominantly.

The essential factor which determines the stereochemistry of the epoxidation must be the stereoelectronic arrangement between the olefinic π orbital and the hydroxyl group anchoring the oxidizing species. From this viewpoint, we wish to propose the following hypothetical models (**III** and **IV**) as preferred transition state geometries for the peroxy acid and vanadium-catalyzed epoxidations, respectively.

Table VII. Dihedral Angle between Double Bond and C_3, C_4 Single Bond of Preferred Conformer of Cycloalkenes

cycloalkene	structure	$\omega C_3{=}C_2{-}C_1{-}C_n$ deg	ref
cyclohexene	quasi-chair	15	20
cycloheptene	chair	58.5	19
(*Z*)-cyclooctene	nonsymmetry	83.0, 90.8	19
(*E*)-cyclooctene	C_2 symmetry	87	19
(*Z*)-cyclononene	nonsymmetry	85.0, 101.7	19
(*E*)-cyclononene	C_2 symmetry	88.8	19
(*Z*)-cyclodecene	$AgNO_3$ complex	109, 116	21
(*E*)-cyclodecene	$AgNO_3$ complex	110	21

Scheme IV



In model **III**, the dihedral angle between the double bond and the hydroxyl, $\omega C_3{=}C_2{-}C_1{-}O$, is regarded as near to 150°, and in model **IV** near to 90°. The values 150 and 90° themselves are rather symbolic than realistic and are for the convenience of the mechanistic considerations.

In order to rationalize the stereochemical outcome of epoxidations by using these models, first, some information on the conformations of reactant allylic alcohols is needed. Although the conformational analysis of alicyclic compounds has been extensively developed,[18,19] little information is available on the conformations of cyclic allylic alcohols. The unknown conformations of cyclic allylic alcohols may be estimated from the known ones of the corresponding cycloalkenes.[19-21] The dihedral angles between the double bond and the β-position C-C bond ($\omega C_3{=}C_2{-}C_1{-}C_n$) of the most stable conformers of various cycloalkenes are summarized in Table VII. It is noted that the dihedral angle gradually increases from common (e.g., 15° for cyclohexene)[20] to medium ring (e.g., 109 or 116° for (*E*)-cyclodecene).[21]

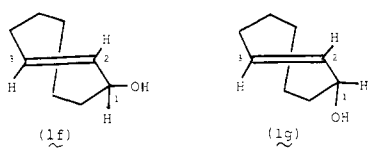
In general the partial geometries about the $C_1{-}C_2$ axis of cyclic allylic alcohols can be classified into the six types A-F in Scheme IV, excluding the energetically unfavorable "eclipse" conformers.

Under these postulations, the epoxidation stereochemistry can be explained as follows. In common-ring allylic alcohols, a conformational equilibrium between A and B can be attained. At the transition state for epoxidation, A easily transforms to IV, and B to III. Since the active oxygen anchored by the hydroxyl group approaches the double bond from the upper side of the $C_1{-}C_2{=}C_3$ plane, both peroxy acid and vanadium-catalyzed epoxidations provide the cis epoxy alcohol.

For medium-ring allylic alcohols, whose dihedral angles, $\omega C_3{=}C_2{-}C_1{-}C_n$, are expected to be near to 90° from Table VII, C and D are important as the initial state conformation. On the way to the transition state, D transforms to III. Therefore, the peroxy acid epoxidation gives the trans epoxide. C itself corresponds to neither III nor IV, but the transition state IV like A may be attained by the minimal conformational change from C: the right-handed 60° rotation around the $C_1{-}C_2$ axis. The transition state IV like E, which can be formed from D by the left-handed 60° rotation about the same axis, must bring about the trans direction for the vanadium-catalyzed epoxidation. For medium-ring alcohols, one might reasonably anticipate that the conformational change from C to A is more feasible than from D to E. Thus, the vanadium-catalyzed reaction gives the cis epoxide predominantly.

For large-ring alcohols, the contributions of E and F might be no more negligible than the initial state conformers. The participation of E may largely reduce the cis stereoselectivity of the vanadium epoxidation. Where the preferred transition state geometry III is not attainable, the peroxy acid epoxidation can occur nonstereoselectively, as described in the earlier section. Neither E nor F, themselves favors the transition state III. Thus, going from the medium- to large-ring region, the peroxy acid epoxidation becomes less stereoselective.

Only one exception to the general trend was encountered in the case of **1f**, which on vanadium-catalyzed epoxidation yielded the trans epoxide (**3f**) predominantly. This apparent anomaly, however, can also be resolved by the detailed examination of our transition state models III and IV. Cyclic *E* allylic alcohols consist of two diastereoisomers, conveniently designated as the (1*RS*,2*RS*) and (1*SR*,2*RS*) isomers, respectively.[22] It should be estimated that there is a rather high rotational barrier in the interconversion between the two diastereoisomers (**1f** and **1g**), which virtually hinders the establishment of preequilibrium between them under the epoxidation conditions.[23]

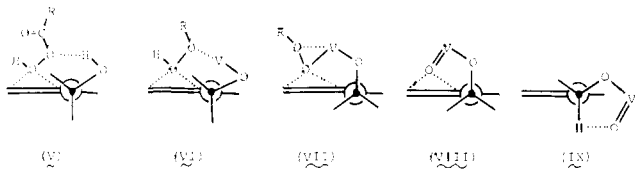


An examination of molecular model suggests that the partial geometries about the $C_1{-}C_2$ axis of **1f** and **1g** resemble the conformations D and C, respectively. In the vanadium epoxidation of **1f**, the restricted conformational change from D to E leads to the trans epoxide (**3f**), while **1g**, via the conformational change from C to A, gives the cis epoxide (**3g**). The predominant cis-epoxide formation in the peroxy acid epoxidation of **1g** may be attributed to the steric hindrance against the inside attack of active oxygen to the double bond by the rather clouded methylene loop of the (*E*)-cyclooctene ring.

The rotational barrier in the interconversion between the diastereoisomeric (*E*)-cyclonon-2-en-1-ols might be much lower than that between **1f** and **1g**.[23] (*E*)-Cyclonon-2-en-1-ol (**1h**), prepared by a method similar to the stereoselective synthesis[24] of **1f**, was no more epimerically pure but consisted of an equilibrium mixture of two diastereoisomers, (1*RS*,2*RS*) (80%) and (1*SR*,2*RS*) (20%).

In the vanadium-catalyzed epoxidation of **1h**, since the reequilibration of the starting alcohols is easily attained by the

Scheme V. Mechanisms of Epoxidation and Dehydrogenation of Allylic Alcohol



transformation of (1*RS*,2*RS*) to (1*SR*,2*RS*), the preferential attack of active oxygen to the (1*SR*,2*RS*) epimer followed by the conformational modification from C to A might give the cis epoxide. On the other hand, in the peroxy acid epoxidation the preferential attack to (1*RS*,2*RS*) epimer leads to the selective formation of the trans epoxide. Thus, our transition state models III and IV give a sufficient explanation of the stereochemical outcome of peroxy acid and vanadium-catalyzed epoxidations of cyclic allylic alcohols, respectively.[25]

It can be said that the difference in transition state geometry of allylic alcohol between III and IV originates from the different stereocontrol mechanisms between the two epoxidations. In Scheme V are shown the most reasonable mechanism for the peroxy acid epoxidation and four possible mechanisms for the vanadium-catalyzed oxidations. It should be noted that these mechanisms are drawn putting particular emphasis on the dihedral angle ($\omega C_3{=}C_2{-}C_1{-}O$) of allylic alcohol.

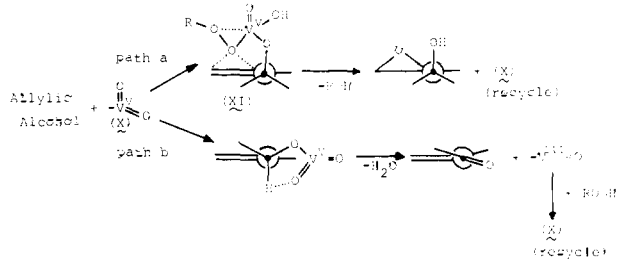
The peroxy acid epoxidation, whose direction is controlled by the hydrogen bonding between the hydroxyl and the peroxy oxygen, must involve a 6.5-membered ring transition state constructed by C_2, C_1, O, H, O, O, and the center of the double bond, as shown in V. The geometry of alcohol in V corresponds to the larger dihedral angle ($\omega C_3{=}C_2{-}C_1{-}O$) in model III than that in model IV.

For the vanadium-catalyzed epoxidation of allylic alcohols, two types of mechanisms have been published,[3c,26] both of which involve the coordination of the alcoholic hydroxyl and the intact alkyl hydroperoxide. The two mechanisms are discriminated by the coordination site of the peroxide to vanadium: one involves the coordination through its oxygen proximal to the alkyl substituent[3c] and the other through its distal oxygen.[26] It appears that the former mechanism involves a 6.5-membered ring transition state and the latter a 5.5-membered ring one, as depicted in VI and VII, respectively. The geometry of alcohol in VI rather resembles V and fails to explain the stereochemical outcome of the epoxidation. The mechanism VII, on the other hand, fulfills the angular requirement of transition state model IV and, thus, appears to be consistent with the stereochemical outcome.

Recently, Isobe et al. found that a dioxovanadium complex was formed by the reaction of $VO(acac)_2$ and *t*-BuOOH.[27] The fact suggests the possibility that the epoxidation proceeds via the oxo-metal version of hydroperoxide. Such a transition state as VIII constructs the 5.5-membered ring consistent with model IV. Most recently Sharpless et al., however, presented an important observation critical for the mechanistic consideration: no oxygen-18 was incorporated into the epoxide from the ^{18}O-enriched water as a cosolvent. This result implies that the oxirane oxygen is not derived from the oxovanadium oxygen. On this criterion, mechanism VIII involving the oxo-metal version of hydroperoxide as an actual epoxidizing species should be excluded.

Although mechanism VII is the most reasonable for the present epoxidation, the oxidation of secondary alcohols should be attributed to the oxo-metal rather than the peroxy-metal species.[28] In the case of the conformationally "fixed" allylic alcohols, e.g., **16** and **23**, where such a desirable geometry as mechanism VII cannot be attained, there might occur a direct oxidation of secondary alcohols by oxovanadium oxygen as shown in mechanism IX.

Scheme VI. Dual Pathway of Vanadium-Catalyzed Oxidation



Thus, the vanadium-catalyzed oxidation of allylic alcohols can be rationalized most reasonably by the dual pathway, as shown in Scheme VI. If the reactant allylic alcohol has a conformational mobility enough to attain the preferred geometry in its transition state, the epoxidation occurs via such a peroxy-metal species as XI (path a), but, otherwise, the oxo-metal species X oxidizes the alcohol function to the ketone (path b). In the latter case, the reduced vanadium species is reoxidized by another molecule of hydroperoxide.

The basic feature of mechanisms VII in Scheme V and XI in Scheme VI, i.e., the coordination of the distal oxygen of the peroxide to the metal, originates from the proposal of Sharpless et al.[9,26] Their proposal was evident mainly by the scrutinization of the coordination chemistry of vanadium. The present work, remarking on the conformational requirement for the substrate allylic alcohol, offers essential refinement on the previous mechanisms.

In conclusion, the present work provides definite evidence for the first time that the preferred transition-state geometry in the vanadium-catalyzed epoxidation involves the quasi-axial hydroxyl conformation of allylic alcohols.

Worth mentioning in this respect is the Simmons-Smith methylene addition reaction,[29] where the direction changes from cis to trans in the medium-ring allylic alcohols and the preferential reactivity of quasi-equatorial alcohols could be rationalized in terms of the quasi-equatorial-like coordination of reactant allylic alcohol to the dimeric organozinc intermediate.[30]

Experimental Section

Reagent grade commercial materials $VO(acac)_2$ (Nakarai), $V(acac)_3$ (Nakarai), VCl_4 (Nakarai), $VO(SO_4)\cdot 3H_2O$ (Wako), V_2O_5 (Wako), $MoO_2(acac)_2$ (Nakarai), and $C_5H_5V(CO)_4$ (ROC/RIC) were used without further purification. *m*-Chloroperoxybenzoic acid (MCPBA) was purchased from Aldrich (active oxygen 85%) and was used as received. *t*-BuOOH (Nakarai) (active oxygen 82%) was dried over 4A molecular sieves and distilled under vacuum, bp 34–35 °C (15 mm) (active oxygen 92%). The active oxygen amount of peroxide was determined by iodometric titration.[34] Infrared spectra were recorded on a JASCO-IR-E spectrophotometer. ^1H NMR and ^{13}C NMR spectra were obtained on a JEO-JNM 4H-100 and JNM FX-100 spectrometer, respectively; tetramethylsilane (Me_4Si) was used as an internal standard. Gas chromatography (GLC) was performed on a Yanaco-G8 instrument using a 2 m × 1.3 mm i.d. column packed with 3% silicone OV-17 on 60–80 mesh Celite or 20% PEG-6000 on 60–80 mesh Celite. Melting and boiling points are uncorrected. Solvents were dried in the usual manner and purified by distillation under a nitrogen atmosphere.

Preparation of Cyclic Allylic Alcohols. Cyclohex-2-en-1-ol (**1a**), (*Z*)-cyclooct-2-en-1-ol (**1b**), and cyclohept-2-en-1-ol (**1d**) were prepared by the following reaction sequence, i.e., allylic bromination with *N*-bromosuccinimide (NBS) followed by acetoxylation with AgOAc and hydrolysis with NaOH/methanol. Cyclopent-2-en-1-ol[35] (**1c**), (*Z*)-cyclonon-2-en-1-ol[36] (**1e**), and (1*SR*,2*RS*)-(*E*)-cyclooct-2-en-1-ol[22b] (**1g**) were prepared by the literature procedures.

Preparation of (1*RS*,2*RS*)-(*E*)-Cyclooct-2-en-1-ol (1f). According to the direction of Reese and Shaw,[24] **1f** was prepared as follows. To a stirred solution of 10.0 g (53.0 mmol) of *exo*-8-bromobicyclo[5.1.0]octane[37] in 50 mL of acetone-water (95:5 v/v)

Table VIII. ^{13}C NMR Spectra of (*E*)- and (*Z*)-Cyclonon-2-en-1-ols[a]

	(*E*)-cyclonon-2-en-1-ols (**1h**)		
	(1*RS*,2*RS*)	(1*SR*,2*RS*)	(*Z*)-cyclonon-2-en-1-ol (**1e**)
C_2	134.2	132.6	135.1
C_3	128.2	127.4	129.3
C_1	74.81	68.28	69.1
	36.48	34.85	36.0
	32.32	32.56	27.6
C_4-C_9	31.39	32.12	26.5
	26.91	27.15	25.8
	22.43	23.01	25.5
	20.18	16.04	23.2

[a] Parts per million downfield from Me_4Si.

was added dropwise 22.0 g (106 mmol) of $AgClO_4$ in 50 mL of the same solvent during 20 min at 0 °C. The resulting mixture was stirred for an additional 1 h. The AgBr dust precipitated was filtered off and the filtrate was extracted with 300 mL of ether. The aqueous layer was treated with 50 mL of 30% NH_4OH solution and extracted with 100 mL of ether. The combined ethereal layer was washed with water and brine and dried over $MgSO_4$. Solvent evaporation followed by distillation gave 4.8 g (72%) of pure **1f**, bp 90–92 °C (10.2 mm) (ref 22a, 92–93 °C (10 mm)).

Preparation of (*E*)-Cyclonon-2-en-1-ol (1h). *exo*-9-Bromobicyclo[6.1.0]nonane[37] was reacted by the same procedure as described above. In this case, however, the solvolysis product was not epimerically pure, but consisted of a mixture of two diastereoisomers, (1*RS*,2*RS*) and (1*SR*,2*RS*) epimers. Any attempts to separate the two epimers failed. The ^1H NMR spectrum of **1h** contained the two sets of methine proton signals at τ 6.12 (rel intensity 0.8) and 5.60 (rel intensity 0.2). Furthermore, the ^{13}C NMR spectrum of **1h** showed nine sets of signals, each of which consisted of two peaks of relative intensity 4:1. The (1*RS*,2*RS*) structure was assigned to the major component on the basis of the larger proton coupling constant $J_{1,2}$ of 7.5 Hz, which is compatible with the transoid C(1)-H, C(2)-H relationship.[38]

In Table VIII are shown the assignment of ^{13}C NMR signals of **1h** as well as that of *Z* isomer (**1e**). This mixture of two diastereoisomers was used as a reactant for the epoxidation. **1h:** mp 65–69 °C (recrystallized from petroleum ether); IR (Nujol) cm^{-1} 3360, 1181, 1153, 1105, 1080, 1020, 994, 912, 736; NMR (CCl_4) τ 4.2–5.0 (m, 2 H, =CH-), 5.60 (m, 0.2H, >CHO-), 6.12 (sextuplet, $J_{1,9}$ = 9.0 $J_{1,9}$ = 5.0, $J_{1,2}$ = 7.5 Hz, 0.8 H, >CHO-), 7.80–9.2 (m, 12 H, $-CH_2-$).

Preparation of (*E*)-Cyclododec-2-en-1-ol (1i). Commercial cyclododecene (a mixture of *E* and *Z*) was brominated with NBS. The product was treated with AgOAc to give a 9:1 mixture of (*E*)- and (*Z*)-cyclododec-2-en-1-yl acetates. The mixture was fractionally distilled and the medium fraction of bp 103–104 °C (0.7 mm) was collected, whose GLC analysis showed that the *E* acetate was concentrated by 99% purity. This *E* acetate was hydrated with NaOH/methanol to give almost pure **1i**, bp 97–98 °C (0.8 mm) (ref 39, 133 °C (3 mm)).

General Procedure for Vanadium-Catalyzed Epoxidation of Allylic Alcohol with *t*-BuOOH (Method A). $VO(acac)_2$ (13.3 mg, 0.05 mmol) in 10 mL of dry benzene was charged into a 50-mL round-bottomed flask, and the atmosphere was replaced with a nitrogen stream. Allylic alcohol (10.0 mmol) in 5 mL of benzene was introduced through the side arm. To this solution, then, was added 1.17 g (12.0 mmol) of *t*-BuOOH in 5 mL of benzene dropwise during 15 min. The resulting solution was stirred at 40 °C for 24 h until peroxide was almost consumed. The reaction mixture was analyzed by GLC to determine the product yields by the internal standard method. The results are summarized in Tables II and III. From the reaction mixture, the solvent was removed in vacuo and the residue was chromatographed on a Florisil column to remove the metal complex using petroleum ether and ether as an eluent. The eluate was concentrated. From the residue the products were isolated for the purpose of characterization either by preparative GLC or by fractional distillation.

The structure of epoxy alcohols was determined either by the agreement of IR and NMR spectroscopic data with authentic specimens prepared by the peroxy acid epoxidation (see method C) or by the $LiAlH_4$ reduction to give the structure known cycloalkane 1,2- and 1,3-diols.

Effects of Metal Valency and Ligands on Vanadium-Catalyzed Epoxidation of 1b. The reaction of 0.63 g (5.0 mmol) of **1b** with 0.60 g (6.0 mmol) of *t*-BuOOH was performed in the presence of 0.025 mmol of catalyst. The following vanadium compounds were used as the catalyst: VCl_4, $VO(SO_4)\cdot 3H_2O$, $V(acac)_3$, V_2O_5, and $C_5H_5V(CO)_4$. Other reaction conditions were the same as described in method A. The results are given in Table I.

General Procedure for Molybdenum-Catalyzed Epoxidation of Allylic Alcohol with *t*-BuOOH (Method B). To a solution of 16.3 mg (0.05 mmol) of $MoO_2(acac)_2$ and 10.0 mmol of allylic alcohol in 15 mL of dry benzene at 80 °C was added 1.17 g (12.0 mmol) of *t*-BuOOH in 5 mL of benzene dropwise during 15 min. The resulting solution was stirred for 5 h at 80 °C. The reaction mixture was worked up in a manner similar to that described above. The results are given in Tables II and III.

General Procedure for Epoxidation of Allylic Alcohols with MCPBA (Method C). To a stirred solution of 10.0 mmol of allylic alcohol in 20 mL of CH_2Cl_2 at 0 °C was added 2.0 g (10.0 mmol) of MCPBA in 20 mL of CH_2Cl_2 dropwise during 1 h. Stirring was continued for 24 h at 0 °C. The resulting mixture was filtered. The filtrate was washed with Na_2SO_3 solution, $NaHCO_3$ solution, water, and brine and dried on $MgSO_4$. The solvent-evaporated residue was analyzed by GLC to determine the product yields. Epoxy alcohols were isolated either by preparative GLC or fractional distillation. The results are also summarized in Tables II and III.

Physical, Spectroscopic, and Analytical Data for Cyclic Epoxy Alcohols. *cis*-2,3-Epoxycyclohexan-1-ol (**2a**), bp 86 °C (6 mm) (ref 11, 100–102 °C (12 mm)).

trans-2,3-Epoxycyclohexan-1-ol (**3a**), bp 87 °C (5 mm) ref 11, 104–108 °C (16 mm)).

cis-2,3-Epoxycyclooctan-1-ol[22b] (**2b**), bp 72 °C (1.5 mm).

trans-2,3-Epoxycyclooctan-1-ol (**3b**), bp 97–99 °C (1.5 mm) (ref 22b, 99–100 °C (1 mm)).

cis-2,3-Epoxycyclopentan-1-ol[40] (**2c**); bp 38 °C (1.0 mm); NMR (CCl_4) 5.83 (d-d, J = 7.2, 7.2 Hz, 1 H, >CHO-), 6.05 (s, 1 H, OH), 6.65 (m, 2 H, >CHO-), 7.8–9.0 (m, 4 H, $-CH_2-$).

trans-2,3-Epoxycyclopentan-1-ol[40] (**3c**); NMR (CCl_4) τ 5.81 (m, 1 H, >CHO-), 6.66 (m, 1 H, >CHO-), 6.82 (d, J = 2.3 Hz, 1 H, >CHO-), 7.9–8.8 (m, 4 H, $-CH_2-$).

cis-2,3-Epoxycycloheptan-1-ol (**2d**); bp 83 °C (3 mm) (ref 12, 78–79 °C (1.4 mm)).

trans-2,3-Epoxycycloheptan-1-ol (**3d**), bp 85 °C (1.5 mm) (ref 12, 88 °C (1.9 mm)).

2*c*,3*c*-Epoxycyclononan-1-ol (**2e**): bp 84 °C (1 mm); mp 67–69 °C; IR (film) cm^{-1} 3400, 1077, 1040, 1007, 963, 897, 824, 726; NMR (CCl_4) τ 5.57–5.82 (m, 1 H, >CHO-), 7.20 (m, 2 H, >CHO-), 7.57 (s, 1 H, OH), 7.8–8.8 (m, 12 H, $-CH_2-$). Anal. Calcd for $C_9H_{16}O_2$: C, 69.20; H, 10.32. Found: C, 69.13; H, 10.40.

2*t*,3*t*-Epoxycyclononan-1-ol (**3e**): bp 104–105 °C (1.8 mm); IR (film) cm^{-1} 3300, 1020, 967, 865, 834, 760; NMR (CCl_4) τ 6.25 (s, 1 H, OH), 6.30–6.70 (m, 1 H, >CHO-), 6.9–7.4 (m, 2 H, >CHO-), 7.7–8.9 (m, 12 H, $-CH_2-$). Anal. Calcd for $C_9H_{16}O_2$: C, 69.20; H, 10.32. Found: C, 68.95; H, 10.14.

2*t*,3*c*-Epoxycyclooctan-1-ol (**3f**): bp 79–81 °C (1.0 mm); IR (film) cm^{-1} 3330, 1041, 1005, 900, 765, 725; NMR (CCl_4) τ 5.00 (s, 1 H, OH), 6.5–6.8 (m, 1 H, >CHO-), 7.2–7.4 (m, 2 H, >CHO-), 7.7–9.0 (m, 10 H, $-CH_2-$).

2*c*,3*t*-Epoxycyclooctan-1-ol (**2g**): IR (film) cm^{-1} 3400, 1088, 1041, 990, 911, 833, 810; NMR (CCl_4) τ 5.92 (m, 1 H, >CHO-), 6.91 (d-t, J = 11, 2.5 Hz, 1 H, >CHO-), 7.35 (m, 1 H, >CHO-), 7.60 (s, 1 H, OH), 7.7–9.0 (m, 10 H, $-CH_2-$).

2*c*,3*t*-Epoxycyclononan-1-ol (**2h**): IR (film) cm^{-1} 3400, 1127, 1082, 956, 938, 892, 820; NMR (CCl_4) τ 5.92 (m, 1 H, >CHO-), 6.96 (sextet, J = 10, 3.2, 3.2 Hz, 1 H, >CHO-), 7.30 (m, 1 H, >CHO-), 7.70 (s, 1 H, OH), 7.70–8.80 (m, 12 H, $-CH_2-$). Anal. Calcd for $C_9H_{16}O_2$: C, 69.20; H, 10.32. Found: C, 68.45; H, 10.39.

2*t*,3*c*-Epoxycyclononan-1-ol (**3h**): mp 80–82 °C (recrystallized from cold ether); IR (Nujol) cm^{-1} 3300, 1041, 981, 860, 825, 783; NMR (CCl_4) τ 6.72 (s, 1 H, OH), 6.84 (m, 1 H, >CHO-), 7.1–7.4 (m, 2 H, >CHO-), 7.7–8.8 (m, 12 H, $-CH_2-$). Anal. Calcd for $C_9H_{16}O_2$: C, 69.20; H, 10.32. Found: 68.72; H, 10.24.

2*c*,3*t*-Epoxycyclododecan-1-ol (**2i**): IR (film) cm^{-1} 3380, 1099, 1075, 1027, 913, 894, 741; NMR (CCl_4) τ 6.00 (m, 1 H, >CHO-),

7.06 (sextet), J = 9, 2.1, 2.1 Hz, 1 H, >CHO-), 7.24 (m, 1 H, >CHO-), 7.68-8.04 (m, 2 H, $-CH_2-$), 7.92 (s, 1 H, OH), 8.8-8.9 (m, 16 H, $-CH_2-$). Anal. Calcd for $C_{12}H_{22}O_2$: C, 72.68; H, 11.18. Found: C, 72.13; H, 11.24.

2t,3c-Epoxycyclododecan-1-ol (**3i**): IR (film) cm^{-1} 3340, 1030, 898, 854, 808, 740; NMR (CCl_4) τ 6.82-7.10 (m, 1 H, >CHO-), 7.26 (s, 1 H, OH), 7.33-7.40 (m, 2 H, >CHO-), 7.77-8.04 (m, 2 H, $-CH_2-$), 8.20-9.00 (m, 16 H, $-CH_2-$). Anal. Calcd for $C_{12}H_{22}O_2$: C, 72.68; H, 11.18. Found: C, 72.04; H, 11.99.

Epoxidation of Cyclooct-4-en-1-ol (4). **4** was prepared by the reductive ring opening of 1,5-cyclooctadiene monoepoxide[41] with $LiAlH_4$ in ether. **4**: bp 70-71 °C (2.5 mm); IR (film) cm^{-1} 3400, 3040, 1650, 1049, 1032, 990. Reaction of 1.26 g (10.0 mmol) of **4** with t-BuOOH/V catalyst system by method A gave, according to the GLC analysis, 0.74 g (60%) of cyclooct-4-en-1-one[42] (**7**), 0.42 g (33%) of unreacted **4**, 0.03 g (2.4%) of *cis*-4,5-epoxycyclooctan-1-ol[41] (**5**), and 0.04 g (2.7%) of a mixture of *trans*-1,5-epoxycyclooctan-2-ol[42] (**6a**) and *trans*-1,4-epoxycyclooctan-5-ol[42] (**6b**). **6a** and **6b** were derived from *trans*-4,5-epoxycyclooctan-1-ol.

Molybdenum-catalyzed epoxidation of **4** by method B gave 0.67 g (47%) of **5** and 0.62 g (44%) of **6a** + **6b** accompanied by 0.05 g (4%) of **7** and 0.04 g (3%) of **4**.

Treatment of **4** with MCPBA by method C gave 0.58 g (41%) of **5**, 0.70 g (49%) of **6a** + **6b**, 0.06 g (5%) of **4**, and a trace amount of **7**.

Epoxidation of Cyclooct-3-en-1-ol (8). **8** was prepared by $LiAlH_4$ reduction of 1,3-cyclooctadiene monoepoxide.[43] **8**: bp 60-61 °C (1.2 mm); IR (film) cm^{-1} 3400, 3040, 1650, 1040, 992, 980. Reaction of 1.26 g (10.0 mmol) of **8** with t-BuOOH/$VO(acac)_2$ catalyst system in the usual manner of method A afforded 0.42 g (34%) of cyclooct-3-en-1-one,[42] 0.20 g (14%) of a mixture of *cis*- and *trans*-3,4-epoxycyclooctan-1-ols,[42] and 0.64 g (51%) of unreacted **8**.

Preparation of 2,6-Cyclooctadien-1-ol (9). **9** was prepared by the procedure of Cantrell and Solomon,[44] and purified by washing with 20% $AgNO_3$ aqueous solution, bp 63-64 °C (1.3 mm) (ref 44, 45-48 °C (0.3 mm)).

Epoxidation of 9. Method A. **9** (1.24 g 10.0 mmol) was treated with 1.17 g, (12.0 mmol) of t-BuOOH and 13 mg (0.05 mmol) of $VO(acac)_2$ in the usual manner of method A. After reaction for 24 h, GLC analysis showed the formation of 1.20 g (86%) of *cis*-2,3-epoxycyclooct-6-en-1-ol (**11**), 0.03 g (2%) of *trans*-2,3-epoxycyclooct-6-en-1-ol (**14**), and 0.04 g (3%) of 2,6-cyclooctadien-1-one.[44] Fractional distillation under reduced pressure gave 10.2 g (74%) of pure **11**: bp 79-81 °C (2 mm); IR (CCl_4) cm^{-1} 3587, 3020, 1650, 1026, 1000, 925, 895, 792, 757; NMR (CCl_4) τ 4.1-4.7 (m, 2 H, -CH=), 6.02 (m, 1 H, >CHO-), 6.85 (m, 2 H, >CHO-), 7.14 (s, 1 H, OH), 7.2-8.1 (m, 6 H, $-CH_2-$).

Method C. Reaction of 1.24 g (10.0 mmol) of **9** with 2.00 g (10.0 mmol) of MCPBA by method C followed by distillation gave 1.10 g (79%) of **14**: bp 87-88 °C (1.2 mm); IR (CCl_4) cm^{-1} 3610, 3017, 1650, 1035, 973, 913, 870, 809; NMR (CCl_4) τ 4.0-4.6 (m, 2 H, -CH=), 5.76 (m, 1 H, >CHO-), 6.40 (s, 1 H, OH), 6.8-7.2 (m, 2 H, >CHO-), 7.2-8.2 (m, 6 H, $-CH_2-$). Both **11** and **14** by Jones oxidation[45] were converted to the common epoxy ketone.

2,3-Epoxycyclooct-6-en-1-one: bp 66.5 °C (1.8 mm); IR (film) cm^{-1} 1690, 1655, 992, 837; NMR (CCl_4) τ 4.3-4.9 (m, 2 H, -CH=), 6.58 (m, 1 H, $-CH_2-$), 6.81 (m, 2 H, >CHO-), 7.25 (m, 1 H, $-CH_2-$), 7.7-8.3 (m, 4 H, $-CH_2-$).

Preparation of 2,4-Cyclooctadien-1-ol (10). **10**, contaminated by 20% of bicyclo[3.3.0]oct-3-en-2-ol, was prepared by the procedure of Moon and Ganz.[46] This alcohol mixture (3.70 g, 30.0 mmol) was treated with 6.00 g (32.0 mmol) of *p*-nitrobenzoyl chloride in 50 mL of pyridine at 0 °C. The crude benzoate (7.20 g, 26.3 mmol) was recrystallized three times from hot methanol to give 4.2 g (58%) of relatively pure 2,4-cyclooctadien-1-yl *p*-nitrobenzoate; mp 112-113 °C. Hydrolysis of the benzoate with NaOH/methanol gave 1.6 g (49%) of **10** in 99% purity. **10**: bp 57 °C (1.2 mm) (ref 44, 49-52 °C (0.3 mm)).

Epoxidation of 10. Method A. Vanadium-catalyzed epoxidation of 1.24 g (10.0 mmol) of **10** with 1.17 g (12.0 mmol) of t-BuOOH for 50 h gave 1.09 g (78%) of 9-oxabicyclo[3.3.1]non-3-en-*exo*-2-ol (**13**), 0.13 g (11%) of 2,4-cyclooctadien-1-one,[44] and 0.06 g (4%) of *trans*-2,3-epoxycyclooct-4-en-1-ol (**15**) by GLC analysis. The reaction mixture was worked up in the usual manner. Fractional distillation followed by sublimation gave 0.98 g (70%) of pure **13**: bp 94-95 °C (1.4 mm); mp 71-72 °C; IR (CCl_4) cm^{-1} 3590, 3030, 1645, 1070, 1030, 992, 885, 878, 847, 802, 743; NMR ($CDCl_3$) τ 3.80 (d-d, J = 9.3, 3.8 Hz, 1 H, H-3), 4.06 (d-d, J = 9.3, 3.8 Hz, 1 H, H-4), 5.66 (m, 1 H, H-5), 5.86 (m, 1 H, H-1), 6.32 (d, J = 3.8 Hz, 1 H, H-2), 7.80 (s, 1 H, OH), 7.8-8.8 (m, 6 H, $-CH_2-$). Anal. Calcd for $C_8H_{12}O_2$: C, 68.55; H, 8.63. Found: C, 68.15; H, 8.41.

Method C. **10** (2.50 g, 20.2 mmol) was treated with 4.10 g (20.2 mmol) of MCPBA by method C at 0 °C for 48 h. GLC analysis showed the formation of 2.58 g (91%) of *trans*-epoxycyclooct-4-en-1-ol (**15**) and a trace amount of **13**. Fractional distillation afforded 2.18 g (77%) of pure **15**: bp 77-80 °C (0.9 mm); IR (film) cm^{-1} 3300, 3000, 1657, 1040, 920, 862, 840, 818; NMR (CCl_4) τ 4.10 (m, 2 H, H-4 and H-5), 6.36 (m, 1 H, H-1), 6.40 (m, 1 H, H-3), 6.80 (s, 1 H, OH), 6.96 (d-d, J = 8, 4 Hz, 1 H, H-2), 7.4-8.6 (m, 6 H, $-CH_2-$).

Determination of Relative Oxidation and Epoxidation Rates of 1b, 4, 8, 9, and 10. The competitive kinetic technique was used to determine the relative oxidation rates. Equimolar amounts (respectively 10.0 mmol) of the two olefinic alcohols were dissolved in 20 mL of benzene solution of 27 mg (0.2 mmol) of $VO(acac)_2$. To the stirred solution at 40 °C was added dropwise 0.20 g (2.0 mmol) of t-BuOOH. After 24 h, the amounts of recovered olefinic alcohols were determined by GLC.

The relative rate was calculated using the usual first-order expression $k_B/k_A = \ln (B/B_0)/\ln (A/A_0)$. The validity of the kinetic order was ascertained using the two olefinic alcohols, **1b**, A and **9**, B. Two runs were made with $A_0 = B_0$, $0.5B_0$, and $2B_0$, respectively. Calculated rate ratios of k_B/k_A were 0.42, 0.50, and 0.38, identical within experimental uncertainty.

In separate experiments, each olefinic alcohol was reacted with t-BuOOH/V catalyst system by method A. The selectivity (S) of epoxy alcohols to the total oxidates was determined by GLC. The relative epoxidation rate between two olefinic alcohols A and B was calculated using the expression $k_B'/k_A' = k_BS_B/k_AS_A$. The relative oxidation and epoxidation rates of **4**, **8**, **1b**, **9**, and **10** are given in Table V.

Epoxidation of *cis*- and *trans*-5-*tert*-Butylcyclohex-2-en-1-ol (16 and 17). **16** and **17** were prepared by the method of Whitham et al. **16**: bp 117-119 °C (17.6 mm) (ref 11, 114-116 °C (20 mm)). **17**: bp 70-71 °C (1.5 mm) (ref 11, 110-111 °C (12 mm)). Each epimer of **16** and **17** was reacted with the t-BuOOH/V catalyst system by method A and with MCPBA by method C, with the exception that reaction time was prolonged to 50 h in these cases, respectively.

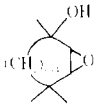
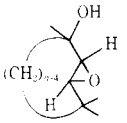
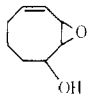
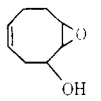
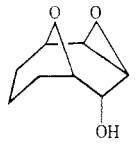
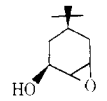
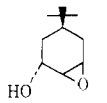
The structure of epoxy alcohols **18**, **19**, **20**, and **21**, collected by preparative GLC, was identified by comparison of IR and NMR spectral data with those in the literature.[11] The product yields and epoxide stereoselectivity are summarized in Table VI.

Preparation of 9-Oxabicyclo[3.3.1]non-3-en-2-one (26). To a stirred solution of 1.40 g (10.0 mmol) of exo enol **13** in 30 mL of acetone at 0 °C was added dropwise 3.7 mL (10.0 mmol) of 2.7 M Jones reagent[45] during 4 h. Extraction and distillation gave 0.85 g (62%) of enone **26**: bp 52 °C (1 mm); IR (film) cm^{-1} 3040, 1678, 1650, 1086, 1067, 1045, 1002, 894, 884, 820, 830; NMR (CCl_4) τ 3.07 (B part of ABX, J = 10, 4.5 Hz, 1 H, H-4), 3.73 (A part of ABX, J = 10 Hz, 1 H, H-3), 5.47 (t, J = 4.2 Hz, 1 H, H-1), 5.86 (m, 1 H, H-5), 7.7-8.8 (m, 6 H, $-CH_2-$); mass m/e 138 $[M]^{\cdot+}$.

Preparation of 9-Oxabicyclo[3.3.1]non-3-en-*endo*-2-ol (23). **26** (2.80 g, 20.0 mmol) in 60 mL of ether was treated with 1.00 g (25.0 mmol) of $LiAlH_4$ in 30 mL of ether at −75 °C for 24 h. Hydrolysis, extraction, and distillation gave 1.08 g (77%) of **23** in 98.8% purity (contaminated by 1.2% of **13**. **23**: bp 98-100 °C (1.2 mm); IR (film) cm^{-1} 3320, 3000, 1655, 1067, 1029, 902, 880, 867, 780; NMR (CCl_4) τ 4.16 (broad d, J = 10 Hz, 1 H, H-3), 4.43 (d-d-d, J = 10, 3.3, 2 Hz, 1 H, H-4), 5.58 (m, 1 H, H-2), 5.86 (m, 1 H, H-5), 6.14 (m, 1 H, H-1), 7.22 (broad s, 1 H, OH), 7.9-8.8 (m, 6 H, $-CH_2-$).

Epoxidation of 13. 13 (1.40 g, 10.0 mmol) was treated with t-BuOOH/V catalyst system by method A. GLC analysis showed the formation of 1.14 g (73%) of *exo*-3,4-epoxy-9-oxabicyclo[3.3.1]-nonan-*exo*-2-ol (**24**) and 0.15 g (11%) of **26**. After the usual workup, the residue was chromatographed on 40 g of Florisil column. Elution with petroleum ether and ether (1:1 v/v) and recrystallization from CH_2Cl_2 and ether (1:1 v/v) gave 0.85 g (55%) of pure **24**: needle, mp 132-133 °C; IR (CCl_4) cm^{-1} 3570, 1073, 1030, 853, 762; NMR ($CDCl_3$) τ 5.86 (m, 1 H, H-1), 6.28 (m, 1 H, H-5), 6.43 (d, J = 3.8 Hz, 1 H, H-3), 6.48 (m, 1 H, H-2), 6.87 (d-d, J =3.8, 1.6 Hz, 1 H, H-4), 7.16 (broad d, J = 11.3 Hz, 1 H, OH), 7.8-8.7 (m, 6 H, $-CH_2-$). Anal. Calcd for $C_8H_{12}O_3$: C, 61.54; H, 7.69. Found: C, 61.65; H, 7.73.

Table IX. Hydroxyl Bands of Cyclic 2,3-Epoxy Alcohols

	cis	trans	$\Delta\nu_{OH} = \nu^{free} - \nu^{intra}$
			
$n = 5$	3596	3633	37
$n = 6$	3595 (3575)[a]	3625	30
$n = 7$	3605 (3585)[a]	3622	17
$n = 8$	3562	3615	53
$n = 9$	3555	3610	55
			
$n = 8$ (*1RS,2RS*)		3624	
(*1SR,2RS*)	3590		
$n = 9$	3573	3618	45
$n = 12$	3564	3610	46
	3596	3615	19
	3587	3610	23
	3565	3633	68
	3595	3624	29
	3575	3620	45

[a] Shoulder peak.

The reaction of 1.40 g (10.0 mmol) of **13** with 2.20 g (11.0 mmol) of MCPBA was found to proceed much more slowly and, after 2 days reaction, 1.02 g (65%) of **24**, 0.11 g (8%) of **26**, and 0.25 g (18%) of unreacted **13** were detected by GLC analysis.

Epoxidation of 23. 23 (1.40 g, 10.0 mmol) was treated with 2.20 g (11.0 mmol) of MCPBA at 25 °C for 3 days. GLC analysis indicated the formation of 0.66 g (42%) of *exo*-3,4-epoxy-9-oxabicyclo[3.3.1]-nonan-*endo*-2-ol (**25**) and 0.19 g (14%) of **26** and the recovery of 0.41 g (29%) of **23**. After the usual workup, the residue was chromatographed on 30 g of Florisil column. Elution with petroleum ether and ether (1:1 v/v) gave 0.52 g (33%) of **25** as a colorless syrup. **25:** bp 127–130 °C (0.2 mm) (partially decomposed); IR (CCl_4) cm^{-1} 3634, 1230, 1087, 1063, 880, 825; NMR (CCl_4) τ 5.90 (m, 1 H, H-1), 5.93 (m, 1 H, H-5), 6.13 (m, 1 H, H-2), 6.28 (broad d, J = 7.8 Hz, 1 H, OH), 6.98 (d, J = 3.8 Hz, 1 H, H-3), 7.04 (d, J = 3.8 Hz, 1 H, H-4), 7.8–8.8 (m, 6 H, $-CH_2-$).

The close structural relation between **24** and **25** was confirmed by the Jones oxidation of them to give a common epoxy ketone, *exo*-3,4-epoxy-9-oxabicyclo[3.3.1]nonan-2-one: mp 49–51 °C (recrystallized from petroleum ether); IR (Nujol) cm^{-1} 1723, 1245, 1089, 1045, 884, 857, 826, 783, 752.

The vanadium-catalyzed reaction of 1.40 g (10.0 mmol) of **23** with *t*-BuOOH by method A was performed during 48 h. GLC analysis showed the formation of 1.23 g (89%) of **26** and 0.04 g (3%) of **25**.

Acknowledgments. We wish to thank the donor of a grant (275443) from the Ministry of Education, Japan, for support of this work.

Appendix

Some characteristic features in the IR and NMR spectra of a series of cis and trans epoxy alcohols produced by the stereoselective epoxidation of cyclic allylic alcohols are summarized briefly. The hydroxyl frequencies and the methine proton chemical shifts of epoxy alcohols are shown in Tables IX and X, respectively.

(1) The infrared spectra of cis epoxy alcohols in dilute carbon tetrachloride solution show absorption bands due to the intramolecular hydroxyl (ν_{OH}^{intra}) in the frequency region of 3605–3550 cm^{-1}. On the other hand, trans epimers show either the free hydroxyl band (ν_{OH}^{free}) in the frequency region higher than 3605 cm^{-1} or the intermolecular hydrogen bonding absorption (ν_{OH}^{inter}) in the range of 3460–3400 cm^{-1}, depending on the concentration of solution. The separation between ν_{OH}^{free} and ν_{OH}^{intra}[31] increases with increasing the ring size from common to

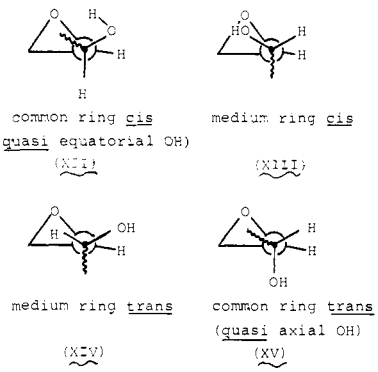


Table X. ^{1}H NMR Chemical Shifts of Methine Protons of Cyclic 2,3-Epoxy Alcohols

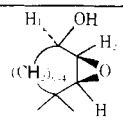
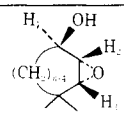
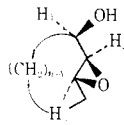
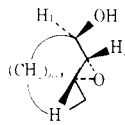
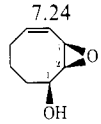
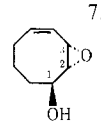
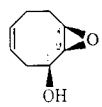
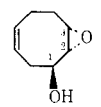
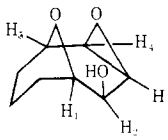
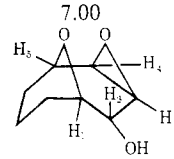
	cis			trans			$\Delta\tau_{H\text{-}1}$ ($= \tau_{trans} - \tau_{cis}$)
	H-1	H-2	H-3	H-1	H-2	H-3	
							
$n = 5$	5.83	6.65	6.65	5.81	6.82	6.66	−0.02
$n = 6$	6.10	6.78	6.78	6.00	6.98	6.77	−0.10
$n = 7$	6.15	7.03	6.85	6.28	6.85–7.20		+0.13
$n = 8$	5.67	7.1–7.4		6.35	6.85–7.20		+0.68
$n = 9$	5.70	7.1–7.4		6.50	6.9–7.4		+0.80
							
$n = 8$ (1*RS*,2*RS*)				6.62	7.15–7.4		
(1*SR*,2*RS*)	5.92	7.35	6.91				
$n = 9$	5.92	7.30	6.96	6.84	7.1–7.4		+0.92
$n = 12$	6.00	7.24	7.06	6.95	7.2–7.5		+0.95
							
	6.10	7.04	6.85	6.36	6.96	6.40	+0.26
							
	6.02	6.85	6.85	5.76	7.00	6.92	−0.26
							
	H-2	H-3	H-4	H-2	H-3	H-4	$\Delta\tau_{H\text{-}2}$
	6.48	6.43	6.87	5.90	6.98	7.04	−0.58

Table XI. Kinetic Parameters for Racemization of Optically Active (*E*)-Cycloalkenes

	$t_{1/2}$	$\delta H^{\ddagger}$, kcal/mol
(*E*)-Cyclooctene	122 h (133 °C)	35.6 (155 °C)
(*E*)-Cyclononene	20 s (20 °C)	19.4 (−10 °C)
(*E*)-Cyclodecene	too fast to be measured	

medium; medium-ring cis epoxy alcohols exhibit stronger intramolecular bands than common ring ones. This can be rationalized in terms of the conformation change of cis epoxy alcohols from common to medium ring as illustrated in XII and XIII, respectively. In the medium-ring region, the hydroxyl group overlaps more effectively with the adjacent oxirane ring, which makes the intramolecular hydrogen bonding stronger.

(2) ^{1}H NMR spectra of medium-ring trans epoxy alcohols show alcoholic methine proton signals at remarkably higher fields than the corresponding cis epimers as shown in Table X. In the cases of nine- and twelve-membered ring epoxy alcohols, the difference between trans and cis epimers ($\Delta\tau = \tau_{trans} - \tau_{cis}$) reaches to almost 100 Hz. The higher field shift of trans C_1 protons must be due to the magnetic anisotropic effect[32] exerted by the adjacent oxirane ring just overlapping with the C_1 proton, as shown by XIV. C_1 protons of common-ring trans epoxide **XV** are not affected by such effect. Alternately in common-ring epoxy alcohols the anisotropic effect exerted by the neighboring C–C single bond[33] is predominant for the C_1 protons, which deshields the equatorial proton much more than the axial one. Thus $\Delta\tau$ shows minus values for common-ring epoxy alcohols.

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Secondary Deuterium Isotope Effects for Certain Acyl Transfer Reactions of Phenyl Formates[1a]

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Abstract: Kinetic α secondary deuterium isotope effects, k_D/k_H, for formyl group transfer from either the 4-methoxyphenyl or 4-nitrophenyl esters, or both, of formic and deuterioformic acids to a variety of oxygen acceptors have been measured at 25 °C in aqueous solution: hydroperoxide ion, 1.12; 2-propynol anion, 1.13; hexafluoropropan-2-ol anion, 1.14; and water, 1.22. In addition, corresponding isotope effects have been obtained for general-base-catalyzed formyl group transfer from the same substrates to acetate, 1.21, formate, 1.23, and trimethylamine *N*-oxide, 1.20. The α secondary deuterium isotope effect for acid-catalyzed hydrolysis of both esters has been determined to be 1.24. These data are interpreted to reflect considerable, and perhaps complete, carbon–oxygen bond formation in the transition state for addition of oxygen nucleophiles to phenyl formates. Finally, corresponding isotope effects were determined for reaction of fluoride, 1.19, and azide, 1.14, which also suggest substantial covalent bond formation between ester and nucleophile in the transition state.

Addition of nucleophilic reagents to the acyl carbon atom, as in the hydrolysis and aminolysis of esters, will result in progressive rehybridization of the acyl carbon atom of the substrate from sp^2 to sp^3, corresponding to formation of a tetrahedral addition intermediate, and then from sp^3 to sp^2, as the tetrahedral species decomposes to products. Should the reaction occur without formation of a tetrahedral intermediate, a related type of rehybridization should occur, although sp^3 geometry will not be fully attained at any stage along the reaction coordinate. Since the magnitude of kinetic α secondary deuterium isotope effects is largely determined by changes in the frequency of the out of plane bending mode which accompanies sp^2–sp^3 rehybridization,[2,3] it follows that measurements of such effects should yield useful information concerning transition-state structures for acyl transfer reactions of formic acid derivatives.

Bilkadi et al. have, in fact, pursued such measurements for hydrolysis and hydrazinolysis of methyl and ethyl formates and were able to define the transition state for these reactions in considerable detail,[4] particularly for those reactions for which oxygen-18 isotope effects had also been measured.[5] In the work described herein, we have elected to examine α secondary deuterium isotope effects for acyl transfer reactions of phenyl formates. This system offers the possibilities of (1) ready modification of substrate reactivity through change of polar substituents in the leaving group, (2) examination of a large number of nucleophilic reagents which react with these esters at convenient rates, and (3) correlation of the results with those in the extensive literature for acyl transfer reactions of phenyl acetates.[6-8] Results reported herein, the first phase of anticipated studies, deal mainly with reactions of oxy anions with 4-methoxyphenyl and 4-nitrophenyl formates.

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