than 350 nm). The absorbances of Figures 1, 2, and 4 are observed values in the flash photolysis cell with 10 cm of optical path. Temperature of solution was controlled by immersing the flash photolysis cell in a bath cooled by low-temperature methanol in the vessel with windows.

Procedure. On the addition of toluene, the dark reaction was monitored by the absorption band of $K_2[Ce(NO_3)_6]$ at 350 nm in order to check the reactions of aromatic compounds with $K_2[Ce(NO_3)_6]$. Under the conditions of temperature (<20 °C) and concentrations of toluene ($<10^{-3}$ M) and $K_2[Ce(NO_3)_6]$ ($<10^{-3}$ M), the consumptions of both materials were not observed in acetonitrile. For each flash exposure, a freshly prepared solution was used. The presence of oxygen in solution did not affect the decay rate of $NO_3^{\bullet}$; all measurements were performed in aerated solution.

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Registry No. CH_3OH, 67-56-1; CH_3CH_2OH, 64-17-5; $(CH_2)_4O$, 109-99-9; $C_6H_5OCH_3$, 100-66-3; C_6H_6, 71-43-2; C_6H_5F, 462-06-6; C_6H_5CN, 100-47-0; $C_6H_5CH_3$, 108-88-3; D_2, 7782-39-0; *m*-$CH_3C_6H_4CH_3$, 108-38-3; *p*-$NO_2C_6H_4CH_3$, 99-99-0; *m*-$NO_2C_6H_4CH_3$, 99-08-1; *p*-$CNC_6H_4CH_3$, 104-85-8; *m*-$CNC_6H_4CH_3$, 620-22-4; *p*-$CH_3C(O)C_6H_4CH_3$, 122-00-9; *m*-$FC_6H_4CH_3$, 352-70-5; *m*-$ClC_6H_4CH_3$, 108-41-8; *p*-$ClC_6H_4CH_3$, 106-43-4; *p*-$CH_3C_6H_4CH_3$, 106-42-3; *p*-$CH_3OC_6H_4CH_3$, 104-93-8; $K_2[Ce^{IV}(NO_3)_6]$, 17126-44-2; $NO_3^{\bullet}$, 12033-49-7; *p*-methylanisole, 38144-90-0.

Lewis Acid Promoted Decomposition of Substituted 1,3,2λ⁵-Dioxaphospholanes: Kinetic and Thermodynamic Studies

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The kinetics of Lewis acid mediated decomposition of a series of substituted 1,3,2λ⁵-dioxaphospholanes, prepared by transphosphoranylation of 1,2-diols with diethoxytriphenylphosphorane (DTPP), is reported. The rate data, obtained from ^{31}P NMR spectroscopic measurements, emphasize the influence of (i) variations in the coordination potential (i.e., cationic charge) of the Lewis acids, (ii) methyl group substitution at C-4 and C-5 in the 1,3,2λ⁵-dioxaphospholanyl substructure, and (iii) changes in solvent polarity. Also, the propensity for 1,2-hydride migratory processes attending conformationally restricted *bicyclic* 1,3,2λ⁵-dioxaphospholanes versus epoxide formation from the collapse of simple *cyclic* 1,3,2λ⁵-dioxaphospholanes were examined. The results are best explained by invoking a "site-selective" coordination by the catalyst to one of the "ethereal" oxygens within the 1,3,2λ⁵-dioxaphospholanyl moiety initiating P–O bond cleavage and ultimately affording the requisite betaine intermediate(s). Methyl substitution on the 1,3,2λ⁵-dioxaphospholanyl hydrocarbon backbone decreases the rate of P–O bond cleavage, and the 1,2-hydride migratory process within conformationally rigid bicyclic 1,3,2λ⁵-dioxaphospholanes requires ca. 2.0 kcal/mol more energy than the decomposition of the *monocyclic* 1,3,2λ⁵-dioxaphospholanes via 3-exo-tet cyclization to the respective cyclic ethers. Mechanistic implications of various reactions are discussed.

Introduction

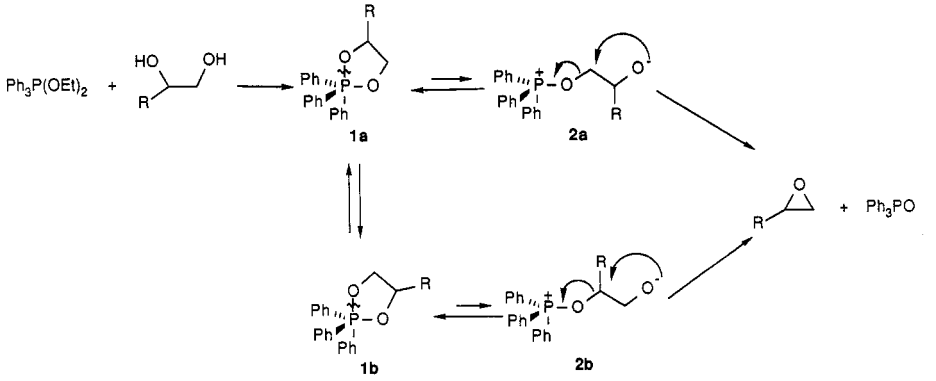
Recent research from our laboratories has demonstrated that both cyclic and acyclic dioxaphosphoranes are useful reagents for preparing a variety of heterocycles, including cyclic ethers,[1-6] cyclic sulfides,[4,5,7] chiral aziridines,[4,5,8] and diastereomeric 1,4-oxathianes.[9] The transphosphoranylations of, particularly, mono- and disubstituted 1,2-diols with diethoxytriphenylphosphorane (DTPP) give the requisite 1,3,2λ⁵-dioxaphospholane intermediates, which subsequently decompose to the corresponding oxiranes in high yields (40 °C, 48 h). By contrast, the sterically more congested, tri- and tetrasubstituted 1,3,2λ⁵-dioxaphospholanes from the condensation of the corresponding 1,2-diols with DTPP require higher reaction temperatures (80–100 °C, 48 h) for initiating *any* appreciable reaction. In fact, these higher temperatures cause a diminution in the yield of the epoxides and accelerate production of a variety of side products. In this light, we reported that lithium bromide (LiBr) catalyzes the smooth and rapid cyclodehydration of these substituted 1,2-diols, through the corresponding 1,3,2λ⁵-dioxaphospholanes, giving remarkably high yields of the epoxides at ambient temperature while suppressing formation of the side products.[10]

A mechanistic rationale for oxaphosphorane-promoted cyclodehydration of a 1,2-diol is presented in Scheme II. Transphosphoranylation of vicinal diols with DTPP produces the intermediate 1,3,2λ⁵-dioxaphospholanes, **1a** and **1b**, which undergo rapid Berry pseudorotation and afford time-averaged NMR resonances (^{31}P δ −35 to −50 ppm).[11]

(1) Robinson, P. L.; Barry, C. N.; Kelly, J. W.; Evans, S. A., Jr. *J. Am. Chem. Soc.* **1985**, *107*, 5210–9.
(2) Bass, S. W.; Barry, C. N.; Robinson, P. L.; Evans, S. A., Jr. *Phosphorus Chemistry: Proceedings of the 1981 International Conference*; Quin, L. D., Verkade, J. G., Eds; *ACS Symposium Series* **1981**, *171*, 165.
(3) Robinson, P. L.; Bass, S. W.; Jarvis, S. E.; Evans, S. A., Jr. *J. Org. Chem.* **1983**, *48*, 5396.
(4) Kelly, J. W.; Evans, S. A., Jr. *J. Org. Chem.* **1986**, *51*, 4473.
(5) Kelly, J. W.; Evans, S. A., Jr. *J. Org. Chem.* **1986**, *51*, 5490.
(6) Robinson, P. L.; Evans, S. A., Jr. *J. Org. Chem.* **1985**, *50*, 3860.
(7) Robinson, P. L.; Kelly, J. W.; Evans, S. A., Jr. *Phosphorus Sulfur* **1987**, *31*, 59–70.
(8) Kelly, J. W.; Eskew, N. A.; Evans, S. A., Jr. *J. Org. Chem.* **1986**, *51*, 95–7.
(9) Murray, W. T., Kelly, J. W.; Evans, S. A., Jr. *J. Org. Chem.* **1987**, *52*, 525–9.
(10) Murray, W. T.; Evans, S. A., Jr. *Nouv J. Chem.*, in press.

0022-3263/89/1954-2440$01.50/0

Scheme I



Scheme II

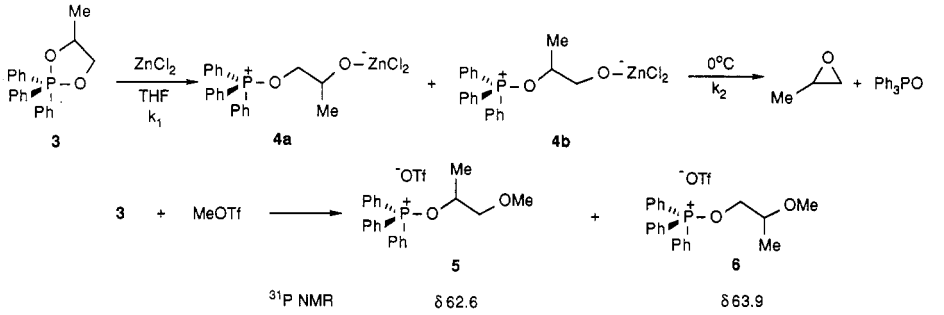


Table I. Rate Constants for the Decomposition of Substituted 1,3,2λ⁵-Dioxaphospholanes

entry	dioxaphospholane	catalyst	temp, °C	rate constant[a,b]
1	3	none	52	5.7×10^{-5} s^{-1}
2	3	LiBr	31	2.0×10^{-4} M^{-1} s^{-1}
3	3	Bu_4NBr	27	<50% done after 3 months
4	3	LiI	31	2.7×10^{-4} M^{-1} s^{-1}
5	3	$LiClO_4$	31	4.3×10^{-4} M^{-1} s^{-1}
6	3	$ZnCl_2$	25	3.1×10^{-2} M^{-1} s^{-1} (k_1)
7	3	$ZnCl_2$	0	1.2×10^{-4} s^{-1} (k_2)
8	9	$ZnCl_2$	25	1.26×10^{-2} M^{-1} s^{-1} (k_1)
9	10	$ZnCl_2$	25	1.23×10^{-2} M^{-1} s^{-1} (k_1)
10	13	LiBr[c]	52	9.2×10^{-5} M^{-1} s^{-1}
11	13	$ZnCl_2$	25	1.2×10^{-4} s^{-1} (k_2)
12	13	LiBr[d]	52	2.9×10^{-4} M^{-1} s^{-1}

[a] The rate constant reported in entries 2, 4–6, 8–10, and 12 were calculated from $k = k_{obsd}/[\text{Lewis acid}]_{av}$. [b] All rate constants are ±0.15 based on a minimum of three rate determinations. [c] Solvent: 89:11 THF/benzene. [d] Solvent: 44:56 THF/benzene.

Thermolysis (40–60 °C, 12 h) of **1a** and **1b** causes P–O bond cleavage, generating betaines **2a** and **2b**, which subsequently collapse via "3-exo-tet" alkoxide ion displacement of triphenylphosphine oxide (TPPO) to afford the epoxide[12] or nonracemic epoxides if the diol is enantiomerically homogeneous.[3] Tri- and tetrasubstituted 1,3,2λ⁵-dioxaphospholanes, however, appear to be thermodynamically more stable than their mono- and disubstituted analogues (vide infra) responding the *gem*-dialkyl effect caused by the alkyl groups juxtapose the ring oxygens; thus, higher reaction temperatures are required for efficient generation of the betaine intermediates, and this additional energy also encourages formation of the side products. The action of lithium bromide, presumably through cationic Li^+ coordination to the apical oxygen,[13] weakens the phosphorus–oxygen (P–O) bond and facilitates formation of the betaines from 1,3,2λ⁵-dioxaphospholanes, **1a** and **1b**.

These early findings created an intense interest in the mechanistic scope of Lewis acid promoted decomposition of substituted 1,3,2λ⁵-dioxaphospholanes. Herein, we report kinetic results with respect to (i) variations in the nature of the Lewis acid, (ii) substitution on the 1,3,2λ⁵-dioxaphospholanyl backbone, (iii) differences in solvent polarity, and (iv) energetic differences between a 1,2-hydride migration and 3-exo-tet betaine collapse to the cyclic ether.

Results and Discussion

A. Variations in the Nature of the Lewis Acid Effect of the Cation. We initiated our studies by examining the rate of decomposition of 4-methyl-2,2,2-triphenyl-1,3,2λ⁵-dioxaphospholane (**3**) in tetrahydrofuran (THF)/benzene-d_6 solution. This system was chosen because (i) the thermal decomposition of 1,3,2λ⁵-dioxaphospholane **3** may be measured readily, while the more hindered systems are less amenable, (ii) propylene oxide, the cyclization product from the thermolysis of **3**, is well-characterized spectroscopically (i.e., ^1H and ^{13}C

(11) Kelly, J. W.; Evans, S. A., Jr. *J. Am. Chem. Soc.* **1986**, *108*, 7681–5.

(12) Baumstark and co-workers have presented kinetic evidence that supports the generation of betaine intermediates during the thermal decomposition of 1,3,2λ⁵-dioxaphospholanes. See: Baumstark, A. L.; McClosky, C. J.; Williams, T. E.; Chisope, D. R. *J. Org. Chem.* **1980**, *45*, 3593–7.

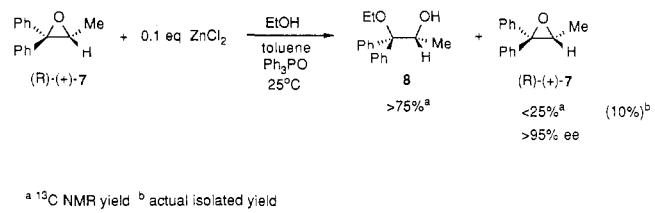
(13) Luckenbach, R. *Dynamic Stereochemistry of Pentaco-ordinated Phosphorus and Related Elements*; George Thieme Verlag: Stuttgart, 1973.

NMR), and (iii) the solubility as well as stability of the 1,3,2λ⁵-dioxaphospholanes and the Lewis acids are best accommodated in THF solvent.[14] We previously reported the kinetic results of the thermolysis and the LiBr-promoted decomposition of **3** (Table I).[10] The lack of any significant decomposition of **3** in the presence of $(n\text{-Bu})_4N^+Br^-$ clearly shows that the catalytic influence of LiBr is associated with Li^+'s ability to weaken the P–O bond within the 1,3,2λ⁵-dioxaphospholane by cationic coordination. We have now extended this study to include zinc chloride ($ZnCl_2$), a stronger Lewis acid than Li^+, which is expected to provide a significant rate enhancement.

This is, indeed, what is observed. In fact, the addition of one equivalent of $ZnCl_2$ to 1,3,2λ⁵-dioxaphospholane **3** at −78 °C (dry ice/acetone bath) initiates rapid and quantitative conversion of **3** to the zinc-coordinated betaine intermediates, **4a** and **4b**, whose identities were confirmed by ^{31}P NMR spectroscopy (δ 63.5 and 62.0 ppm, respectively; Scheme II). These ^{31}P NMR shifts occur in the region expected for triphenyl oxaphosphonium salts,[15] and their assignments were further corroborated by the preparation of the regioisomeric oxaphosphonium salts **5** and **6** via methylation of oxaphospholane **3** with methyl trifluoromethane sulfonate (^{31}P δ 63.9 and 62.6 ppm; Scheme II).

Subsequent warming of **4a** and **4b** allows for the direct assessment of the rate for the 3-exo-tet displacement of TPPO (k_2). At 0 °C, the observed rate of decomposition is $k_{obsd} = 1.2 \times 10^{-4}$ s^{-1}, equivalent to a free energy of activation ($\Delta G^{\ddagger}$) of 20.8 kcal/mol.[16] This activation energy is slightly larger than the $\Delta G^{\ddagger} = 20.2$ kcal/mol characterizing the hydroxide ion induced formation of ethylene oxide from 2-chloroethanol in a 1:1 dioxane/water medium.[17] Here, the higher activation barrier attending the decomposition of **4a** and **4b** is probably associated with several variables including (i) the *decreased* nucleophilicity of the oxyanion of the betaine resulting from zinc coordination and (ii) the enhanced leaving group potential of Cl^- in a stabilizing, polar solvent versus TPPO in THF solvent.

In addition to the direct measurement of the rate of betaine collapse, we have measured the rate of $ZnCl_2$-promoted opening of the 1,3,2λ⁵-dioxaphospholane (k_1). Since formation of the betaines is largely irreversible ($k_2 \gg k_{-1}$), reaction of a 10-fold excess of 1,3,2λ⁵-dioxaphospholane **3** with $ZnCl_2$ provides a pseudo-first-order rate constant for 1,3,2λ⁵-dioxaphospholane ring opening, $k_1 = 3.1 \times 10^{-2}$ M^{-1} s^{-1} at 25 °C. (For a further discussion of $ZnCl_2$-promoted ring opening of 1,3,2λ⁵-dioxaphospholanes, see the section entitled "Substituent Effects".) These results clearly show that the ability of Lewis acids to accelerate 1,3,2λ⁵-dioxaphospholane decomposition is directly related to their coordinating potential with the ethereal oxygens. Synthetically, reasonable caution should be exercised when selecting the "ideal" catalyst in light of the well-documented ability of strong Lewis acids to compromise the structural integrity of epoxides by promoting the Pinacol rearrangement[18] or generating carbocations. In fact, the presence of carbocations is illustrated during the addition of 0.1 equiv of $ZnCl_2$ to 1,1-diphenyl-1,2-epoxypropane (**7**) in toluene solvent. Two equivalents of ethanol and 1 equiv of TPPO were also added to mimic our previous reaction conditions. Here, >75% 1-ethoxy-1,1-diphenyl-2-propanol (**8**) is formed along with 10% recovered epoxide **7** after 18 h (Figure 1).



[a] ^{13}C NMR yield [b] actual isolated yield

Figure 1.

B. Variations in Lewis Acids—Ion Pair/Monomer/Dimer. The discovery that LiBr-catalyzed decomposition of the intermediate 1,3,2λ⁵-dioxaphospholane in THF solvent posed a more fundamental question concerning the structure of "LiBr" during catalysis and how this affects the rate of 1,3,2λ⁵-dioxaphospholane decomposition. Although we have referred to the LiBr catalysis as proceeding via "cationic" coordination, in the main, LiBr exists in organic solvents in large concentrations as LiBr aggregates. In fact, Goralski and Chabenal[19] have shown that LiBr is most probably dimerized in THF solvent, while lithium iodide (LiI) and lithium perchlorate ($LiClO_4$) are more soluble, less aggregated, and monomeric in THF solvent. We, therefore, examined the importance of ion pair/monomer/dimer compositions of the lithium salts on the rate of decomposition of 1,3,2λ⁵-dioxaphospholane **3**.

As has been previously reported,[10] the rate constant for decomposition of **3** in the presence of LiBr at 31 °C is $k = 2.0 \times 10^{-4}$ M^{-1} s^{-1}. With LiI as the Lewis acid, the rate constant increases to $k = 2.7 \times 10^{-4}$ M^{-1} s^{-1} at 31 °C. Finally, $LiClO_4$ causes a further rate enhancement: $k = 4.3 \times 10^{-4}$ M^{-1} s^{-1}. These results are best interpreted in terms of the extent of aggregation as well as the effective charge about lithium in the lithium salts. The formation of LiBr dimers in THF solvent reduces the "relative concentration" of free Li^+ cations available for catalysis as compared to monomeric LiI or $LiClO_4$.[19] The likelihood that dimeric LiBr is capable of catalyzing the decomposition of 1,3,2λ⁵-dioxaphospholanes seems remote because of the reduced effective nuclear charge on the lithium ion. Furthermore, the probability of having both lithium ions in dimeric LiBr available for coordinating with the apical oxygens of two *different* 1,3,2λ⁵-dioxaphospholanes should be extremely low due to unfavorable steric interactions and entropic considerations. The third option, which seems most likely, is that the majority of the catalytic effect of LiBr arises from a low equilibrium concentration of monomeric LiBr and solvent separated $Li^+//Br^-$ ions (i.e., LiBr ⇌ $Li^+//Br^-$). Thus, the rate difference between monomeric and dimeric salts can be attributed to the reduced concentration of available lithium cations in the LiBr-catalyzed decompositions relative to the LiI-assisted reactions.

(14) The intermediate 1,3,2λ⁵-dioxaphospholanes decompose in the presence of protic solvents; therefore, high polarity solvents, which would promote dissolution of the salt, were unsatisfactory for this study.

(15) The ^{31}P NMR shifts reported here are consistent to those reported for analogous oxyphosphonium salts. For example (a) ethoxytriphenylphosphonium tetrafluoroborate (^{31}P δ 62.0 ppm), see: Denney, D. B.; Denney, D. Z.; Wilson, L. A. *Tetrahedron Lett.* **1968**, 85–9. (b) (Neopentyloxy)triphenylphosphonium bromide (^{31}P δ 61.7 ppm), see: ref 5. (c) Varasi, M.; Walker, K. A. M.; Maddox, M. L. *J. Org. Chem.* **1987**, *52*, 4235.

(16) The $\Delta G^{\ddagger}$ values were calculated by using the first-order rate of decomposition along with the Eyring equation, $k = (\kappa T/h) \exp(\Delta G^{\ddagger}/RT)$, where k is the measured rate, κ is the Boltzmann constant, T is the temperature of the reaction, h is Plank's constant, and R is the molar gas constant.

(17) (a) Heine, H. W.; Siegfried, W. *J. Am. Chem. Soc.* **1954**, *76*, 489. (b) Winstrom, L. O.; Warner, J. C. *J. Am. Chem. Soc.* **1939**, *61*, 1205.

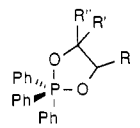
(18) See, for example: Parker, R. E.; Isaacs, N. S. *Chem. Rev.* **1959**, *59*, 737–99.

(19) Goralski, P.; Chabenal, M. *Inorg. Chem.* **1987**, *26*, 2169–71.

Lithium perchlorate ($LiClO_4$) is monomeric in THF solvent and increases the rate of decomposition of 1,3,2λ⁵-dioxaphospholanes considerably when compared to both LiI and LiBr. Intuitively, $LiClO_4$ should be less covalently bound than LiI considering the ionic size and stability of ClO_4^-. The subsequent rate enhancement thus reflects a larger positive charge density about lithium in $LiClO_4$ *or* substantially more $Li^+//ClO_4^-$, resulting in a greater Lewis acidity and stronger binding to the ethereal oxygens.

These results bring a clearer focus to the structure of the Lewis acid and also, in a circuitous way, helps to define the role and possible influence of the anion during the course of the reaction. While it is highly unlikely that the anion interacts significantly with phosphorus (e.g., to form a reactive negatively charged hexavalent phosphorane[20]) due to the bulkiness of the phenyl substituents,[21] the anion does influence reaction rates in an indirect fashion by dictating the structure of the lithium salt in solution. The more soluble, less aggregated lithium salts, which exist primarily as monomers in THF solvent, have a greater effective concentration than the dimeric salts (such as LiBr). This effectively translates into a higher equilibrium concentration of $Li^+//X^-$ (X = I, ClO_4) with more Li^+ available for efficient binding to the ethereal oxygen atoms.

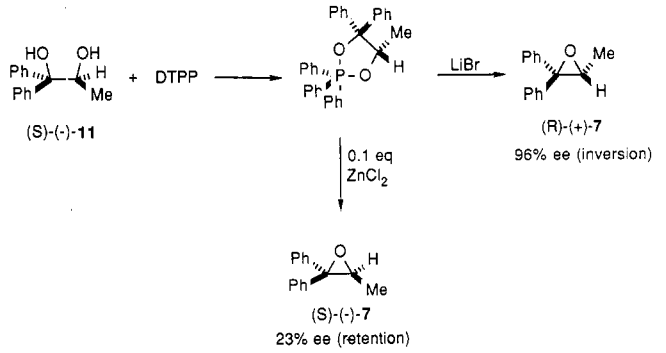
C. Methyl Substituent Effects. The rate of $ZnCl_2$-promoted 1,3,2λ⁵-dioxaphospholane ring opening was further examined with respect to variations in the number of methyl groups on the dioxaphospholanyl backbone. 4,5-Dimethyl-2,2,2-triphenyl-1,3,2λ⁵-dioxaphospholane (**9**) and 4,4,5-trimethyl-2,2,2-triphenyl-1,3,2λ⁵-dioxaphospholane (**10**) were prepared and the kinetics of $ZnCl_2$-catalyzed reaction were monitored. The rate constant for dioxaphospholane ring opening in **9** and **10** at 25 °C was $k_1 = (1.23\text{–}1.26) \times 10^{-4}$ M^{-1} s^{-1}, ca. 2.5 times slower than the analogous rate constant describing the ring opening of **3**. This result implies that the additional methyl groups exert "steric approach control" via repulsive steric interactions with the approaching $ZnCl_2$. Alternatively, it is conceivable that the P–O bond has acquired enhanced stability through the *gem*-dimethyl effect and subsequent ring stabilization. Unfortunately, attempts to measure the rate of decomposition of the tetramethyl analogue gave erratic results, and the data were not useful in supporting either hypothesis.



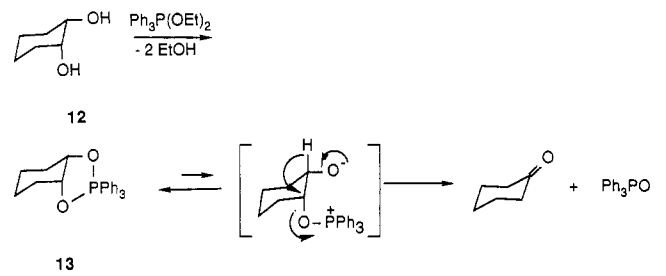
3 R=Me; R'=R"=H
9 R=R'=Me; R"=H
10 R=R'=R"=Me

Stereochemical results, however, do support the steric approach control hypothesis. We have previously demonstrated that reaction of enantiomerically homogeneous (*S*)-(–)-1,1-diphenyl-1,2-propanediol (**11**) [prepared by phenyl magnesium bromide addition to (*S*)-(–)-ethyl lactate] with DTPP in the presence of LiBr gives (*R*)-(+)-1,1-diphenyl-1,2-epoxypropane (**7**) with 96% ee,[10] implying equilibration of the two regioisomeric betaines with $k_{inv} > k_{ret}$. By contrast, reaction of diol **11** with DTPP and 0.1 equiv of $ZnCl_2$ produces epoxide **7**, exhibiting 23% ee, with net *retention* of stereochemistry (Scheme III). Since there is no NMR evidence for equilibration of the betaine intermediates in the $ZnCl_2$-promoted decomposition, this modest stereochemical bias is best interpreted in terms of steric differentiation by $ZnCl_2$ *within* the 1,3,2λ⁵-dioxaphospholane, with preferential P–O bond cleavage at the sterically least hindered site. Finally, independent experiments indicate that the stereochemical integrity at C-2 within epoxide **7** is not compromised in the presence of $ZnCl_2$ (Figure 1, vide supra).

Scheme III



Scheme IV



D. Hydride Migration. It has been previously shown that reaction of *cis*-1,2-hexanediol (**12**) with DTPP affords the conformationally rigid, bicyclic 1,3,2λ⁵-dioxaphospholane **13**, which decomposes to cyclohexanone via a 1,2-hydride migration process (Scheme IV).[1,6,22] Consequently, it was of interest to examine and compare $\Delta G^{\ddagger}$ for this process relative to that attending 3-exo-tet betaine collapse to the epoxide (see Scheme I; R = Me). Reaction of 1,3,2λ⁵-dioxaphospholane **13** with LiBr in THF solvent provides a pseudo-first-order rate constant, $k = 9.2 \times 10^{-5}$ M^{-1} s^{-1} at 52 °C. More importantly, reaction of **13** with 1 equiv of $ZnCl_2$ produces the betaine intermediate (^{31}P NMR δ 61.6 ppm), and this allows for direct measure of $\Delta G^{\ddagger}$ for hydride migration. Decomposition of the betaine is characterized by the rate constant, $k_2 = 1.2 \times 10^{-4}$ s^{-1} at 25 °C, which gives $\Delta G^{\ddagger} = 22.9$ kcal/mol. Comparison of this activation energy with that associated with epoxide formation (vide supra) indicates that the hydride migration is ca. 2.0 kcal/mol higher in energy.

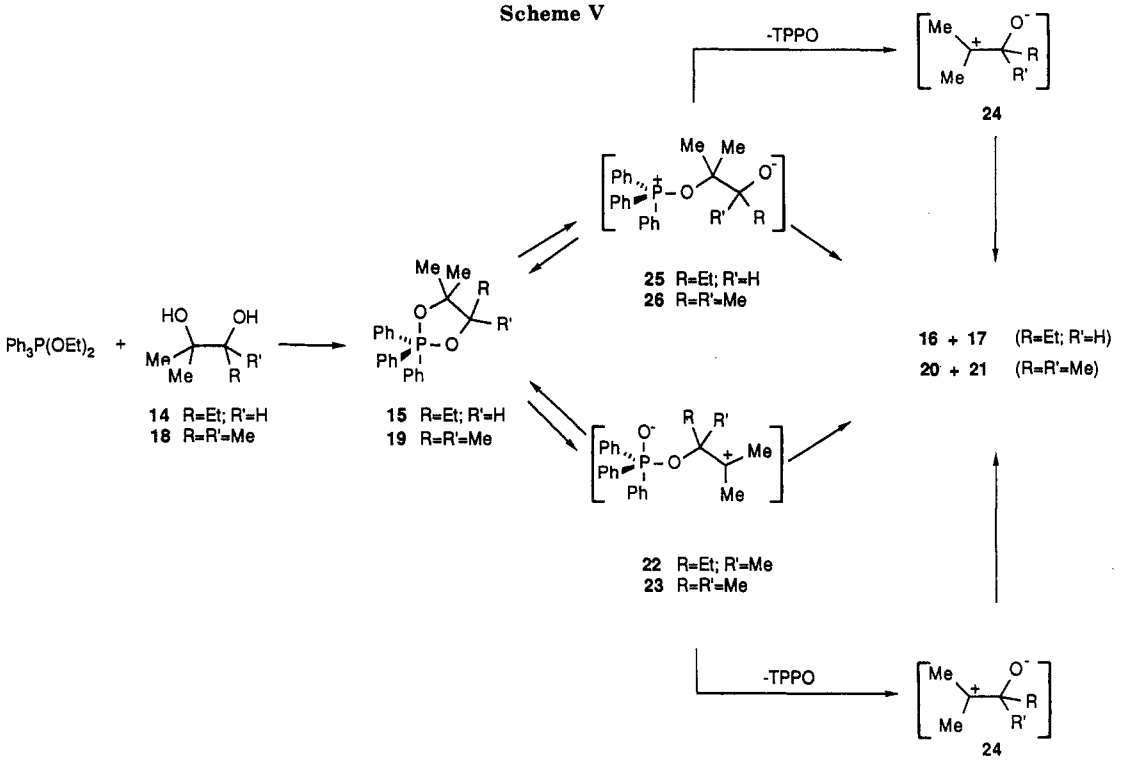
These data, combined with the product analyses from other reactions, help to clarify the mechanistic course initiated by thermolysis of tri- and tetrasubstituted 1,3,2λ⁵-dioxaphospholanes. For example, we have previously demonstrated that the reaction of 2-methyl-2,3-

(20) The intermediacy of hexavalent phosphoranes in substitution reactions at pentavalent phosphorus have been proposed. See, for example: (a) Ramirez, F.; Tasaka, K.; Desai, N. B.; Smith, C. P. *J. Am. Chem. Soc.* **1968**, *90*, 751. (b) Ramirez, F.; Loewengart, G. V.; Tsolis, E. A.; Tasaka, K. *J. Am. Chem. Soc.* **1972**, *94*, 3531. (c) Archie, W. C.; Westheimer, F. H. *J. Am. Chem. Soc.* **1973**, *95*, 5955. (d) Aksnes, G. *Phosphorus Sulfur* **1977**, *3*, 227. (e) Ramirez, F.; Ricci, J. S., Jr.; Okazaka, H.; Maracek, J. F.; Lewy, M. *Phosphorus Sulfur* **1984**, *20*, 279.

(21) The ability for anionic complexation to phosphorus has been proposed for the interaction of LiX (X = Cl, Br, I, ClO_4) with the sterically less hindered 2-methyl-2-oxo-4-methyl-1,3,2λ⁵-dioxaphosphol-4-ene. See: van Lier, J. J. C.; van de Ven, L. J. M.; de Haan, J. W.; Buck, H. M. *J. Phys. Chem.* **1983**, *87*, 3501.

(22) Penzi, G.; Zbiral, E. *Monatsch. Chem.* **1981**, *112*, 1045–54.

Scheme V



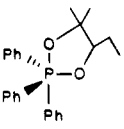
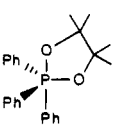
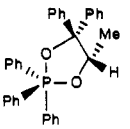
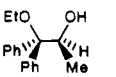
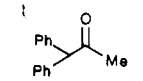
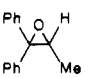
pentanediol (**14**) with DTPP produces the intermediate dioxaphospholane (**15**). Complete thermal decomposition of **15** requires 100 °C for 24 h and gives nearly equal amounts of 2-methyl-3-pentanone (**16**) and 2-methyl-1-penten-3-ol (**17**), as well as a trace of the expected epoxide.[1] Similarly, the reaction of pinacol (**18**) with DTPP affords 1,3,2λ⁵-dioxaphospholane **19**, which decomposes to give allylic alcohol **20** (85%), with a small quantity (15%) of epoxide **21** (Table II).[1] We speculate that the origins of allylic carbinols **17** and **20** (see Table II for applicable structural formulas) may involve a proton abstraction from within (i) carbocations **22** and **23**, which arise via a heterolytic carbon–oxygen bond separation in **15** and **19**, (ii) a zwitterionic intermediate such as **24**, or (iii) most probably from betaines **25** or **26** (Scheme V). Finally, we expect that ketone **16** would be readily formed through a hydride migration within betaine **25**.

A convincing result that supports the proposition for carbocationic intermediates during thermolysis of hindered 1,3,2λ⁵-dioxaphospholanes is the reaction of diol **11** with DTPP at 100 °C. Thermolysis of **11** gives 1,1-diphenyl-1-ethoxy-2-propanol (**8**; 65%), which apparently arises from ethanol trapping of the most stable carbocation within 1,3,2λ⁵-dioxaphospholane **27**.[10] Carbocations **22** and **23** are unstable intermediates and tend to react by intramolecular processes, while the carbocation from **27**, resonance stabilized by the phenyl groups, survives long enough to be captured by ethanol.

E. Solvent Effects. The ability of THF solvent to effectively coordinate metal cations is well known.[23] For this reason, and since the original DTPP/LiBr-promoted cyclodehydrations were performed in toluene solvent, we chose to examine the difference in rates by changing the solvent from a 89:11 mixture of THF/benzene to a 44:56 THF/benzene mixture (see Experimental Section for details). We anticipated that the rate of decomposition would increase in the latter solvent medium due to a diminished ability of the solvent to coordinate to the LiBr, thus increasing the propensity of the metal to coordinate to the 1,3,2λ⁵-dioxaphospholane oxygen atoms and provide the catalytic effect.

The 44:56 solvent medium was prepared by dissolving LiBr in THF solvent while the 1,3,2λ⁵-dioxaphospholane was prepared in benzene solvent. Equal volumes of the two solutions were then admixed, and the kinetics were monitored by following the rate of decomposition of 1,3,2λ⁵-dioxaphospholane **13** and the appearance of TPPO. The LiBr-promoted decomposition of **13** in 44:56 THF/benzene proceeds with $k = 2.9 \times 10^{-4}$ M^{-1} s^{-1} at 52 °C, which is approximately 3 times faster than the decompo-

Table II. Thermolysis of Tri- and Tetrasubstituted 1,3,2λ⁵-Dioxaphospholanes

diol	1,3,2λ⁵-dioxaphospholane	Products[a]	
 **14**	 **15**	 **16** 45%	 **17** 55%[b]
 **18**	 **19**	 **20** 85%	 **21** 15%[b]
 **11**	 **27**	 **8** 65%	 **28** 25%
		 **7** 10%[c]	

[a] Relative yields as determined by ^{13}C NMR spectroscopy in conjunction with: [b]GLC analyses or [c]HPLC analyses.

(23) The ability of ethers to complex lithium salts has been discussed extensively. See: Setzer, W. N.; Schleyer, P. v. R. *Adv. Organomet. Chem.* **1985**, *24*, 353.

sition of **13** in 89:11 THF/benzene (vide supra). Assuming that the rate of actual hydride migration (k_2) is essentially identical in these two solvent systems, the observed rate increase in the 44:56 solvent system can be explained by the enhanced ability of the *less solvated* Li^+ to coordinate to the P–O oxygen of the 1,3,2λ⁵-dioxaphospholane more efficiently.

Conclusions

The results that have been presented here clarify the nature of the activation processes that regulate 1,3,2λ⁵-oxaphospholane-mediated cyclodehydration and oxidative rearrangement processes. Thermolysis of 1,3,2λ⁵-dioxaphospholanes proceed through equilibration of the two regioisomeric betaine intermediates, with the resultant stereochemical bias for chain closure dependent upon the relative rates of intramolecular attack upon the two "regiodistinct" carbon atoms. Additional methyl groups (i.e., tri- and tetrasubstituted 1,3,2λ⁵-dioxaphospholanes) appear to increase the thermodynamic stability of the 1,3,2λ⁵-dioxaphospholanes. At present, we are unable to unequivocally ascertain whether the diminished rates attending decomposition of the heavily methylated 1,3,2λ⁵-dioxaphospholanes is attributed to the increased ground-state stability of the 1,3,2λ⁵-dioxaphospholanes or an increase in excited state energy of the betaine. The net effect of raising the activation energy for thermal ring closure simply encourages C–O bond rupture and formation of carbocations.

Addition of the Lewis acids, $ZnCl_2$ and LiBr, allows for dynamic and preferential coordination to one of the ethereal oxygens, destabilizing the 1,3,2λ⁵-dioxaphospholane and promoting decomposition. Consequently, sufficient energy is available at ambient temperature for sizable accumulation of the requisite betaines, and the reaction is now capable of proceeding at much reduced temperatures. In the LiBr-mediated reactions, there is still an equilibration of the betaines, and the stereochemical course of reaction is governed by the relative rates of intramolecular S_N2 attack and extrusion of TPPO. With the stronger Lewis acid $ZnCl_2$, this situation does not exist. Stereochemical and NMR results clearly document the *irreversible* formation of the betaines before the cyclization; therefore, the stereochemical bias in the resultant epoxide is dictated by the relative ability of $ZnCl_2$ to interact with the two dioxaphospholanyl oxygens. Finally, we have shown that hydride migration in a conformationally restricted system requires ca. 2.1 kcal/mol more energy than 3-exo-tet displacement and epoxide formation in *acyclic* systems.

Experimental Section

^{31}P NMR spectra were recorded on a Bruker-IBM Model AC-200 NMR spectrometer at 80 MHz and the ^{31}P NMR chemical shifts (δ) are reported in tetrahydrofuran (THF) solution relative to external 85% phosphoric acid (H_3PO_4). Diethoxytriphenylphosphorane (DTPP),[1] 1,1-diphenyl-1,2-epoxypropane (**7**),[10,24] 1,1-diphenyl-1-ethoxy-2-propanol (**8**),[10] 1,1-diphenyl-1,2-propanediol (**11**),[10,25] *cis*-1,2-cyclohexanediol (**12**),[26] 2-methyl-2,3-pentanediol (**14**),[1] 2-methyl-3-pentanone (**16**),[27] 2-methyl-1-penten-3-ol (**17**),[28] 2,3-dimethyl-1-buten-3-ol (**20**),[29] and 2,3-dimethyl-2,3-epoxybutane (**21**)[1] have been reported elsewhere while 2,3-dimethyl-2,3-butanediol (**18**; pinacol), 1,2-propanediol (**28**), and 2,3-butanediol (**29**) are commercially available. Diols **18**, **28**, and **29** are oils and were purified and dried prior to use by distillation over sodium hydroxide. Lithium bromide was dried by heating in vacuo at 80 °C for 16 h followed by storage at 110 °C until use; the zinc chloride was dried by fusion immediately prior to use.

Preparation of 1,3,2λ⁵-Dioxaphospholanes. The syntheses of 1,3,2λ⁵-dioxaphospholanes **3**, **9**, **10**, and **13** are essentially identical, and the following is representative. In a clean, dry 500-mL two-necked round-bottom flask, which had been purged with argon, was added 19.5 mL of stock DTPP in toluene (0.93 M, 0.018 mol) and 1.38 g of 1,2-propanediol **28** (1.30 mL, 0.020 mol). The solution was allowed to stir for 6 h at ambient temperature, at which time an inverse-gated decoupled ^{31}P NMR spectrum indicated the presence of 85% 1,3,2λ⁵-dioxaphospholane **3** (δ –37.5) and 15% TPPO (δ 27.0 ppm). The toluene and ethanol solvents were then removed in vacuo, and 75 mL of anhydrous THF was added to produce a 0.23 M solution of **3**. The solution was then stored under argon for future use.

Kinetic Measurements. The kinetics of decomposition of 1,3,2λ⁵-dioxaphospholanes with LiBr, LiI, and $LiClO_4$ as catalysts were run under pseudo-first-order conditions using a 10-fold excess of the Lewis acid. The reaction was assumed to follow simple second-order kinetics, and therefore the specific rate law that was used to extract the rate constants was

$$-d[P]/dt = k[LiX][P]$$

where [LiX] is the concentration of the lithium salt at time t, and is assumed to remain relatively constant during the course of reaction, and [P] is the concentration of 1,3,2λ⁵-dioxaphospholane at time "t". The rate law thus utilized was

$$-d[P]/[P] = k_{obsd}dt$$

in which $k_{obsd} = k[LiX]$.

A plot of $-\ln \{[P]/[P]_0\}$ vs time (t) gives a straight line over 2–3 half-lives with the slope = k_{obsd}. The reported rate constants, therefore, are $k = k_{obsd}/[LiX]$.

For the measurement of the rate of 3-exo-tet cyclization and hydride migration using $ZnCl_2$ as catalyst, the rate law was first order in phosphonium salt (see text for details). Thus, a plot of $-\ln \{[P]/[P]_0\}$ vs time gives a straight line with the slope equal to the rate constant.

Finally, for the determination of the rate of dioxaphospholane ring opening with $ZnCl_2$ as catalyst, the kinetics were monitored under pseudo-first-order reaction conditions, using a 10-fold excess of the dioxaphospholane. Again, a simple second-order reaction was assumed and a plot of $-\ln \{[P]/[P]_0\}$ vs time furnished the k_{obsd}. The reported rate constants were subsequently obtained by $k = k_{obsd}/[ZnCl_2]$. (It should be noted that in this case the assumption is made that the $ZnCl_2$ is acting as a "true" catalyst and is not losing any significant catalytic activity over the course of the reaction.)

(a) Lithium Bromide as Catalyst. In a clean, dry 10-mm NMR tube that had been purged with argon and fitted with a septum was added 0.75 mL of dioxaphospholane **3** (0.175 mmol), 1.25 mL of anhydrous THF, and 0.50 mL of benzene-d_6 (NMR lock solvent). To this was added (via syringe) 2.00 mL of 1.16 M LiBr in THF (2.33 mmol). The tube was then placed immediately in a preequilibrated NMR probe at 31 °C, and a kinetics program was initiated. A typical experiment consisted of 400 scans, with an acquisition time of 0.25 s, and 600 s between data points. Data was acquired until the reaction completed 2–3 half-lives.

(b) Hydride Migration with LiBr Catalyst. The procedure is identical with that above except the probe temperature was increased to 52 °C prior to data acquisition.

(c) $ZnCl_2$ as Catalyst: k_1 Measurement. In a clean, dry, purged (argon) 10-mm NMR tube that had been fitted with a septum was added 2.00 mL of 0.23 M **3** (0.46 mmol) and 0.50 mL of benzene-d_6 (lock solvent). To this was added 2.00 mL of a 0.029 M $ZnCl_2$ solution (0.058 mmol). The tube was then placed in the

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(27) Compound **16** has been reported extensively in the literature. For a representative preparation, see: Taskinen, E. *J. Chem. Thermodyn.* **1974**, *6*, 271–80. Also, for the ^{13}C NMR resonances, see: Hawkes, G. E.; Herwig, K.; Roberts, J. D. *J. Org. Chem.* **1974**, *39*, 1017.
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NMR probe at 25 °C, and the kinetics were monitored. The same procedure was performed when measuring the effect of the methyl group in 1,3,2λ⁵-dioxaphospholanes **9** and **10**.

(d) $ZnCl_2$: k_2 Measurement for Epoxide Formation. To a clean, dry, purged (argon) 10-mm NMR tube that had been fitted with a septum was added 2.00 mL of 1,3,2λ⁵-dioxaphospholane **3** (0.46 mmol) and 0.50 mL of benzene-d_6 (NMR lock solvent). The tube was then cooled to −78 °C (dry ice/acetone bath), and 2.00 mL of a 0.23 M $ZnCl_2$ solution (in THF) was added (0.46 mmol). The tube was immediately placed in the NMR probe at −30 °C, and a ^{31}P NMR spectrum showed complete conversion of **3** to betaines **4a** and **4b** (δ 63.5 and 62.0 ppm). The probe was slowly warmed to 0 °C and at this temperature the disappearance of **4a** and **4b** and appearance of TPPO were monitored.

(e) $ZnCl_2$: k_2 Measurement for Hydride Migration. In a clean, dry argon-purged 10-mm NMR tube equipped with a septum was added 2.00 mL of 0.23 M 1,3,2λ⁵-dioxaphospholane **13** (in THF) and 0.50 mL of benzene-d_6 (NMR lock solvent). The tube was then cooled to −78 °C, and 2.00 mL of 0.23 M $ZnCl_2$ (in THF) was added. The tube was then placed in the NMR probe at −30 °C. The kinetics were subsequently monitored at 25 °C using the ^{31}P NMR resonance at δ 61.1 which is attributable to the requisite oxaphosphonium ion.

(f) Solvent Effects. The procedure was identical with that described in entry b, except 1,3,2λ⁵-dioxaphospholane **13** was prepared in toluene solvent (2.00 mL) to provide a solution for NMR study, which consisted of 2.00 mL of toluene, 2.00 mL of THF, and 0.50 mL of benzene-d_6 (NMR lock solvent).

Reaction of (*S*)-(−)-1,1-Diphenyl-1,2-propanediol with DTPP/LiBr. (*S*)-(−)-1,1-Diphenyl-1,2-propanediol (**11**) (0.500 g, 0.0022 mol) was added to a toluene solution (2.20 mL) of 1.0 M DTPP (0.0022 mol) in a 50-mL round-bottom flask. The solution was allowed to stir at ambient temperature for 3 h to permit complete conversion of (*S*)-(−)-**11** to the 1,3,2λ⁵-dioxaphospholane with DTPP. Afterward, oven-dried LiBr (0.250 g, 0.003 mol) was added. The mixture was allowed to stir for 24 h, and epoxide **7** (0.305 g, 66% isolated yield) was obtained by "rapid" chromatography using 4% ethyl acetate/96% hexanes as eluent. An optical rotation determination indicated inversion of stereochemistry at the stereocenter, and chiral shift ^1H NMR analysis with Eu(hfc)$_3$ indicated 96% ee.

Reaction of (*S*)-(−)-11 with DTPP/$ZnCl_2$. (*S*)-(−)-1,1-Diphenyl-1,2-propanediol (**11**) (0.700 g, 0.003 mol) was added to a toluene solution (3.00 mL) of DTPP (1 M, 0.003 mol) in a 25-mL, round-bottom flask. The solution was stirred for 3 h to effect formation of the requisite 1,3,2λ⁵-dioxaphosphospholane, and then $ZnCl_2$ (0.040 g, 0.0003 mol) was added to the dioxaphospholane at ambient temperature. The solution was allowed to stir for 16 h. Epoxide **7** was isolated by procedures described above, and an optical rotation determination coupled with a chiral shift ^1H NMR study showed retention of stereochemistry at the carbon stereocenter with 23% ee.

Reaction of (*R*)-(+)-7 with $ZnCl_2$: The Control. An anhydrous, toluene solution (1.20 mL) of (*R*)-(+)-**7** (0.210 g, 0.001 mol; 96% ee) was admixed with absolute ethanol (0.092 g, 0.002 mol), triphenylphosphine oxide (0.278 g, 0.0010 mol), and anhydrous $ZnCl_2$ (0.014 g, 0.0001 mol) under an argon atmosphere. The solution was allowed to stir under argon for 18 h, and then analysis by ^{13}C NMR spectroscopy indicated >75% conversion to 1,1-diphenyl-1-ethoxy-2-propanol (**8**), with the remaining product identified as unreacted epoxide **7**. The reaction mixture was purified by "rapid" chromatography using 4% ethyl acetate/96% hexanes as eluent, and **7** (0.018 g) was recovered. Subsequent optical rotation and chiral shift ^1H NMR experiments indicate that epoxide **7** displayed >95% ee, demonstrating that no epimerization of the chiral center has occurred upon interaction with $ZnCl_2$.

Methylation of 1,3,2λ⁵-Dioxaphospholane 3. Methyl trifluormethanesulfonate (0.34 g, 0.002 mol) was added (via syringe) to a solution of dioxaphospholane **3** in dichloromethane solvent (0.7 M, 3.00 mL, 0.0021 mol) under an argon atmosphere in a 10-mm NMR tube at −78 °C. The NMR tube was then placed in a preequilibrated NMR probe at −78 °C. The ^{31}P NMR spectrum is characterized by five distinct resonances; the major ones at δ 63.9 and 62.6 ppm were assigned to the regioisomeric oxyphosphonium salts on the basis of their similarities in the ^{31}P NMR shifts with **4a,b**.

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Electrochemical Models for Cytochrome P-450. N-Demethylation of Tertiary Amides by Anodic Oxidation

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Anodic oxidation of *N,N*-dimethylamides in acetonitrile/water (95:5) containing $NaClO_4$ gives the corresponding *N*-methylamides in high yields. *N*-Methyl-*N*-(hydroxymethyl)benzamide was isolated as an intermediate in the electrochemical N-demethylation of *N,N*-dimethylbenzamide and was characterized by GC/MS as its trimethylsilyl ether. Intramolecular kinetic deuterium isotope effects were measured for the anodic N-demethylation of *N*-methyl-*N*-trideuteriomethyl amides $RCON(CH_3)CD_3$, where R = $PhCH_2CH_2$, Ph, *p*-$O_2NC_6H_4$, and C_6F_5. The observed isotope effects were 2.16 ± 0.07, 2.78 ± 0.21, 2.10 ± 0.17, and 2.60 ± 0.15, respectively. The intermolecular isotope effect for anodic N-dealkylation of *N,N*-dimethylbenzamide was ca. 1.4–1.7. These isotope effects are much lower than those observed for cytochrome P-450 catalyzed N-demethylation of these compounds and are consistent with an ECE (electrochemical/chemical/electrochemical) mechanism involving aminium ion intermediates. These anodic oxidations are mild and highly reproducible and may have potential for synthetic application, particularly for the synthesis of metabolites.

The oxidative N-dealkylation of amines by cytochrome P-450 enzymes is a reaction of central importance in the biotransformation of a great many organic compounds, both endogenous and xenobiotic. The results of numerous studies of enzymic dealkylations,[1-7] as well as chemical[8-12] and photochemical[13,14] reactions that mimic this process,

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