proposition was amply supported by the present study. TMAC forms aggregates in aqueous systems with characteristics much different from those of the conventional cationic micelle. And yet TMAC aggregates are much more efficient than the latter.

All the imidazole compounds act as true catalysts for the hydrolysis of PNPA in the present system. Therefore, both of the acylation and deacylation processes are accelerated by the TMAC aggregate. The turnover rate of the LImAm (**3**)–TMAC system is thus much larger than that of α-chymotrypsin under comparable conditions. We will be able to develop many other catalytic systems by combinations of anionic nucleophiles with appropriate hydrophobic aggregates.

Acknowledgment. The authors are grateful to Dr. T. Matsuo of this department for the use of the surface tension apparatus.

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A Stereochemical Investigation of the Formation and Cyclization of Allenic Phosphonic Acids. Preparation of 4-Substituted 1,2-Oxaphosphol-3-enes[1]

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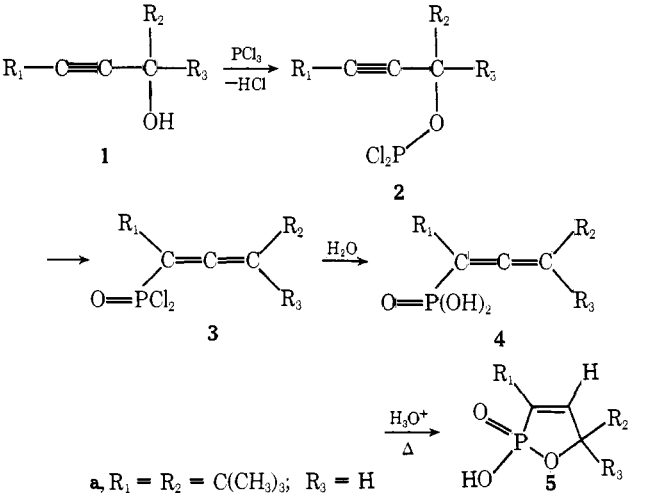
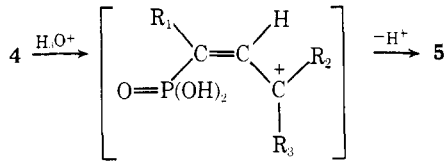
Abstract: Allenic phosphonic acid **4a**, previously found to be inert toward proton-catalyzed cyclization, reacted with bromine (chloroform) and mercuric acetate (acetic acid, chloride ion) to form the 4-bromo (**7a**-Br) and 4-chloromercuri (**7a**-HgCl) derivatives of 2-hydroxy-3,5-di-*tert*-butyl-1,2-oxaphosphol-3-ene 2-oxide in good yield. The reaction of optically pure (*R*)-(+)-2,2,6,6-tetramethyl-4-heptyn-3-ol (**1a**) with phosphorus trichloride gave, after hydrolysis, 102 ± 2% optically pure *R*-(−)-**4a**, indicating that the propargyl phosphite → allenic phosphonate rearrangement occurs via a concerted [3,2] sigmatropic shift with complete stereospecificity. Reaction of optically pure *R*-(−)-**4a** with mercuric acetate–chloride ion led to *R*-(+)-**7a**-HgCl of 86 ± 2% optical purity, while reaction with bromine gave *R*-(+)-**7a**-Br of >41 ± 2% optical purity. Thus, electrophile-promoted cyclizations proceed by moderately to highly stereospecific trans addition. The ^{1}H NMR spectrum of **7a**-HgCl exhibits five-bond Hg–H coupling and apparent restricted rotation of the upfield *tert*-butyl group.

For several years we have been investigating those factors which control the formation of phosphorus-containing products in the reaction of propargyl alcohols with phosphorus trihalides.[2-5] Most recently[5] we described how a series of propargyl alcohols could be made to undergo the transformations shown below.

The formation of dichlorophosphite (**2**) was found to be immediate at room temperature in all cases studied. The success of the rearrangement leading to **3** was critically dependent on efficient removal (*not* neutralization) of the HCl liberated in the first step. The half-life of this rearrangement ranged from ca. 20 min (24 °C) when R_1 = H and $R_2 + R_3 = (CH_2)_4$ to ca. 3 h (60 °C) when $R_1 = R_2 = R_3$ = H. The facility of the acid-catalyzed cyclization was highly dependent on R_2 and R_3 (and to a lesser extent on R_1). When R_2 and R_3 were both alkyl, cyclization proceeded readily at 60 °C in 2 M acid. However, if either R_2 or R_3 were H, the cyclization was completely suppressed, even at >90 °C in 35% perchloric acid. This



observation could be rationalized on the basis of the stability of the cationic precursor to **5:**



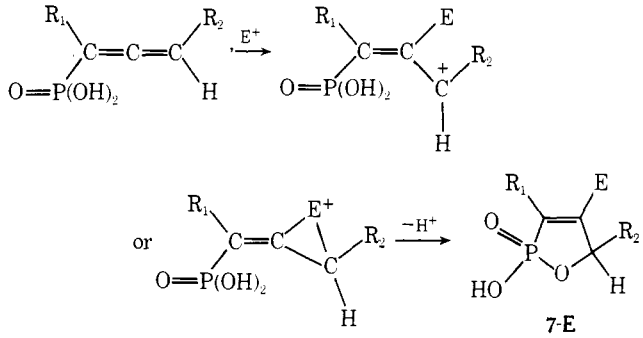
6

If this intermediate depended mainly on stabilization by R_2 and R_3 (vide infra), a tertiary intermediate would be more readily formed than a secondary or primary one.

This report describes the effectiveness of two Lewis acids in promoting the cyclization of a "secondary" allenic phosphonic acid (**4a**). We further report compelling stereochemical evidence that neither the propargyl → allene rearrangement nor the cyclization proceed through symmetrical intermediates or transition states.

Results

The present study was initiated with the belief that electrophiles more powerful than H^+ could indeed cause cyclization of "secondary" or "primary" allenic phosphonic acids, yielding 4-substituted 1,2-oxaphosphol-3-enes:



7-E

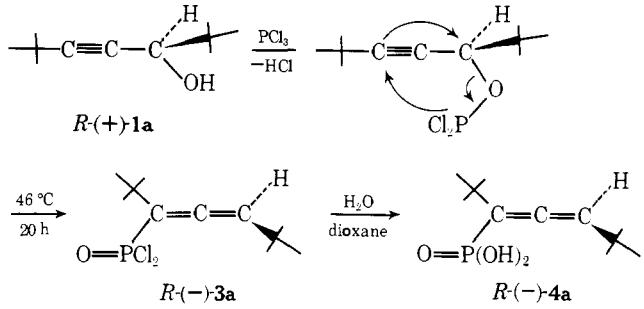
This reaction is another example of electrophilic addition to allenes, a class which has been examined by several groups over the recent past.[6,7] Oxymercuration and bromination[6a,7] of allenes have been studied in detail, especially from the standpoint of stereochemistry (vide infra).

When **4a**[3,5] was allowed to react with a slight excess of bromine in chloroform (24 h, 23 °C), hydrogen bromide was evolved and ^{1}H NMR showed that a single product was formed. Removal of solvent and recrystallization gave a solid with an ^{1}H NMR spectrum indicative[2-5] of **7a**-Br (E = Br): δ ($CDCl_3$) 1.11 (s, 9 H), 1.45 (s, 9 H), 4.47 (d, $^3J_{PH}$ = 8.8 Hz, 1 H), 12.31 (s, 1 H). Infrared and mass spectral data together with the elemental analysis confirmed this assignment (see Experimental Section).

The reaction of **4a** with a slight excess of mercuric acetate in glacial acetic acid could also be conveniently monitored by ^{1}H NMR. Acetate **7a**-HgOAc was formed with a half-life of 8 min at 35 °C (slower in methanol). Although the acetate itself proved difficult to isolate in pure form, the reaction mixture could be quenched with chloride ion to give **7a**-HgCl, which was easily isolated in pure form owing to its minute solubility in most common solvents. The ^{1}H NMR spectrum of this compound [δ (Me_2SO-d_6) 1.03 (s, 9 H), 1.35 (s, 9 H), 4.52 (d, $^3J_{PH}$ = 4.8 Hz, 1 H), 6.75 (s, 1.8 H)[8]] is interesting in several respects. The doublet at δ 4.52 is accompanied by ^{199}Hg satellites (d of d, $^3J_{HgH}$ = 26.0, $^3J_{PH}$ = 4.8 Hz) which constitute ca. 17% of the total signal. This three-bond coupling is much smaller than in systems of the type HC=CHgX ($^3J_{cis}$ = ca. 300, $^3J_{trans}$ = ca. 600 Hz).[9] Since $^3J_{HH}$ in **5a** was only 1.8 Hz (caused by the dihedral angle of 66°),[3] it seems that $^3J_{HgH}$ is governed by the same Karplus-type behavior[10] as is $^3J_{HH}$. The R_1 *tert*-butyl resonance at δ 1.35 is accompanied by satellites with $^5J_{HgH}$ = 7.0 Hz. Although four-bond ^{199}Hg-H couplings through sp^2-hybridized carbons are known (ca. 0–40 Hz),[9] 7.0 Hz is one of the largest five-bond interaction of this type yet reported.

Another interesting feature of this spectrum is that the *tert*-butyl resonance at δ 1.03 (R_2 in **7-E**) is considerably broader and shorter than the one at δ 1.35 (R_1) at ambient temperature. As the temperature is lowered[11a] this difference becomes even more pronounced. The upfield peak is 74% as high as the downfield one at 22 °C ($\Delta\nu_{1/2}$ = 2.0 vs. 1.5 Hz, respectively), and it decreases to 41% at −68 °C ($\Delta\nu_{1/2}$ = 15 vs. 5.3 Hz, respectively. We tentatively attribute this to steric inhibition of R_2 *tert*-butyl rotation by the bulky HgCl group.[11b]

With derivatives **7a**-Br and **7a**-HgCl available in good yield from straightforward reactions, it became possible to explore the stereochemistry of the rearrangement and cyclization reactions. The formation of the allenic phosphonyl derivative from the dichlorophosphite has been postulated[2-5] to be a concerted [3,2]-sigmatropic shift, rather than an S_Ni' (or its variant). Thus the reaction should occur stereospecifically. This has now been experimentally verified. When optically pure *R*-(+)-**1a** with $[\alpha]^{25}_{578}$ +5.67° (*c* 5.00, chloroform)[12,13] reacted with a twofold excess of phosphorus trichloride in the usual way,[5] acid chloride **3a** was found to be optically active with $[\alpha]^{25}_{D}$ −62.5°, $[\alpha]^{25}_{578}$ −65.4° (*c* 15.8, dioxane). Hydrolysis afforded crude active **4a** with $[\alpha]^{25}_{D}$ −44.2°, $[\alpha]^{25}_{578}$ −46.4° (*c* 0.84, acetone). Brewster-Lowe rules[14] predict that the levorotatory allenic enantiomers will have the *R* configuration, as expected for the [3,2] shift:



R-(+)-**1a** *R*-(−)-**3a** *R*-(−)-**4a**

In order to judge the degree of stereospecificity of the **2a** → **3a** rearrangement, it was necessary to establish the optical purity of *R*-(−)-**4a.** Optically active shift reagent Eu(facam)$_3$[15] proved unable to differentiate the enantiomers of **4a.**[16] However, two recrystallizations of the crude material (mp 179.5–185 °C) brought it to constant melting point (191.5–192 °C; racemic **4a** has mp 175–177 °C) and essentially unchanged rotation of $[\alpha]^{25}_{D}$ −43.4°, $[\alpha]^{25}_{578}$ −46.4° (*c* 0.84, acetone). We take this material to be optically pure. Thus, assuming that there was no optical purification during hydrolysis or isolation of the crude product, the propargyl → allene rearrangement must have proceeded with 102 ± 2% stereospecificity.

Reaction of optically pure *R*-(−)-**4a** with mercuric acetate followed by quenching with chloride ion gave crude (+)-**7a**-HgCl, presumed to be *R*,[14,17] with $[\alpha]^{25}_{D}$ +14.3°, $[\alpha]^{25}_{578}$ +14.8° (*c* 2.57, Me_2SO) and mp 253 °C dec. Two recrystallizations from methanol gave fine needles with constant mp 255–257 °C dec, and $[\alpha]^{25}_{D}$ +16.6°, $[\alpha]^{25}_{578}$ +17.0° (*c* 2.57, Me_2SO). Thus, oxymercuration-cyclization occurs ≥86 ± 2% stereospecifically trans.

Addition of bromine to optically pure *R*-(−)-**4a** in chloroform gave a solution with $[\alpha]^{25}_{D}$ +11.5°, $[\alpha]^{25}_{578}$ +11.8° (*c* 2.66, chloroform), assuming 100% conversion. Isolation and three recrystallizations from heptane gave needles of optically pure *R*-(+)-**7a**-Br with mp 174–175 °C and $[\alpha]^{25}_{D}$ +28.4°, $[\alpha]^{25}_{578}$ +29.6° (*c* 1.15, chloroform). The stereospecificity of

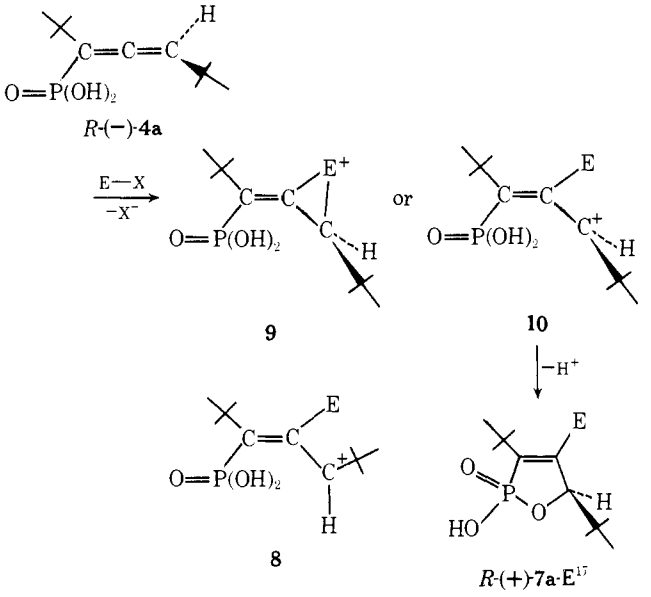
the trans bromination–cyclization must therefore be ≥41 ± 2%. Attempts to further confirm the optical purities of **7a**-Br and **7a**-HgCl with Eu(facam)$_3$ again proved fruitless, as gelatinous precipitates formed with shift reagent.

Discussion

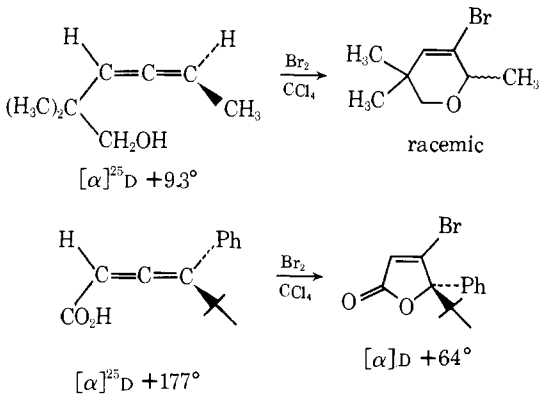
The formation of **7a**-Br and **7a**-HgCl from **4a** demonstrates that electrophiles more powerful than H_3O^+ can promote the cyclization of "secondary" allenic phosphonic acids to the more stable[5] oxaphospholene derivatives. Even more significant are the degrees of stereospecificity observed for the propargyl → allene rearrangement and the allene → oxaphospholene cyclization.

The evidence presented here confirms that the rearrangement is best viewed as a concerted all-suprafacial [3,2]-sigmatropic shift.[2,3,5] Although there have been previous reports of optical retention during the rearrangement of propargyl chlorosulfites (ca. 15–100% retention depending on conditions)[18a] and the oxy-Cope rearrangement of a propargyl ether (no data given on percent retention),[18b] we believe that this is the first report on the stereochemistry of propargyl phosphite rearrangements.

The 86% retention observed during mercury-promoted cyclization demonstrates that ≤14% of the reaction involves planar allylic cation **8** when E = HgOAc. The intermediate must either be cyclic ion **9** or nonplanar ion **10** which is trapped by internal nucleophile (phosphoryl oxygen) prior to randomization. Similarly, the stereospecificity of bromination–cyclization shows that >41% of the reaction proceeds via **9** or **10** (E = Br). Therefore, HgOAc is more than twice as effective as Br at maintaining the configuration of the intermediate.



It is noteworthy to compare these results with other electrophilic additions to optically active allenes. Oxymercuration of both active 2,3-pentadiene[6a] and active 1,2-cyclononadiene[6b] seemed to take place by 100% stereospecific trans addition. Bromination of active 2,3-pentadiene in methanol gave products of stereospecific trans addition.[6a] Bromination of allenes possessing internal nucleophiles has been observed to proceed either with racemization[7a] or retention.[7b] This indicates that the hydroxy group four atoms removed from the site of attack is less efficient at trapping the bromonium ion intermediate before stereochemical randomization than is a carboxyl oxygen three atoms removed. The phosphoryl oxygens in the present system are obviously more comparable to the latter. Thus, it appears that electrophile-promoted cyclization of allenic phosphonic acids, like electrophilic additions to allenes in general, is regiospecific (E becoming attached to the central atom of the allene linkage) and predominantly stereospecific trans. The phosphoryl oxygens in **9** or **10** are able to trap the onium ion intermediate relatively efficiently and therefore racemization is prevented.



Experimental Section

The instruments and general techniques were as described previously.[2-5] Microanalyses were performed by Integral Microanalytical Labs, Raleigh, N.C. Optical rotations were measured with a Perkin-Elmer Model 141 polarimeter (digital output) using 1.00-dm cells ($[\alpha] = 100\ \alpha/c$ where c is in units of g/100 mL solution).

Reaction of 4a with Bromine. A solution of 536.4 mg (3.42 mmol) of bromine in 10.0 mL of chloroform was added dropwise over 65 min to a suspension of 742.5 mg (3.20 mmol) of **4a**[3,5] in 20 mL of chloroform. (The bromine color persisted soon after addition began; the reaction mixture became homogeneous near the end of the addition.) After stirring for 19 h at room temperature, the golden solution was carefully rotary evaporated (to 0.1 mm) to constant mass, 1.09 g. The crude semisolid product was redissolved in 3 mL of hot hexane, centrifuged to clarify, concentrated to 1.5 mL, then allowed to stand at −5 °C. Two crops totaling 790 mg were collected, and recrystallized again from hexane to give 720 mg (72%) of material with mp 126–130 °C. (Sublimation at 120 °C (0.1 mm) seemed to decompose the material). The ^{1}H NMR spectrum of this material is given in the text. IR (CCl_4) 3300–1600 (v br), 2970, 1580, 1480, 1370, 1210 (vs), 1005, 870 cm^{-1}. Mass spectrum (20 eV, direct inlet) *m/e* (rel abundance) 313, 311 (MH^+, 3), 256, 254 (100), 241, 239 (38), 176 (13).[19] Anal. Calcd for $C_{11}H_{20}O_3PBr$: C, 42.46; H, 6.48; Br, 25.68. Found: C, 42.10; H, 6.20; Br, 25.80.

The procedure with *R*-(−)-**4a** was identical with the above. The melting point and specific rotations of the reaction mixture and optically pure *R*-(+)-**7a**-Br are given in the text.

Reaction of 4a with Mercuric Acetate. To a solution of 990 mg (4.26 mmol) of **4a** in 20 mL of glacial acetic acid at 37 °C was added a solution[20] of 1.50 g (4.7 mmol) of mercuric acetate in 20 mL of acetic acid at once. The solution was stirred for 3.3 h at 37 °C, during which it became slightly cloudy. (This reaction could be followed by ^{1}H NMR. As the peaks of **4a**[3] decreased, a new set appeared for **7a**-HgOAc: δ 1.06 (s, 9 H), 1.21 (s, 9 H), 4.66 (d, $^3J_{HgH}$ = 4.7 Hz, 1 H); peaks due to OH and OAc obliterated by solvent.) The mixture was diluted with 10 mL of water and this solution was added to a solution of 300 mg (5 mmol) of sodium chloride in 30 mL of water. This suspension was stirred for 30 min, then filtered. The solid product was washed with water and acetone, then air dried leaving 1.53 g (77%) of **7a**-HgCl with mp >240 °C dec. This material could be recrystallized from a large volume of methanol or ethanol to give material with mp 249 °C dec. Its ^{1}H NMR spectrum is given in the text; IR (KBr) 3600–2000 (v br), 2960, 1570, 1480, 1395, 1365, 1200 (t), 1050, 985, 860 cm^{-1}; its low volatility precluded mass spectral examination. Anal. Calcd for $C_{11}H_{20}O_3PHgCl$: C, 28.27; H, 4.31; Cl, 7.59. Found: C, 28.39; H, 4.26; Cl, 8.00.

The procedure with *R*-(−)-**4a** was identical with the above. The melting points and specific rotations of the crude and optically pure *R*-(+)-**7a**-HgCl are given in the text.

Optically pure *R*-(+)-1a was prepared as previously described.[12] It had mp 59.0–60.6 °C (lit.[12b] 58.8–60.3 °C), $[\alpha]^{25}_{578}$ +6.23° (*c* 7.71, $CHCl_3$), $[\alpha]^{25}_{578}$ +5.67° (*c* 5.00, $CHCl_3$).[21]

Optically Active *R*-(−)-4a. In the usual way,[5] a solution of 500 mg

(2.98 mmol) of active *R*-(+)-**1a** in 10 mL of dry hydrocarbon-stabilized chloroform was added over 50 min (22 °C) to a solution of 820 mg (6.0 mmol) of phosphorus trichloride, with a vigorous stream of nitrogen to carry off the liberated HCl.[5] This was followed by the addition of 10 mL ml chloroform over 2 h (22 °C). The solution was heated to 46 °C for 19.3 h. Rotary evaporation left 791 mg (ca. 99%) of a mixture of 85% *R*-(−)-**3a** and 15% of the propargyl chloride. This mixture was dissolved in enough dioxane to make 5.00 mL; its rotation is given in the text. The dioxane solution was added dropwise over 3 min to 5 mL of 50% aqueous dioxane at 0 °C. This solution was stirred for 15 min at 0 °C, then 90 min at room temperature. Rotary evaporation (to 0.05 mm) left 570 mg (83%) of crude *R*-(−)-**4a** (melting point and rotation given in the text). This was recrystallized twice from 2 mL of 1:1 (v/v) acetone–acetonitrile to give optically pure material with melting point and rotation given in the text.

References and Notes

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(6) See, for example, (a) W. L. Waters, W. S. Linn, and M. C. Caserio, *J. Am. Chem. Soc.*, **90**, 6741 (1968); **92**, 4018 (1970), and references cited therein; (b) R. D. Bach, *ibid.*, **91**, 1771 (1969).
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(8) The excess OH integration is caused by the hygroscopic nature of these compounds.[2-5]
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(10) M. Karplus, *J. Am. Chem. Soc.*, **85**, 2870 (1963).
(11) (a) To prevent freezing the Me_2SO-d_6 solution was diluted with an equal volume of MeOH-d_4. (b) Temperature dependent ^1H NMR resonances for the *tert*-butyl groups in hindered compounds have been reported: J. E. Anderson and H. Pearson, *J. Chem. Soc. B*, 1209 (1971).
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(13) See footnote 14 of ref 12a.
(14) S. F. Mason et al., *Chem. Commun.*, 1261 (1971). For an excellent review on the subject of optically active allenes, see R. Rossi and P. Diversi, *Synthesis*, 25 (1973).
(15) H. L. Goering, J. N. Eikenberry, G. S. Koermer, and C. J. Lattimer, *J. Am. Chem. Soc.*, **96**, 1493 (1974).
(16) This reagent is marketed as Eu(tfac) by Norell Chemical Co. The solution consisted of 0.18 mmol of *R*-(−)-**4a** and 0.048 mmol of Eu(facam)$_3$ in 0.40 mL of acetone-d_6. The chemical shifts with (without[3]) shift reagent were δ 1.13, (1.04), 1.90 (1.19), 5.20 (5.31), 8.13 (6.31). Racemic **4a** gave an identical spectrum. Addition of more shift reagent broadens the peaks but does not resolve them.
(17) The heterocycle shown has the *R* configuration provided that E has a higher Prelog priority than carbon.
(18) (a) R. J. D. Evans, S. R. Landor, and R. Raylor Smith, *J. Chem. Soc.*, 1506 (1963); (b) E. R. H. Jones, J. D. Loder, and M. C. Whiting, *Proc. Chem. Soc., London*, 180 (1960).
(19) Like several of the other oxaphospholes encountered in this study,[2-5] **7a**-Br exhibited a stronger set of $(M + H)^+$ ions than molecular ions.
(20) Gentle warming required to dissolve the solute.
(21) The *specific* rotation of optically pure *R*-(+)-**1a** increases linearly with concentration: $[\alpha]^{25}_{578}$ +4.8° (*c* 1.00), +5.67° (*c* 5.00), +6.23° (*c* 7.71, chloroform).

Intramolecular Aminolysis of Amides. The Cyclization of 2-Aminomethylbenzamide to Phthalimidine

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Abstract: Rate constants for cyclization of 2-aminomethylbenzamide to phthalimidine have been determined in H_2O at 30 °C and $\mu = 0.5$. Hydroxide ion catalysis takes place at high pH with $k_{OH} = 0.16\ M^{-1}\ s^{-1}$, which is approximately the same as k_{OH} for cyclization of 2-hydroxymethylbenzamide to phthalide but 10^4-fold less than k_{OH} for cyclization of methyl 2-aminomethylbenzoate to phthalimidine. Thus, as in the case of aliphatic esters, the rate constants for intramolecular cyclization of amides are nearly independent of the nature of the nucleophilic group, but are highly dependent on the leaving group, i.e., whether the compound is an ester or an amide. The magnitude of k_{OH} is 10^4 greater than k_{OH} for hydroxide ion catalyzed hydrolysis of benzamide, illustrating the facility of the intramolecular reaction. Below pH 9 the cyclization reaction becomes nearly pH independent, but at approximately pH 7, k_{obsd} begins to decrease markedly, indicating a change in rate-determining step and, as a consequence, an intermediate in the reaction. Hydronium ion catalysis is observed from pH 2–5, but k_{obsd} is constant from pH 2 to 5 M HCl. Pronounced buffer catalysis occurs which is both general acid and general base catalysis or their kinetic equivalents. Bronsted plots of log k_B for general base catalyzed cyclization of the neutral species and log k_B^1 for general base catalyzed cyclization of the protonated species vs. the pK_a of the catalyst have slopes of 0.4, implying that in these reactions proton transfer and bond making or breaking are concerted processes.

Chemical intramolecular reactions bear a striking resemblance to enzymatic reactions proceeding through an enzyme–substrate complex.[1-3] An understanding of intramolecular catalysis is therefore of crucial importance in attempts to understand how enzymes function. Ester substrates acylate the enzyme α-chymotrypsin much more rapidly than do amides.[1,4] This dissimilarity could reside in alignment in the enzyme–substrate complex, or in mechanistic differences for the two types of substrates. Furthermore, it appears that the rate constants for acylation of the enzyme by amide substrates are completely explainable in terms of intracomplex nucleophilic attack by the hydroxyl group of serine-195 along with general base catalysis by histidine-57,[5,6] but this may not be the case for acylation by esters where other mechanistic factors may be involved.[5] Thus, it is important to determine how esters and amides differ quantitatively in susceptibility to intramolecular nucleophilic attack by various nucleophiles and whether significant mechanistic differences exist.

A neighboring hydroxymethyl group is an excellent nucleophile in cyclization of the ethyl ester[5] and amide[6,7] of 2-hydroxymethylbenzoic acid to phthalide. Rate constants for apparent hydroxide ion catalysis are 10^5 greater than for hydroxide ion catalyzed hydrolysis of ethyl benzoate and benzamide. We have recently investigated the intramolecular aminolysis of the sterically similar methyl 2-aminomethylbenzoate.[8] Important similarities were found with the cyclization reactions of ethyl 2-hydroxymethylbenzoate, but significant mechanistic differences were observed in comparison