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A REAFFIRMATION OF STEREOELECTRONIC CONTROL IN THE ALKALINE HYDROLYSIS OF METHYL AND ETHYL ETHYLENE PHOSPHATE

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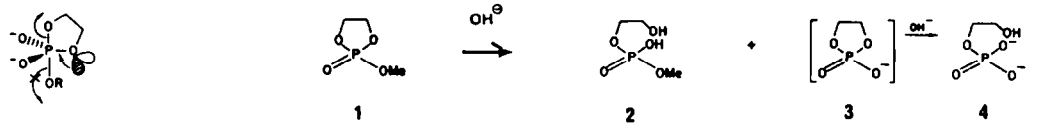
Abstract - A reinvestigation of the product distribution in the hydrolysis of ethyl and methyl ethylene phosphates has confirmed our earlier suggestion (Taira et al., J. Org. Chem., 1984, 4531) that the stereoelectronic effect is an important factor in these reactions. In contrast to the claims of Kluger and Thatcher (J. Am. Chem. Soc., 1985, 107, 6006; J. Org. Chem., 1986, 51, 207), the increase in exocyclic cleavage product, methanol, with increasing strong base is shown to arise from an artifactual side-reaction in the base catalyzed hydrolysis of methyl ethylene phosphate. The initial product of endocyclic cleavage, methyl hydroxyethyl phosphate, reacts with a second molecule of methyl ethylene phosphate to yield a "triester" dimer which subsequently releases methanol to yield a "diester" dimer. Although a small amount of exocyclic cleavage product is observed in strong alkali (2 - 4% ± 1.5% for methyl ethylene phosphate and < .5% ±1.5% for ethyl ethylene phosphate) the proportion does not vary with alkali when the hydrolysis reaction is run under dilute conditions to minimize the dimerization reaction. Even these small proportions of exocyclic cleavage are still completely consistent with arguments regarding stereoelectronic control in these reactions.

Introduction

The rate of hydrolysis of five-membered cyclic phosphates such as methyl ethylene phosphate (MEP) and ethylene phosphate (EP) is 10^6 to 10^8 times faster than that of their acyclic analogues, respectively. Westheimer and coworkers[1-5] proposed that this rate of acceleration was due to the energy released in going from a strained cyclic ester to a "strain-free" cyclic phosphorane transition state. Also they suggested that the exocyclic cleavage product is consistent with the required pseudorotation of a pentaoxyphosphorane intermediate.[5]

However, as pointed out by Gerlt, Westheimer and Sturtevant[6], the amount of ring strain is insufficient to explain the total lowering of activation energy of the five-membered ring cyclic phosphates. Gorenstein et al.[7,8] proposed, based upon molecular orbital calculations on the basic hydrolysis of model phosphate diesters, that a significant fraction of this difference in reactivity between five-membered cyclic phosphates and their acyclic counterparts comes from orbital stereoelectronic effects in the trigonal bipyramid transition state. Thus in the cyclic transition

Scheme I



A 1 2 3 4

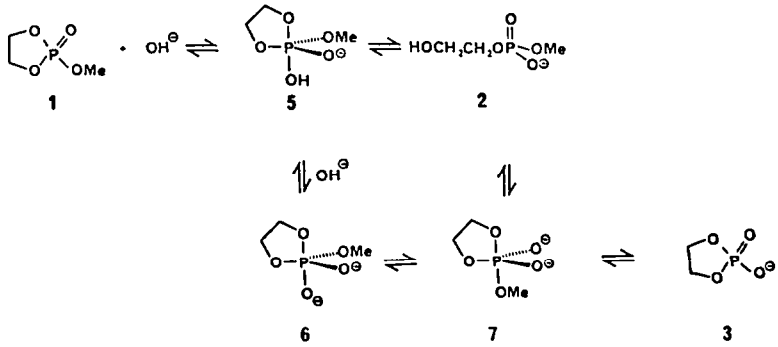
state, A, the two lone pairs on the basal ring oxygen are oriented partially antiperiplanar (app) to the axial ring ester bond leaving group. The MO calculations suggested that this app lone pair orientation could significantly facilitate P-O ester bond cleavage and that proper orbital overlap (stereoelectronic effect) could be responsible for as much as 11 kcal/mol lowering of transition-state energies.[7,8]

However, a major difficulty with the stereoelectronic effect explanation for a portion of the rate acceleration was the observation of significant exocyclic cleavage in the product determining step of the reaction.[1,5] As shown in Scheme I, hydrolysis of 1 (MEP) yielded not only the

endocyclic cleavage product, methyl 2-hydroxyethyl phosphate 2, but as much as 1 - 50% of an exocyclic product, 2-hydroxyethyl phosphate, 4, formed by rapid hydrolysis of the initially formed ethylene phosphate 3. These results had been explained by Westheimer and coworkers[1,5] in terms of ring strain and pseudorotation. Based on GC and proton NMR analysis, very small amounts (1% or less) of the exocyclic cleavage product 2 was reported at dilute hydroxide concentration (pH 10 - 13). However, at higher hydroxide concentration, 5 M and 10 M, 9% and 15% of exocyclic cleavage was observed respectively.

The increased exocyclic cleavage of MEP in strong alkali hydrolysis was explained in terms of a mechanism (Scheme II) involving initial formation of a trigonal bipyramid (tbp) pentacoordinate intermediate[5], which after proton removal, yields the dianionic intermediate 6. Rapid pseudorotation of 6 yields 7, which in turn breaks down to give the exocyclic cleavage product, 3, ethylene phosphate (EP). The pK_a of the apical hydroxyl group of the monoanionic phosphorane intermediate was estimated to be greater than 13 and formation of the dianionic phosphorane, in very strong alkali, would place the oxyanion in an unfavorable apical position, thereby increasing the rate of pseudorotation to 7. Knowles and coworkers[9] have shown that the substitution reaction indeed leads to retention of configuration, consistent with the overall mechanistic scheme. Thus,

Scheme II



increased hydroxide concentration would increase the percentage of exocyclic cleavage.

Because the formation of the exocyclic cleavage product was implied to be second order in hydroxide concentration, an alternative kinetically equivalent mechanism was proposed by Gillespie et al. [10] involving formation of a hexacoordinate intermediate in strong alkali. The more recent preparation[11,12] of stable hexacoordinate phosphorus anions $(PhO)_6P^-$ and $(CH_3O)_6P^-$ and the kinetic data[3] supporting a hexacoordinate intermediate in the hydrolysis of $(ArO)_5P$ suggest that the earlier hypothesis for the involvement of a hexacovalent intermediate in the strong alkali hydrolysis of MEP is certainly quite reasonable. However, this was ruled out by Gorenstein and Taira[14] by an O-18 exchange study, and more recently by Kluger and Thatcher[15] using the same labeling methodology[14] on the exocyclic cleavage product.

An important controversy in the recent literature has developed over results and interpretation of the product distribution in the strong alkaline region.[15,16] As argued above, according to the stereoelectronic effect,[7,8,14] intermediate A is highly favored for endocyclic cleavage: note the basal oxygen lone pairs of the ring-constrained pentacovalent transition state are app only to the apical endocyclic ester bond and not to the exocyclic bond. Therefore we should expect very little exocyclic cleavage product even at very high concentrations of NaOH. In our lab, Taira et al.[18,19] carried out the hydrolysis of MEP at low concentration of ester in 5 M NaOH with a rapid quench method and analyzed the reaction products by phosphorus NMR instead of the earlier proton NMR and GC methodology. Our laboratory found that compared with Kluger et al.'s earlier results[5], that there is much less (0 ± 3% vs. the reported 4 - 15%) exocyclic cleavage product produced in the strong base catalyzed hydrolysis of MEP. These results were consistent with the prediction of the

stereoelectronic effect.[7,8]

However, recently Kluger and Thatcher[15,16] rechecked Kluger et al.'s earlier results[5] by proton (and to a lesser extent ^{31}P) NMR. By monitoring the appearance of the methanol peak, they found that at strong alkaline condition the fraction of "methanol" (which they equate with the exocyclic cleavage product) in fact now appears to increase to as much as 24% exocyclic cleavage in saturated NaOH (18.5 M) and (9.2% exocyclic cleavage even in 5.6 M NaOH). It is very important to note that Kluger et al.'s earlier study and our own[7,8,9] were largely done at low concentrations of MEP (< .02 M). Kluger and Thatcher's reinvestigation[16] was done at much higher concentrations (.3 - .9 M) MEP although more recently[15] two lower concentration runs were described. In order to resolve the discrepancy between these reports we have repeated our own work as well as followed the experimental protocol of Kluger and Thatcher at various MEP concentrations with results reported in this paper. It is indeed "important to set the record straight." (From Kluger and Thatcher[15]). Most importantly we show that the large increase in percent exocyclic cleavage (to as much as 24%) claimed by Kluger and Thatcher is due to an artifactual dimerization reaction.

Experimental Section

^{1}H and ^{31}P NMR spectra were recorded on a Bruker WP-200 spectrometer at 200 and 80.1 MHz respectively, or ^{1}H NMR on a 60 MHz Varian EM-360 spectrometer. ^{31}P NMR chemical shifts in parts per million are referenced to external 85% H_3PO_4. ^{1}H NMR chemical shifts in parts per million are referenced to external Me_4Si.

Materials. Chemicals were generally of highest purity available. Deuterium oxide (99.9%) and sodium deuteroxide were obtained from Aldrich Chemical Co. Concentrations of deuteroxide were determined by titration against standardized HCl. 2,6-lutidine, benzene, and ethylene glycol were freshly distilled before use.

Methyl and ethyl ethylene phosphate were prepared and purified as previously described.[19] At low temperatures the distilled methyl ethylene phosphate crystallized, indicative of the purity of the product. Purity was assessed by ^{31}P NMR and careful examination of the spectra, however, always revealed small, trace impurities (< 1%) that could not be removed upon further purification. They were not identified although ^{31}P chemical shifts indicated some additional five-membered ring esters and possibly oligomers were present. Upon storage at -5° C, these impurities slowly increased and most runs were done on freshly prepared and distilled methyl ethylene phosphate. The ethyl ethylene phosphate showed essentially no impurities (< 0.2%) by ^{31}P NMR.

Ethylene phosphate. To about 2 g of sodium iodide in 60 mL of reagent grade acetone, 150 μL of MEP was added via a syringe with vigorous stirring and under nitrogen. The reaction mixture was then heated at reflux for 48 h. After cooling to room temperature, the precipitated product was recrystallized from ethanol.[20] ^{1}H NMR (D_2O) δ 4.2 ppm (d, $J_{POCH} \approx 12$ Hz, 4 H).

Product and Kinetic Analysis

Rapid quench method A. Both Kluger and Thatcher's method[15] based upon a variation of our method and our original method[18,19] (see below-rapid quench method B) were used although for most runs, Kluger and Thatcher's method was used. Reactions samples were contained in a vial and magnetically stirred to ensure efficient mixing. This is different from the reported method by Kluger and Thatcher who conducted the reaction in the NMR tube with mixing by shaking the NMR tube. Thus, 0.3 mL of the proper concentration of sodium deuteroxide was charged into a vial via an Eppendorf micropipet and with magnetical stirring, pure MEP or a dioxane solution of MEP under nitrogen was transferred via a syringe to the reaction vial all at once. After the completion of the hydrolysis of MEP, the resulting mixture was immediately (within 5 sec) submerged in a dry-acetone ice bath. When the frozen mixture started to stir, the concentrated HCl (or DCl; our earlier method used H_2SO_4; see below) was added to make the resulting solution less alkaline (pH 10 - 13). We found that the initial exocyclic cleavage product, (EP), could be isolated and further hydrolysis of it to 2-hydroxyethyl phosphate, 4, largely eliminated if the pH is adjusted to 8 - 10 (by pH meter). The quenched solution was then transferred to a 5 mm NMR tube for product analysis.

Rapid Quench Method B. Product analysis was also determined by our original[14,18,19] method. A low concentration of MEP was hydrolyzed in 5 M NaOH using a rapid freezing and sulfuric acid quench method. The resulting mixture was passed through EDTA and Chelex - 100 treated glass wool and immediately followed by ^{31}P NMR on a Bruker 80 MHz NMR spectrometer (32.4 MHz).

Non-quench Method. The same procedure as in the rapid quenching methods was used except that the solution was not neutralized by strong acid. After the solution was transferred to an NMR tube, the NMR spectrum was recorded at various time intervals.

Reaction Progress was followed by integrated phosphorus and proton NMR spectra. All reactions were

conducted in deuterium oxide, and in general the term "hydroxide" refers to a deuteroxide. Concentrations extrapolated to time of mixing were obtained by plotting the logarithm of the ratio of the integrated signals of ethylene phosphate and methyl hydroxyethyl phosphate to the combined integrated signals of all hydrolyzed products.

RESULTS AND DISCUSSION

Product Analysis by Proton NMR. 0.3 M MEP was added to 0.3 mL of 5 M NaOD solution as described in the experimental section. The resulting mixture was quenched using both our own rapid quench (method B) and Kluger and Thatcher's modification of our acid quench method (A) and analyzed by proton NMR (60 MHz). The singlet peak due to the methanol (3.55 ppm, confirmed by adding a genuine sample of methanol) was integrated relative to that of the methoxyl peaks (doublet) of methyl hydroxyethyl phosphate. The uncertainty of the integration method is about 2%. We never observed the 7 - 24% of methanol product reported by Kluger and Thatcher[15,16] when the reactions were run at low concentrations of MEP. Results obtained by kinetic extrapolation to zero time and by quenching are generally in good agreement. At higher concentrations of methyl ethylene phosphate the initial methanol produced indeed increased with an increase in NaOD concentration (Figure 1). Comparable results were obtained using our original freeze-sulfuric acid quench method (B). Results shown in Figure 1 generally agree with those reported by Kluger and Thatcher.[15,16] Thus at this higher concentration of MEP, we were able to reproduce Kluger and Thatcher's reported 7% $\pm$ 2 % of methanol product in 5 M NaOD.

Product Analysis by Phosphorus NMR. P-31 NMR as an analytical method is preferred because it more directly monitors all of the products unlike proton NMR method which can only conveniently monitor the methanol produced. However, as suggested by Kluger and Thatcher, the potential differential nuclear Overhauser effect (NOE) and partial saturation might affect the accuracy for quantitative purposes. A precaution was taken to have a sufficient relaxation delay to prevent any partial saturation of the signals (total recycle time $\geq$ 6 s). While it is possible that the products have different NOE's the products determined by ^{1}H and ^{31}P NMR are comparable. Thus the total amount of exocyclic cleavage and dimer "diester" (see below) as monitored by ^{31}P NMR is comparable to the amount of methanol product analyzed by ^{1}H NMR (see Figure 1). Within the accuracy of study then, the NOE in different products appears to be essentially the same.

When we originally examined the hydrolysis mixture by ^{31}P NMR at high concentrations ($\geq$ .3 M MEP), we found that there were several other peaks upfield of those of methyl hydroxyethyl phosphate 2. These were not present in base hydrolysis at low concentrations of MEP. Thus, the percentage of exocyclic cleavage based upon proton NMR analysis of the methanol peak is in doubt unless one can clear up the identity of these unknown products present in significant amounts (ca. 10% - 25% of the total product signals). The ^{31}P chemical shifts around -0.2 to -1.6 ppm region is indicative of acyclic di- or triesters, which are likely a result of oligomerization between MEP and other primary hydrolyzed products - as in earlier reports[22,23] these oligomer products are formed to a significant extent in base-catalyzed hydrolysis at high concentrations of five-membered cyclic phosphates. In all cases, however, we have only seen a 2 - 4% exocyclic cleavage based upon the sum of the ^{31}P signal areas of ethylene phosphate and hydroxyethyl phosphate (Tables I and II). In contrast to Kluger and Thatcher's result, this ratio does not change greatly with base concentration even when the reaction is not run under dilute conditions (Tables I and II). In the case of ethyl ethylene phosphate (EEP) this number is even lower (<< 2%). Thus, the inconsistency between proton and phosphorus NMR analysis must lie in the formation of oligomers which will be dependent upon MEP concentration.

Dimer Formation. In order to compare our current and previous results with those reported by Kluger and Thatcher,[15,16] it is important to compare the different methods used in these experiments. When Kluger's experiment using high concentrations of MEP was repeated in our lab, beside the expected endocyclic and a small amount now observed exocyclic product signals, there were a number of other peaks in the upfield region of the ^{31}P NMR spectrum which have never been discussed in the hydrolysis of MEP before or observed by us when the reaction was run at low concentration of MEP.[18,19] We suggested in a private communication to Kluger that the additional peaks other than the endo- and exocyclic cleavage products which have similar or even greater intensity than the

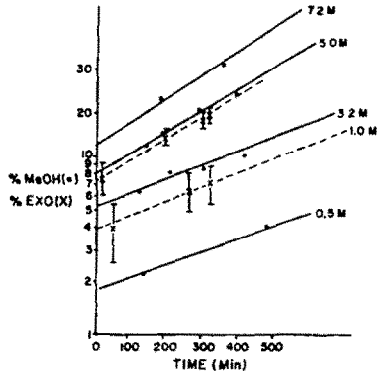


Fig. 1 Percent exocyclic cleavage or methanol produced in 0.33 M NaOD [at various hydroxide concentrations] as a function of time as monitored by $^{31}P(x)$ or 200 MHz $^{1}H(x)$ NMR (35 °C, non-quench method; see experimental section). Calculated percentage exocyclic cleavage ignores dimer and oligomer peaks.

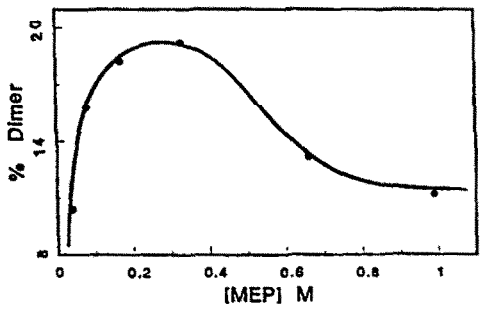


Fig. 2. % dimer formation in 0.33 M NaOD at various substrate concentrations as followed by ^{31}P NMR using rapid quench method A (see experimental section).

exocyclic cleavage product are dimers or oligomers of MEP which are produced due to the high concentration of MEP which Kluger and Thatcher used. Later Kluger and Thatcher[5] confirmed that the additional peaks are indeed the dimer form of MEP. They proposed a mechanism for this "dimer" formation (Scheme III) in which the initial hydrolysis products of MEP react with one another to form 2-hydroxyethyl-2-(ethyl methyl phosphate)phosphate (HEMPP, 8).

Scheme III

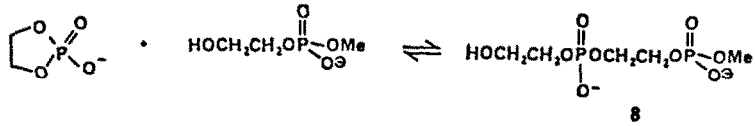


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Table I. ^{31}P NMR product analysis of MEP hydrolysis using rapid quench method A.

[MEP] M	[NaOD] M	Product analysis, %[e] [EXO][a]	[ENDO][b]	[DIM][c]	[oligomer][d]
0.04	5.40	4.1	81.2	10.4	4.3
0.08	5.40	3.0	78.0	15.8	3.2
0.17	5.40	2.7	72.7	18.2	6.4
0.33	5.40	4.4	70.5	19.2	5.9
0.66	5.40	3.2	79.4	13.2	4.3
0.99	5.40	3.3	82.0	11.2	3.0

[a]The sum of ethylene phosphate and hydroxyethyl phosphate.
[b]Hydroxyethyl methyl phosphate
[c]The sum of all the dimer peaks in the ^{31}P NMR spectra.
[d]Unidentified broad upfield peaks, possibly higher oligomers.
[e]Estimated error ± 1.5% based upon the signal to noise ratio in spectra.

Table II. Product analysis (after acid quench method A) at various NaOD concentrations, analyzed by ^{31}P.

[MEP] M	[NaOD] M	Product analysis[a], % [EXO]	[ENDO]	[DIM]	[oligomer]
0.33	1.25	2.9	67.9	23.0	6.1
0.33	3.40	3.1	74.9	17.4	4.7
0.33	5.40	4.4	70.5	19.2	5.9
0.33	9.20	4.7	73.3	14.8	7.6
0.33	12.00	2.9	74.0	14.7	8.4

[a]see Table I for definition of products and estimated error (± 1.5%)

From this mechanistic scheme, they concluded that the methanol observed from the reaction mixture was solely due to the exocyclic cleavage of MEP.

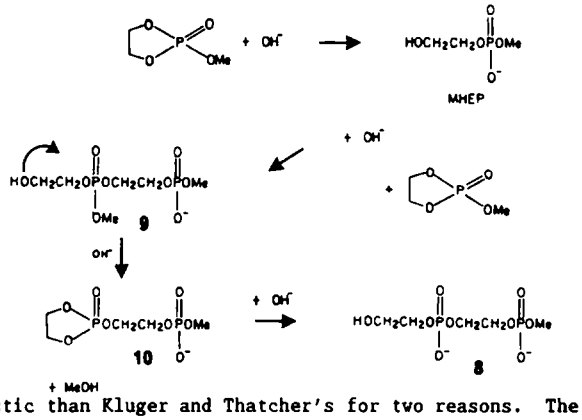
Mechanism of Dimer Formation. Is this (dimer and oligomer) formation the source of the discrepancy between our labs? Obviously dimer formation should be dependent upon MEP concentration and as shown in Fig. 2 this is indeed true.

Initially the amount of "dimer" formation increases as expected with increasing MEP concentration as shown in Figure 2. Apparently at higher concentrations of MEP, some higher degree of polymerization[22,23] also occurs and the amount of dimer decreases somewhat. These polymers have higher molecular weights and will tumble more slowly in solution which likely result in broad (unobservable) signals in the high resolution ^{31}P NMR spectra. Indeed heating of MEP yields glassy polymeric materials. The extent of polymer formation at high MEP concentration will result in a decrease in "dimer." Figure 2 shows that the "dimer" reaches a maximum at 0.33 M MEP. Additional broader upfield ^{31}P signals tentatively identified as higher oligomers also increase with initial increasing MEP concentration but then decrease with a further increase in MEP (Table I).

Kluger and Thatcher claim that dimer formation is a secondary product resulting from further reaction with exocyclic cleavage product. Thus all methanol produced must come from exocyclic cleavage product according to their analysis (Scheme III). Kluger and Thatcher thus used methanol formation as a quantitative measurement of the amount of exocyclic cleavage. Our laboratory has used ^{31}P NMR for quantitative analysis of the hydrolysis products which we believe is more reliable than Kluger and Thatcher's method if methanol can be generated from another alternative route not involving the exocyclic cleavage pathway. Note Kluger and Thatcher used a relatively high concentration of substrate (MEP > .3 M) in order to obtain spectra on a continuous wave proton NMR spectrometer (60 MHz).

However, are there any other alternative reactions which can produce methanol without going through the exocyclic cleavage of MEP¿ The ansver can be found from the extra peaks in the ^{31}P NMR spectra. Kluger and Thatcher[15] suggest that some of these peaks (and there are many peaks in this "dimer" region - see for example Fig. 3) are produced from the reaction of initial hydrolysis products. We now propose another mechanism for the "dimer" formation shown in the following Scheme IV.

Scheme IV



This mechanism is more realistic than Kluger and Thatcher's for two reasons. The first is a concentration factor. In the rapid quench hydrolysis method, the MEP concentration is always larger than the ethylene phosphate concentration except during the last few percent of reaction. The second important reason is a reactivity factor. As is well known, in strong alkaline condition, ethylene phosphate which is in the anionic form is much more resistant to attack by an anionic nucleophile than the neutral triester MEP. In the alkaline hydrolysis of trimethyl phosphate, the second ester cleavage step is much slower than the first ester bond cleavage. From the above argument, it is very clear that if methyl hydroxyethyl phosphate reacts to yield "dimer" it most likely will react with MEP instead of EP.

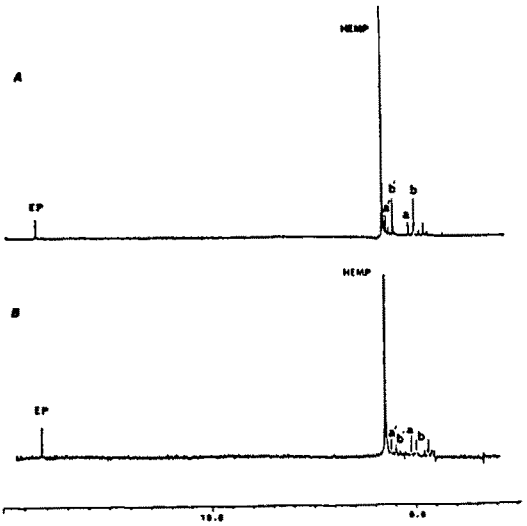
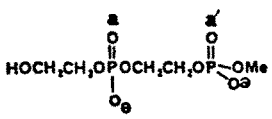
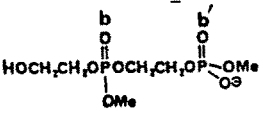


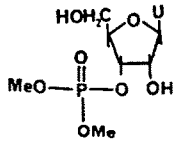
Fig. 3 ^{31}P NMR spectra of the hydrolysis products of MEP (0.33 M) using rapid quench method A in 1.0 M NaOD (a) and 5.0 M NaOD (b). Note in order to emphasize the minor products (EP and dimer peaks) the vertical scale has been expanded and as a result MHEP, 2, is now off-scale. Some of the upfield "dimer" and oligomer peaks have been identified (see discussion). a and a′ correspond to ^{31}P signals of "diester dimer" 8





and b and b′ correspond to ^{31}P signals of "triester dimer" 9

Resolution of Differences Between Various Groups. As indicated from the above mechanism of Scheme IV, the initially formed "dimer" is the reaction product of MHEP and MEP (not EP). This "dimer" 9, 2-hydroxyethyl-2-methyl-2-(ethyl methyl phosphate) phosphate contains one diester phosphoryl group and one triester phosphoryl group. The diester phosphoryl group hydrolyzes very slowly which would be similar to that of MHEP in alkaline solution.[19] However, for the triester phosphoryl part with the β-hydroxy group, the hydrolysis rate will be significantly enhanced due to an anchimeric acceleration.[19,20] Thus, the triester 11 with a β-hydroxy group hydrolyzes very fast in base with a half life of 9 min at pH 9.[20] The hydrolysis of the "triester 11 dimer" will rapidly release methanol.



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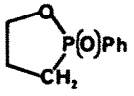

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In the alkaline hydrolysis of MEP, the initial triester "dimer" 9 would have a very short lifetime. With anchimeric assistance from the β-hydroxy group, it will cyclize to generate methanol and cyclic triester dimer 10 (Scheme IV). Further rapid hydrolysis of 10 finally yields phosphodiester dimer 8. It is this second form of the "dimer" ("diester dimer" 8) which Kluger and Thatcher presumably observed. The ratio between the "dimer" in either phosphodiester (8) or phosphotriester (9) form should depend upon the initial hydroxide ion concentration. At high NaOH concentration, "dimer" 9 in the triester form should rapidly hydrolyze to the diester form 8. On the other hand, at low NaOH concentration, we might expect that the "dimer" will exist largely in the triester form 9. Figure 3 shows the ^{31}P NMR spectrum of MEP hydrolysis products using the rapid quench method. The spectra were recorded after the hydrolysis mixtures were neutralized to pH = 8 ~ 9. Figure 3 clearly shows different peak intensities for the various dimer peaks at either 1.0 or 5.0 M NaOD. At 1.0 M NaOH (Figure 3A), the peak intensities of the triester "dimer" 9 are higher than those of the diester "dimer." In 5.0 M NaOD, the peak intensities for those signals are

reversed which is consistent with the above argument. Note our diester "dimer" 8 and Kluger and Thatcher's 2-hydroxyethyl-2-(ethyl methyl phosphate) phosphate (HEMPP) are identical compounds. This has been confirmed by addition of an authentic sample of "diester" dimer 8 formed by reaction between ethylene phosphate and methyl hydroxyethyl phosphate.

As shown in Tables I and II and Figures 2 and 3, the amount of methanol produced will be a function not only of MEP concentration, but of hydroxide concentration as well. At low concentration of hydroxide largely "triester dimer" 9 will be formed while at higher concentration of hydroxide, 9 will further hydrolyze to 8, thus explaining the increased proportion of methanol with increasing base (see below) observed by Kluger and Thatcher.

Because "dimer" is indeed also produced from the reaction between MEP and MHEP, methanol can thus be generated by an additional route other than through the exocyclic cleavage of MEP, i.e. hydrolysis of the "triester dimer" 9. Integration of the methanol peak in the ^{1}H NMR spectrum is thus invalid for the determination of the percent exocyclic cleavage in the hydrolysis of MEP. ^{31}P NMR, however, can properly analyze the complete product distribution. Analysis of methanol by ^{1}H NMR produced at high MEP and NaOH concentrations provide similar results to the completely relaxed ^{31}P NMR spectra if consideration is taken of all of the different product ^{31}P signals which can give rise to the ^{1}H methanol signal.

One of the strongest arguments given by Kluger and Thatcher for the significant involvement of the exocyclic cleavage pathway is the apparent increase in exocyclic cleavage product with base. Kluger and Thatcher have argued that our triester-dimer Scheme IV is inconsistent with the hydroxide dependence to the amount of methanol produced (again incorrectly defined by them as % exocyclic cleavage). They argue that only their Scheme III provides for a second-order hydroxide dependence to the amount of methanol produced. Qualitatively this can be shown to be incorrect. Kluger and Thatcher[16] have argued against our Scheme IV for formation of methanol via subsequent hydrolysis of the "triester dimer." They claim that "although the addition of methyl hydroxyethyl phosphate to methyl ethylene phosphate is base catalyzed, the addition of hydroxide to methyl ethylene phosphate will also increase in rate and thus no differential increase in HEMPP would be observed." However our Scheme IV requires two equivalents of hydroxide to form triester dimer: note that one mole of hydroxide is required to initially yield endocyclic cleavage product, followed by a second mole of OH^- to ionize the β-hydroxy group on MHEP in the subsequent attack of the alkoxide on MEP. At low concentration of base, the β-hydroxy group will not be ionized, and triester dimer 9 will not rapidly recyclize to generate 10 and methanol (see Figure 3). At higher base concentrations the second equivalent of base can again deprotonate the β-hydroxy group to anchimerically accelerate the production of methanol. Thus the amount of diester dimer 8 and methanol should increase with increasing base at high MEP concentrations. Thus disregarding the artifactual production of methanol from the dimerization reaction, in contrast to the claims of Kluger and Thatcher there is little if any increase in exocyclic cleavage with base (Table II). However, analysis based upon our new ^{31}P NMR data does possibly show ~ 3 ± 1.5% (S/N ratio ~ 60) of exocyclic cleavage product for MEP hydrolyzed in 1-9 M NaOH. Still, an initial report from our laboratory[15,16] of 0 ± 3% at low MEP concentration (in dioxane) indeed was and still is correct within the signal-to-noise (S/N of 30) of the early spectra taken on a much older and lower field spectrometer (Bruker WP-80, 80 MHz ^{1}H). The new results were obtained at higher field (200 MHz) on a much more sensitive spectrometer (IBM 200SY). Actually even this 3 ± 1.5% exocyclic cleavage is very difficult to establish with current methodology. Thus, if the hydrolysis is conducted at the concentrations reported in our laboratory's initial report[15,16] (0.017 M MEP, added as a dilute solution of MEP in dioxane), the apparent amount of exocyclic cleavage and dimer products are even less ($\lesssim$ 1%). This suggests that local high concentrations of MEP resulting from addition of neat MEP in Kluger and Thatcher's method[15,16] could be responsible for the increased amount of dimer and exocyclic cleavage product. (Note in neutral or acidic solution, 10 - 50% exocyclic cleavage is observed[5] - addition of neat MEP to dilute base with subsequent rapid hydrolysis and acid production

could neutralize the base and generate regions of very low basicity.)

Stereoelectronic Effect. In the dianionic intermediate A, the two lone pairs on the basal ring oxygen (assumed sp^3 hybridized[17]) are oriented partially antiperiplanar (app) to the axial ring ester bond of the leaving group. The molecular orbital calculations suggested that this app lone pair orientation could significantly facilitate P-O ester bond cleavage and that proper orbital overlap (the stereoelectronic effect) could be responsible for a significant lowering[7,8] of transition state energies. Indeed, in the five-membered cyclic esters the ring constrains the lone pairs in a stereoelectronically favorable orientation while in the acyclic transition state, proper app lone pair overlap would require "freezing" of one or more rotational degrees of freedom about the ester bonds.[8] It is thus significant that a considerable portion of the rate difference between acyclic and cyclic reactions is entropic[24] as predicted from the stereoelectronic effect.[8]

Although exocyclic cleavage from the dianionic intermediate A is still assisted by the lone pair electrons on the equatorial anionic oxygens, the endocyclic cleavage is favored because it is assisted by all three equatorial oxygen lone pairs, especially those on the equatorial ring oxygen.

We have found that the alkaline hydrolysis of MEP has at most 3 ± 1.5% exocyclic cleavage in strong base which corresponds to about 2 kcal/mol in lowering the activation energy of the transition states between exocyclic and endocyclic cleavage.

Because the pK[25] of ethanol (pK = 15.9) is greater than that of methanol (pK = 15.4), exocyclic cleavage of the better leaving group could be favored by 0.4 kcal/mol. Thus the minimum stereoelectronic effect for cleavage of comparable leaving groups may well be at least 2.5 kcal/mol. Most significantly we have reinvestigated[19] the amount of exocyclic cleavage in ethyl ethylene phosphate and even at high concentration of the cyclic phosphate in 1 - 5 M NaOH observed < .2% exocyclic cleavage.

In the accompanying paper we have measured the rate of base catalyzed hydrolysis of 12 and its corresponding acyclic analogue. A free energy of activation difference between reaction of the acyclic and cyclic esters of about 5.2 kcal/mol is found. This leads us to believe that a report of 5.5 kcal/mol of ring strain by Kaiser et al.[26] is correct although Kluger and Thatcher claim 8 kcal/mol is more realistic. Additionally, the ring strain in related systems are in the range of 4 - 6 kcal/mol[1]. Thus, this still leaves about 3.2 kcal/mol extra stabilization energy of the cyclic vs. acyclic phosphorus triester unexplained, which we attribute to the stereoelectronic effect.

These results confirm that the rate enhancement in the hydrolysis of five-membered cyclic phosphate esters is not only derived from the ground state ring strain energy but that part of the reactivity also very likely arises from the stereoelectronic effect.

Conclusion

Contrary to Kluger and Thatcher's claims, we never suggested that the stereoelectronic effect "requires intermediate [A] to react exclusively to give endocyclic cleavage." (From Kluger and Thatcher[15]) We clearly indicated that the stereoelectronic effect could be responsible for as much as "10^3 - 10^5 rate acceleration." (From Taira et al.[18]). What would invalidate our argument, however, is a large increase in the percent exocyclic cleavage with increasing base. Because we have now established that this increase (to as much as 24% as claimed by Kluger and Thatcher) is due to an artifactual dimerization reaction, the stereoelectronic effect continues as a quite viable explanation for a significant portion of the rate acceleration in five-membered ring cyclic phosphate esters.

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