

Heats of Reaction of Cyclic and Acyclic Phosphate and Phosphonate Esters. "Strain Discrepancy" and Steric Retardation

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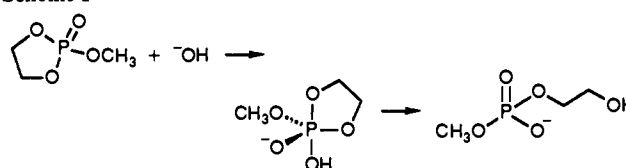
Abstract: The millionfold enhancement of the rate of hydrolysis of five-membered cyclic phosphate esters compared to their acyclic analogues is purely enthalpic and arises at least partially from destabilization of the four-coordinate cyclic reactant compared to the acyclic analogue, assuming that both react with hydroxide through unstrained five-coordinate transition states. Calorimetric analysis of the hydrolysis of cyclic and acyclic phosphates and phosphonates is reported in which the absolute value of the difference in enthalpy of hydrolysis of the cyclic and acyclic species is considerably *less* than the difference in activation enthalpies (about 2 kcal/mol discrepancy). This requires that the acyclic esters react via transition states which are relatively *higher* in energy than those of the corresponding cyclic esters. The additional energy of the acyclic transition states is likely to be the result of steric interactions which are absent in the cyclic species.

Phosphate and phosphonate esters contained in five-membered or smaller rings are much more rapidly hydrolyzed than their acyclic counterparts.¹⁻³ The enhanced rate of hydrolysis was proposed by Westheimer to arise from productive destabilization of the cyclic ester relative to the five-coordinate transition state of the hydrolysis reaction by ring strain.^{4,5} In analyzing the reaction, it was assumed that the transition states for reaction of the both cyclic and acyclic species were free of strain and therefore the strain energy in the cyclic species would be relieved in the formation of the transition state.⁶ This has been confirmed by molecular mechanics and theoretical calculations.^{2,6} It is also supported by structural analysis⁷ which is consistent with significant ring strain being present in the cyclic four-coordinate phosphorus species. The reaction pathway for the hydrolysis of methyl ethylene phosphate with ring opening is summarized in Scheme I.

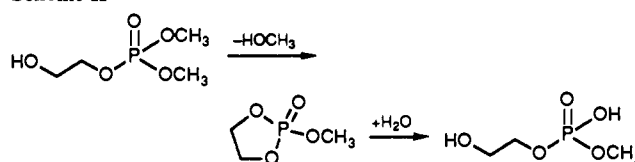
In 1959, Cox, Wall, and Westheimer developed a method employing isoperibol calorimetry by which the extent of ring strain can be estimated. The heat released upon hydrolysis of a cyclic ester to give an acyclic species is compared to that released in the hydrolysis of a related acyclic ester.⁸ Since acyclic phosphate esters react too slowly to give reliable calorimetric measurements, an acyclic species which reacts rapidly via neighboring group participation is used. This overcomes the kinetic barrier while maintaining the thermodynamic properties of the system (Scheme II).

Of course, the rate of reaction via the neighboring group mechanism does not provide a basis for kinetic comparison of the second-order process by which, for example, hydroxide reacts with cyclic and acyclic species. However, ΔH measured for the reaction that leads from the acyclic triester to the acyclic diester (Scheme II) is the standard for heat released upon hydrolysis of an acyclic species and can be compared to the heat released in a cyclic ester hydrolysis reaction. The only assumption that is required is that the heat generated by conversion of the ester function to a hydroxyl group in the cyclic case is the same as that in the conversion of a methoxy group to methyl alcohol in the neighboring group case.

Scheme I



Scheme II



No other functional group changes are involved, and alkyl chains remain in solution before and after the reaction. The same assumption would be necessary if an acyclic ester without neighboring group were used in the standard reaction. The differential in heat released upon hydrolysis of the cyclic and acyclic species is thus conveniently accessible.

Westheimer's early calorimetric measurements supported the ring-strain hypothesis: the heat of reaction of methyl ethylene phosphate was higher than that of related acyclic triesters by about 8 kcal/mol.⁸ However, later measurements by Westheimer and co-workers with the same compounds yielded a difference of only 5.5 kcal/mol, an amount insufficient to account for the acceleration.⁹ This is consistent with an earlier suggestion of Ramirez that steric interactions in the five-coordinate transition state of the acyclic species may be greater than those in the five-coordinate transition state of the cyclic species.¹⁰ In this hypothesis, the transition states are not comparably strain-free: the acyclic transition state is relatively higher in enthalpy compared to its strain-free hydrolysis product than is the transition state of the cyclic species compared to its hydrolysis product. Gorenstein proposed an alternative explanation for the discrepancy by noting stereoelectronic orientational effects which stabilize transition states involving the cyclic species.¹¹ Such effects would lead to a rate differential due to a smaller entropy of activation for the cyclic species. The possibility of an entropic differential was later ruled out by our studies, which showed that there were no sig-

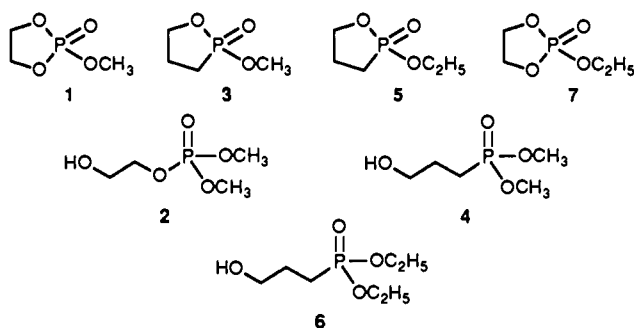
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nificant differences in the entropies of activation of comparable cyclic and acyclic species.¹²

The relatively low heat of reaction which is the basis for the discrepancy⁹ is itself uncertain since there appeared in 1975 a note of unpublished results that the excess enthalpy in **1** compared to **2** could be as high as 9 kcal/mol.¹³ With such uncertainty, we felt it necessary to redetermine the calorimetric data independently. The difference in the heats of hydrolysis of cyclic and acyclic species ($\Delta\Delta H$) depends on accurate measurements of ΔH for each reaction. The availability of modern computer-controlled calorimetric equipment provides an opportunity to obtain the necessarily accurate values. Furthermore, since previous calorimetric studies of phosphate triester hydrolysis were limited to methyl ethylene phosphate and its acyclic analogue, methyl β -hydroxyethyl phosphate, we decided to study a wider series of compounds in addition to reinvestigating the original subjects. A broader range of electronically and sterically different species using the same protocols and assumptions would test the generality of the proposed reaction patterns.

On the basis of these considerations, we have now determined the heats of reaction with hydroxide of four five-membered-ring cyclic phosphorus esters and three acyclic analogues: methyl ethylene phosphate (**1**), dimethyl β -hydroxyethyl phosphate (**2**), methyl (γ -hydroxypropyl)phosphonate cyclic ester (methyl propylphosphonate, **3**), dimethyl (γ -hydroxypropyl)phosphonate (**4**), ethyl (γ -hydroxypropyl)phosphonate cyclic ester (ethyl propylphosphonate, **5**), diethyl (γ -hydroxypropyl)phosphonate (**6**), and ethyl ethylene phosphate (**7**).



Experimental Section

Materials and Methods. Chemicals for synthesis were purchased from the Aldrich Chemical Co. and distilled prior to use. Solvents were purchased from Caledon Laboratories Ltd. and BDH Chemicals. ¹³C (proton decoupled) and ¹H NMR spectra were obtained with a Varian Gemini-200 spectrometer. Proton-decoupled ³¹P NMR spectra were recorded on a Varian XL-200 spectrometer, and chemical shifts were recorded relative to external 85% phosphoric acid. A Radiometer pH meter 27 (GK-202B combination electrode) was used for pH measurements.

Syntheses. Dimethyl (γ -acetoxypropyl)phosphonate and diethyl (γ -acetoxypropyl)phosphonate were prepared and converted to dimethyl (γ -hydroxypropyl)phosphonate (**4**) and diethyl (γ -hydroxypropyl)phosphonate (**6**) by the procedure of Finke and Kleiner.¹⁴ Methyl ethylene phosphate¹⁵ (**1**), methyl propylphosphonate¹⁶ (**3**), ethyl ethylene phosphate¹⁷ (**7**), and dimethyl β -hydroxyethyl phosphate⁸ (**2**) were prepared by published procedures.

Ethyl propylphosphonate¹⁸ (**5**) was prepared by a modification of the published procedure for methyl propylphosphonate.¹⁶ Diethyl (3-bromopropyl)phosphonate¹⁹ (35 g, 0.14 mol) was heated at 160–170 °C under nitrogen for 2 h. The resulting liquid was vacuum distilled (Hickman still) and then redistilled with a 28-cm vacuum-jacketed Vigreux column

(bp 58–60 °C, 0.05 Torr; lit.¹⁸ bp 74 °C, 0.6 Torr).

Calorimetry. Heats of solution and reaction were measured using batch isoperibol calorimetry with a Tronac Model 458 calorimeter (Tronac Instruments, Provo, UT) interfaced to a computer (MS-DOS, Intel 80386 processor) and an FS605 Calorimeter Interface from Frankford Analytical Services Inc. (Rochester, NY, at the time of purchase, currently available from Tronac). Methodology for calorimetric determinations was based on algorithms in the program FS101 from Frankford Analytical Services.

Calorimeter Calibration. The Tronac Model 450 isoperibol calorimeter measures temperature changes via a thermistor. The thermistor constant, the change in temperature with voltage (T_k), was determined by measuring the heat capacity of the system (reaction vessel and contents) with different solvents whose heat capacities differed greatly (water, benzene, and carbon tetrachloride): $T_k = 2.949 \times 10^{-5}$ °C/mV. The calorimeter was also calibrated by measuring the heat of solution of tris(hydroxymethyl)aminomethane in a 0.1000 M HCl solution. The values obtained were consistently within ± 0.02 kcal/mol of the reported value of -7.11 kcal/mol.^{20,21}

Heats of Solution. The reactant (35–65 mg) was weighed on a Mettler AE240 balance in a thin-walled glass ampoule (as supplied by Tronac). The ampoule neck was sealed with a fine flame (soldering torch). For samples added as a solution, the compound was weighed into the ampoule, and 500 μ L of distilled, deionized water was added via a gas-tight Hamilton microliter syringe. The sealed ampoule was then placed in the holder of the calorimeter head shaft. Freshly distilled, deionized water was heated to boiling and cooled under nitrogen until the temperature was slightly below 25 °C, and 50 mL was transferred using a calibrated volumetric pipet to a 75-mL Dewar flask designed to fit the calorimeter. The vessel was placed onto the calorimeter head shaft, which was then immersed in a water bath (60 L) whose temperature was controlled at 25.000 ± 0.002 °C. The mechanical stirrer (600 rpm) was started, and the water in the Dewar vessel was heated electrically until the temperature of the water in the vessel was close to but still less than 25 °C. Heating was stopped, and the system was allowed to arrive at a steady state in which the temperature increase from the mechanical stirrer was constant. When the temperature reached 25.0 °C, the ampoule containing the sample was broken using the breaker located in the header shaft. The heat of breaking the ampoules was negligible and could not be detected in control runs. After ampoule breakage and dissolution of the sample, the system was monitored until the temperature increase from the mechanical stirrer was again constant. The heat capacity of the system was then determined using the electric heater.

Since **3** hydrolyzes relatively slowly, an independent method for measuring the effect of dissolution was possible. The heats of dilution of 0.4–0.45 M aqueous solutions of **3** and **4** (0.5 mL) into 50 mL of water were measured. In these cases (Table I), the heats of solution were negligible while the heats of alkaline hydrolysis were the same as those determined by using neat samples and subtracting the heats of solution in water from the total heat evolved during hydrolysis.

Heat of Reaction. The heat evolved from the hydrolysis of each ester was determined as described above for heats of solution, except that potassium hydroxide solution (0.1000 M) was used as solvent. The temperature rise from a typical determination of the total heat evolved during hydrolysis was about 0.06 °C (approximately 2000 μ V). Methyl ethylene phosphate is known to hydrolyze by cleavage of the endocyclic ester linkage in 0.01 M base.^{15,22} Polymerization of the ester occurs only at higher base concentrations.^{15,23–25} A sample of **1** was hydrolyzed under the conditions used for calorimetry (15 mg in 50 mL of 0.1000 M potassium hydroxide). The resulting solution was lyophilized. The residue was dissolved in deuterium oxide and analyzed by ³¹P NMR spectroscopy. Products due to exocyclic cleavage or polymerization were not detected.

Calorimetric Data Analysis. A thermogram (μ V vs time) is generated by the computer. The thermogram consists of five regions: (1) a pre-reaction period, where the increase in temperature (μ V) is due largely to the mechanical stirrer; (2) a reaction period, where the ampoule containing the substrate has been broken and the change in temperature is largely a result of the reaction of the substrate with solvent; (3) a post-reaction period, where the temperature change is again due largely to

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Table I. Thermochemical Parameters for Hydrolysis of Cyclic and Acyclic Phosphorus Esters at 25 °C^a

compd	ΔH_t^b	ΔH_s^c	ΔH_r^d	$\Delta H_c - \Delta H_{ac}^e$
1	-30.6 ± 0.2	-0.56 ± .02	-30.1 ± 0.2	
2	-26.8 ± 0.1	-2.68 ± .02	-24.2 ± 0.1	-5.9 ± 0.3
3	-29.91 ± .04	-2.9 ± 0.1	-27.1 ± 0.1	
4	-27.2 ± 0.1	-3.88 ± .04	-23.4 ± 0.3	-3.7 ± 0.3
3 ^f	-27.0 ± .01	0	-27.0 ± 0.1	
4 ^f	-23.4 ± 0.1	0	-23.4 ± 0.1	-3.6 ± 0.2
5	-31.4 ± 0.1	-1.17 ± 0.06	-30.2 ± 0.3	
6	-29.2 ± 0.1	-5.54 ± 0.07	-23.7 ± 0.2	-3.5 ± 0.2
7	-30.9 ± 0.1	-3.69 ± 0.04	-27.2 ± 0.1	

^a Values reported are the average of three determinations. All values are expressed in kilocalories/mole. The uncertainty is reported as the standard deviation. ^b Total heat evolved from hydrolysis in KOH solution. ^c Heat of solution in water. ^d Net heat of reaction = (total heat evolved) - (heat of solution). ^e (Net heat of reaction of cyclic compound) - (net heat of reaction of acyclic compound). ^f Compound was predissolved in H₂O as described in the Experimental Section.

the mechanical stirrer; (4) a heater calibration period, where the temperature change is largely a result of the electrical heater; and (5) a postcalibration period, where the temperature change is again due largely to the stirring. From the amount of heat produced by the electric heater and slopes of regions of the plots, the heat capacity of the system is calculated. The program calculates and plots power vs time. The energy released during the hydrolysis and during the heater calibration period appears as an "energy burst" above the baseline. The program integrates from the point where energy is first released during the hydrolysis to the point where the energy output returns to the steady-state value. This yields the amount of heat generated during the reaction time period (in calories). Temperature changes during the reaction due to nonreaction contributions (mechanical stirrer, heat leakage, and resistance heating of the thermistor) are determined by measuring the slopes of the post-reaction and pre-reaction periods. The program subtracts nonchemical contributions from the total energy change, which yields the heat generated by chemical reactions and dilution. This value is divided by the number of moles of reacting substrate to give the total amount of heat generated by chemical reactions and dilution, in kilocalories/mole.

Results

Calorimetric Measurements. Thermochemical parameters for the alkaline hydrolysis of cyclic and acyclic esters are presented in Table I. The heats of alkaline hydrolysis of these esters were determined by subtracting their measured heats of solution in water (hydrolysis is slow in neutral solution) from the total heat evolved during hydrolysis in potassium hydroxide solutions. We have assumed that the heat of solution in water is the same as the heat of solution in higher ionic strength potassium ion solutions. We also measured the heats of solution and hydrolysis of 0.4–0.45 M aqueous solutions of methyl propyl phosphonate, dimethyl (γ -hydroxypropyl)phosphonate, and ethyl propyl phosphonate. In these cases, the heats of solution were negligible, while the heats of alkaline hydrolysis were the same as those determined by using neat samples and subtracting the heats of solution in water from the total heat evolved during hydrolysis in potassium hydroxide solutions. This indicates that all of the heat evolved during the dissolution and mixing process of the neat samples is complete before reaction of the compounds with hydroxide occurs.

Comparison Compounds. The acyclic materials in the present study of heats of reaction, 2, 4, and 6 were chosen because they react rapidly due to participation by the neighboring hydroxyl group. Heat is evolved over the short period of time to the completion of the reaction and can be measured accurately. The validity of the approach is justified by Westheimer in his original study of the heats of reaction of 1 and 2: "A comparison of heats of hydrolysis for these esters [1 and 2] is a valid one; the formation of a new alcoholic function during the hydrolysis of the cyclic ester [1] is balanced by the formation of methanol [from 2]".⁸ The assumption of this study is that ring strain is manifested in the differences in heats of reaction of the cyclic and acyclic systems and is inherent to the ring itself. A less precise study of trimethyl phosphate hydrolysis confirmed the assumption.⁸ In contrast, kinetic comparisons must come from reactions involving the same molecularity with acyclic or cyclic transition states. Thus, dif-

Table II. Enthalpies of Activation for Alkaline Hydrolysis of Phosphates and Phosphonates^a

compd	ΔH^\ddagger , kcal/mol
1	7.8
trimethyl phosphate	15.6
3	7.9
dimethyl methylphosphonate	14.0
5	7.6
diethyl ethylphosphonate	13.4
7	7.4
triethyl phosphate	14.1

^a From ref 12 and references cited therein. Acyclic analogues are those which do not have neighboring hydroxyl groups (as do the acyclic compounds used for calorimetry in the present study). All reactions involve a bimolecular process with hydroxide.

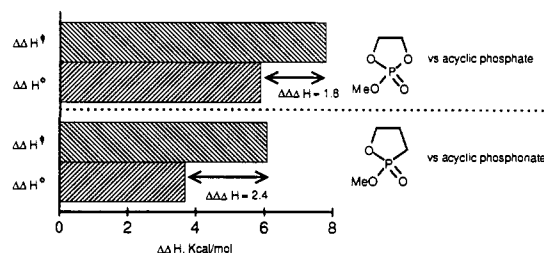


Figure 1. Differences in enthalpy of activation for the alkaline hydrolysis of cyclic and acyclic phosphates and of cyclic and acyclic phosphonates are greater than the differences in enthalpies of activation in related reactions. The values for differences in enthalpies of activation are for second-order reactions of cyclic phosphates and acyclic phosphates with hydroxide, both classes reacting via bimolecular transition states (the reactions do not differ in entropy of activation so enthalpies correspond to free energies). The values for differences in heats of reaction ($\Delta\Delta H$) come from reactions of cyclic phosphates and acyclic phosphates which react with neighboring group participation. The data are from Tables I and II.

ferences in activation parameters must come from reactions of acyclic species that do not involve neighboring group participation.

Differences in Heats of Reaction. The heat evolved in the alkaline hydrolysis of the cyclic phosphate 1 is 5.9 kcal/mol greater than that evolved in the hydrolysis of the acyclic analogue, 2 (Table I). This is identical, within experimental error, to the report of 5.5 kcal/mol⁹ but less than is cited in other reports.^{8,13} We also measured the heats of alkaline hydrolysis of the cyclic methyl phosphonate, 3, and its acyclic analogue, 4, the cyclic ethyl phosphonate, 5, and its acyclic analogue, 6, and the cyclic ethyl phosphonate, 7 (Table I). The ethyl phosphonate and its acyclic analogue show heats of hydrolysis that differ to about the same extent as do the methyl esters. The difference in heats of hydrolysis of the cyclic and acyclic phosphonates, however, is only 3.6 kcal/mol. The heat of reaction for hydrolysis of ethyl ethylene phosphate (7) is about the same as for methyl ethylene phosphate.

Comparison of Activation Enthalpies of Cyclic and Acyclic Species. The differences in enthalpies of activation for reactions of the cyclic species in our study and related acyclic species (which hydrolyze without neighboring group participation) have been presented in our previous paper.¹² Those data are summarized in Table II. We also have shown that the hydrolysis reactions of cyclic and acyclic esters (when cyclic methyl esters are compared with acyclic methyl esters and cyclic ethyl esters are compared with acyclic ethyl esters) do not differ in entropy of activation so that comparison of kinetics involves only enthalpy terms.

The differences in heats of reaction ($\Delta\Delta H^\ddagger$) of cyclic and acyclic species are smaller than the differences in enthalpies of activation ($\Delta\Delta H^\ddagger$) of cyclic and acyclic species in our kinetic studies.¹² Since there is no difference in entropy of activation, it is now established that there is a significant discrepancy between the strain energy which can possibly be released in hydrolysis and the difference in activation enthalpies (Figure 1). That is, the cyclic esters hydrolyze more rapidly due to processes entirely arising from the enthalpy term in the activation free energy. The amount of this energy that is manifested as ground-state ring strain in the cyclic

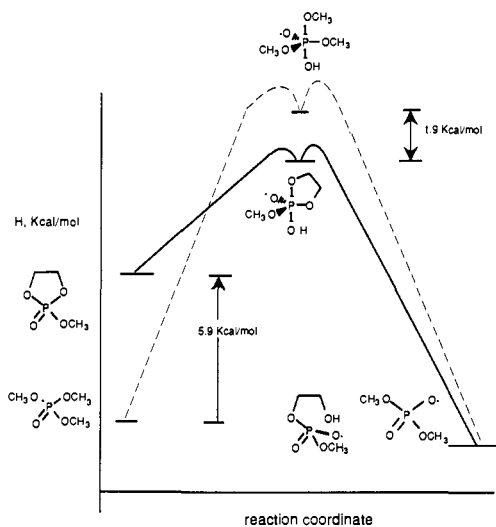


Figure 2. Schematic enthalpy diagram for the hydrolysis of methyl ethylene phosphate with an arbitrary equal end point for the strain-free hydrolysis products from both cyclic and acyclic species. The acyclic transition state fits only at a relatively higher point on the enthalpy scale than does the cyclic transition state, given the relative positions of other species. The difference in activation enthalpy in the forward reaction of trimethyl phosphate and **1** is from our earlier study.¹³ The difference in initial enthalpic states is based on the difference in heats of reaction of **1** and **2** and the assumption that this applies to differences in enthalpy of hydrolysis of **1** and any related acyclic methyl ester (as explained in the text).

ester is less than the amount necessary to account for the acceleration.

Discussion

In all cases, the difference in heats of reaction of the cyclic and acyclic esters is significantly less than the difference in activation enthalpies for the hydrolysis reactions. For the phosphates, the discrepancy is 1.8 kcal/mol and for the phosphonates it is 2.4 kcal/mol (Figure 1).

The difference in activation enthalpies for cyclic and acyclic methyl phosphates is 7.9 kcal/mol and for the methyl phosphonates it is 6.1 kcal/mol. The discrepancy in the differences in enthalpies of reaction compared to enthalpies of activation is clearly beyond the range of experimental uncertainty. Since the rate effect is manifested entirely in the enthalpy of activation, what is the source of the difference? The transition state for hydrolysis of **1** and **3** is more stable relative to reactants than the transition state for the hydrolysis of acyclic esters by the extent of the energetic discrepancy above. This is illustrated in the enthalpy diagrams in Figure 2. The higher relative energy of the acyclic transition state, which is due entirely to enthalpic factors,¹² can be analyzed in terms of the structure of the related trigonal bipyramidal intermediates which, being high in energy and rapid to react, should resemble the associated transition states. The discrepancy factor is somewhat larger for the phosphonates, but a consistent explanation should account for the existence of the additional barrier as well as the difference between phosphates and phosphonates.

Steric Effects in Phosphoranes. Phosphoranes (five-coordinate phosphorus compounds) containing five-membered rings are significantly more stable than acyclic phosphoranes, and spiro phosphoranes containing two five-membered rings are particularly stable.² Ramirez and co-workers proposed that this might be due to unfavorable steric interactions in the acyclic phosphoranes as compared to the cyclic phosphoranes.²⁶ Ramirez also suggested that part of the rate enhancement of cyclic five-membered phosphorus esters was due to the presence of fewer steric interactions in the cyclic transition state than in the acyclic transition state. Alternatively, solvation of the acyclic transition state may

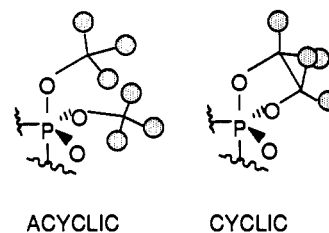
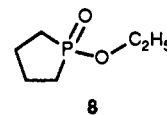


Figure 3. Two additional hydrogen atoms (of methyl groups) interact in the five-coordinate state in the acyclic compared to cyclic species.

be disfavored. Molecular models reveal the presence of considerably more steric crowding in the acyclic five-coordinate species than in the cyclic species (Figure 3), but the absence of reliable force field parameters for five-coordinate phosphorus prevents us from doing detailed molecular mechanics calculations (a theoretical analysis of this problem is currently being conducted by Professor Carmay Lim).

The transition state for hydrolysis of **1** is only 1.8 kcal/mol lower in energy than that for the hydrolysis of its acyclic analogue, trimethyl phosphate, and this energy is entirely enthalpic.¹² The energy difference may indicate that steric interactions in the acyclic phosphate are reduced in comparison to the acyclic phosphonate. Another possibility is that, for **1**, not all of the strain energy is relieved at the transition state. More heat is released upon hydrolysis of the cyclic phosphates than upon hydrolysis of the cyclic phosphonates, showing that the cyclic phosphates are more strained. Partial double bonding in the endocyclic P—O—C bonds may result in an increase in strain.⁷ There are two ring oxygens which can π -bond with the phosphorus in **1** as compared to one ring oxygen in **3**. If all of the strain in **1** is not relieved at the transition state, then the partial double bonding in the ring P—O bonds is not removed at the transition state (as has been suggested by Haake and Westheimer).⁵ The partial double bonding between the ring oxygens and the phosphorus destabilizes the cyclic transition state to a lesser extent than in the ground state. Ramirez and co-workers observed that bond lengths indicate π -bonding does occur in pentaoxyphosphoranes although to a lesser extent than in phosphoryl esters.^{26,27} Thus, Ramirez's proposal that the rate enhancement is due to differential steric effects between cyclic and acyclic transition states may be correct if there is a large amount of enthalpic strain in the acyclic transition states.

The rate of hydrolysis of the cyclic phosphinate, **8**, is only 60 times faster than that of its acyclic analogue.²⁸ The small dif-



ference in rates has been attributed to the formation of a high-energy intermediate that must necessarily have a methylene group in an apical position.^{3,28,29} Although ring strain is relieved at the cyclic transition state, this is opposed by the energetically unfavorable consequences of having a methylene group in an apical position.² If a significant portion of the strain in cyclic five-membered phosphorus esters is due to π -bonding between endocyclic oxygens and the phosphorus, then **8** should be less strained than a phosphonate or cyclic phosphate since **8** does not have any ring oxygens. The strain energy in the phosphonate **3** is 2.2 kcal/mol less than in **1**. If we assume that there is a decrease in strain of 2.2 kcal/mol for each endocyclic oxygen, then the strain energy in **8** is only 1.5 kcal/mol.

Conclusions

The rate enhancement in cyclic five-membered phosphorus esters had been shown to be due exclusively to enthalpic factors.¹² Westheimer's proposal that the rate enhancement is due to relief

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of ring strain is widely accepted and correct, but it does not explain the full amount of the acceleration in the cyclic species.⁴ In particular, it appears that the acyclic transition states used as standards are destabilized compared to the corresponding cyclic cases. Although the rate enhancement in cyclic phosphates and phosphonates is the same, their strain energy is not the same. Our results suggest that the degree to which the cyclic esters are strained depends upon the number of oxygens in the ring. Further

work is necessary to establish the source of the higher energy of the acyclic transition states, but it appears reasonable that crowding should be a serious problem in a five-coordinate species.

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Expression of Dipolar Character in Diyl Trapping Chemistry

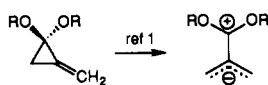
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Abstract: A set of new reactions is described and illustrated in eqs 1-5. Diazenes which customarily participate in diradical processes, compounds **1a** and **9** for example, lead to intermediates which are intercepted by water. Diazene **3** is converted to an intermediate which is intercepted both by water and, when the dielectric constant of the medium is sufficiently high, by *n*-PrOH. The chemistry is believed to arise through the intermediacy of a "dipolar diradical", which is described by an unequal weighting of the zwitterionic (Ψ_α and Ψ_β) and diradical (Ψ_δ) resonance formulations to the overall wave function for the system: $\Psi = \alpha\Psi_\alpha + \beta\Psi_\beta + \delta\Psi_\delta$.

Introduction

Recently, Nakamura reported a new [3 + 2] cycloaddition leading to the facile construction of functionalized five-membered-ring carbocycles.¹ The process is initiated thermally and occurs between 2-methylenecyclopropanone ketals and electron-deficient alkenes. It has been suggested, and the existing data is supportive, that a dipolar synthetic equivalent of the corresponding trimethylenemethane diradical is an intermediate. Particularly good evidence stems from the fact that the intermediate can be intercepted by methanol. The direction of the polarization with the positive charge being localized on the ketal-bearing carbon is certainly reasonable; molecular orbital (MO) calculations also support this view.¹



The diradicals which are commonly associated with the inter- and intramolecular diyl trapping reactions, in contrast, express dipolar character only in so far as they are intercepted most rapidly by electron-deficient diylphiles.² There is a substantial body of evidence, including the direct observation of triplet diradicals by ESR for a wide range of substituents R and R' in the formulation shown, to support a diradical rather than a zwitterionic intermediate.³ In keeping with this suggestion is the result of

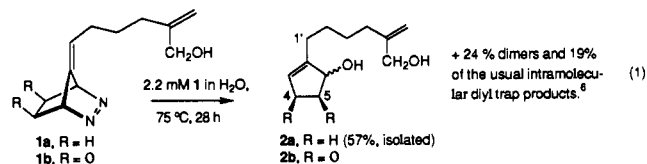


MO calculations which place the difference in energy between the highest energy singlet and the zwitterionic state of the parent

trimethylenemethane at greater than 4 eV.^{4,5}

A New Reaction. We report a series of new reactions which we believe can best be explained as proceeding through the intermediacy of a dipolar diyl. The wave function for this state can qualitatively be described as a linear combination of dipolar and diradical contributions, with the dipolar portion of sufficient magnitude to govern the mode of reactivity (*vide infra*).^{1b,5}

In conjunction with another project, we heated diazene **1a** to 75 °C in water.⁶ We thought that the hydrophobic diyl would undergo intramolecular diyl trapping in a manner which would lead to a different regio- and stereochemical outcome than we had previously observed when the diyl was generated in acetonitrile or THF. The usual diyl trapping products were obtained,⁶ but in diminished yield, while the isomer ratio was basically unchanged. We were surprised to notice the presence of a new compound, diol **2a**, a product which clearly resulted from the interception of an intermediate by water!⁷



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(5) Trimethylenemethane is a nondisjoint hydrocarbon and as such, no molecular orbitals exist where the two electrons in question can be located entirely on different atoms. Consequently, even for this simple system, the lowest energy singlet wave function contains ionic terms. As stated by Borden and Salem (*J. Am. Chem. Soc.* **1973**, *95*, 932): "The large ionic component in the singlet wave function for planar trimethylenemethane is responsible for its high energy". For an excellent account of the covalent vs zwitterionic character of the wave functions for diradicals, see: (a) Salem, L.; Rowland, C. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 92. (b) *Electrons in Chemical Reactions - First Principles*; Salem, L., Ed.; Wiley: New York, 1982; pp 89-93.

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