Organophosphorus Compounds. Part 43. A Molecular Mechanics Study: the Structural Effect of Cyclic Esters of Phosphorus-based Acids in Hydrolytic Reaction

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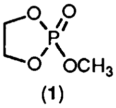
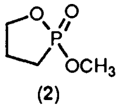
Hydrolytic reactions of some cyclic esters of alkylphosphates and phosphonates have been studied using molecular mechanics calculations (Allinger 1977 force field, MM2 1985 program). Either the ratio of the ring opening and retention products, of hydrolysis of five-membered cyclic esters of alkylphosphates and alkylphosphonates or the structural effect of ring size and the *endo*-ring substituent on the hydrolytic rate constant (*k*) can be determined from the steric energy difference between the substrate and its pentaco-ordinated transition state (ΔE or $\Delta\Delta E$). ΔE and $\Delta\Delta E$ can be evaluated by the method of molecular mechanics calculations MM2 1985.

A great deal of attention has been devoted to the hydrolytic behaviour of cyclic esters of phosphorus acids. Interest in this reaction has been largely associated with the understanding of the mechanism of enzymatic hydrolysis[1-3] and the pseudorotation process[4,5] of these physiologically active phosphorus esters.[6-10] Unfortunately, there are few reports concerned with quantitative or semiquantitative studies of the hydrolytic reaction of cyclic organophosphorus esters.[11] The electronegativity and HMO investigations provide a good explanation of the observed product ratio of the ring opening and retention in the hydrolysis of 2-methoxy-2-oxo-1,3,2-dioxaphospholane (**1**) and 2-methoxy-2-oxo-1,2-oxaphospholane (**2**), but these methods are unable to rationalize the effects of ring size and endocyclic substituent on the hydrolytic rate constant. The substituent effect on the alkaline hydrolysis of both cyclic and acyclic phosphonyl chlorides has been investigated successfully by us[12-14] using Allinger's 1977 force field, MM2 1985 program. However, the effect of the ring size and endocyclic substituents has not been considered in that treatment. In this paper, molecular mechanics calculations (MM2 1985) are used to investigate the hydrolysis reaction of the following cyclic phosphorus compounds including (**1**), (**2**), 2-ethoxy-2-oxo-1,2-oxaphospholane (**3**), 2-ethoxy-2-oxo-1,2-oxaphosphorinane (**4**), 2-ethoxy-2-oxo-1,2-oxaphosphepane (**5**), diethyl ethylphosphonate (**6**), 1-methoxy-1-oxo-2,2,3-trimethylphosphetane (**7**), and 1-methoxy-1-oxo-2,2,3,4,4-pentamethylphosphetane (**8**).



(1)



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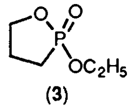

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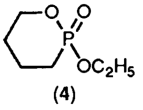

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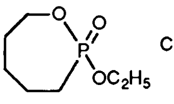
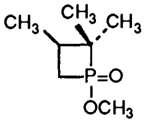


(5)

$C_2H_5P(O)(OC_2H_5)_2$

(6)



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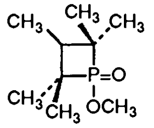


(8)

The calculation results indicate that the ratio of the ring opening and retention products in the hydrolysis of (**1**) and (**2**), and the effect of the ring size and the endocyclic substituents are mainly controlled by the steric energy difference (ΔE or $\Delta\Delta E$) between the substrate and its pentaco-ordinated transition state.

Calculations

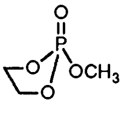
Allinger's 1977 force field and MM2 1985 program[15] were used and all calculations were carried out on a Vax-780 computer at Shanghai Institute of Organic Chemistry, Chinese Academy of Science. Since only van der Waals parameters are used in the program, the other parameters for the tetraco-ordinated and pentaco-ordinated phosphorus compounds were calibrated in our laboratory.[12] For the calculations of pentaco-ordinated phosphorus compounds the MM2 force field was modified by us.[12] In order to evaluate the difference in stability of trigonal bipyramid (TBP) and square pyramid (SP), 1,3- van der Waals (VDW) interactions between the atoms directly bonded to the pentaco-ordinated phosphorus atom were added into the MM2 force field. A similar method has been used to modify the MM1 force field by Holmes.[16] In the present treatment the VDW radius for 1,3-VDW interactions is different and larger than that for 1,4- or longer VDW interactions. This not only gives a reliable energy difference value between TBP and SP, but also the correct bond angles around the pentaco-ordinated phosphorus atom bonding with different atoms. If the initial conformation is assigned as trigonal bipyramidal or square pyramidal, after minimization the structure will basically remain TBP or SP because different natural bond length and bond angle parameters for TBP and SP are assigned in the program. However, the minimization structure may deviate slightly from the standard TBP or SP owing to steric interactions. In the present case only TBP or SP were considered since they are two well studied geometries in crystal structures. Also the leaving group in the alkaline hydrolysis reaction of phosphorus esters is usually considered to be located in the axial position of a trigonal bipyramid.

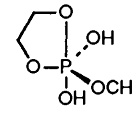
Some parameters for particular groups are so far not available owing to a lack of experimental data. In such cases some approximation was made, for example, the calculation parameters for the bonds P–O⁻ and P–OH₂ were replaced by these for P–OH. The geometry of each compound and transition state was optimized by using the MM2 1985 program, and the most stable conformation was selected for comparison purposes.

However, the general molecular mechanics calculations are only representative of the gas-phase conditions. In order to study the reactions in solution, the solvent effect should be taken into consideration, but this effect is very difficult to evaluate in a simple way. Fortunately, in the present investigation the reactions proceed through the TBP intermediates from the same substrate and in the same solvent and the difference is only

Table 1. Steric energies of various conformations for (1) and its transition state.

Conformation	Steric energies/ kcal mol^{-1}
(**1a**)	15.9
(**1b**)	21.0
(**1c**)	22.3
(**1d**)	22.4
(**1e**)	24.2
(**1f**)	20.3
(**1g**)	20.9


(1a)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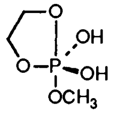
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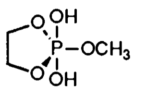
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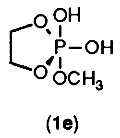
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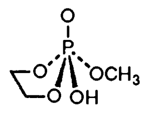
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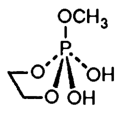
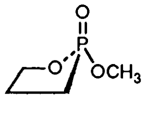
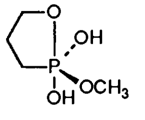

(1g)

Table 2. Steric energies of compound (2) and the conformations of its transition state.

Conformation	Steric energies/ kcal mol^{-1}
(**2a**)	17.9
(**2b**)	21.9
(**2c**)	28.3
(**2d**)	25.7
(**2e**)	28.6
(**2f**)	23.2
(**2g**)	21.9


(2a)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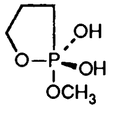
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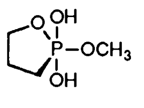
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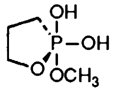
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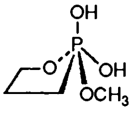
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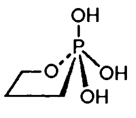
(2g)

in the structure of leaving group located in the axial position. Therefore, when only the relative significance of different pathways is compared, the solvent effect is not so important. Such an approximation has also been applied by previous authors.[17,18]

Results and Discussion

Westheimer and co-workers[6,19] reported that in the acidic hydrolysis of compound (**1**) the ratio of the ring opening and retention products was 100 : 1; whereas in the alkaline hydrolysis of (**2**), the rate of the ring opening was 10^6 times faster than that of the ring retention. They proposed that the difference in the rates was determined by the energy of the transition state. Holmes successfully based an explanation of these experimental data on electronegativities and HMO calculations, for the case when pseudorotation is considered.[9,10,20] The effect of the ring size on the rate constant of hydrolysis of (**3**), (**4**), and (**5**) is described by Aksnes,[21] but it could not be rationalized either in terms of electronegativities or by use of HMO calculations.[11] However, molecular mechanics calculations provide a good explanation for various structural effects.

The Structural Effect of the Ring on the Rate of Ring Opening and Retention.—The acidic or alkaline hydrolytic reaction of compounds (**1**) and (**2**) has been well investigated.[6-10,22] The rate constants of the ring opening and retention are very different. We propose that the hydrolysis rate constant is governed by the difference in steric energy (ΔE) between the substrate and the pentaco-ordinated transition state of the phosphorus esters. The absolute ΔE values derived from the molecules with different co-ordination numbers have no definite significance, but these ΔE values give a reasonable, relative comparison for the same homologous series, when a reference is selected the $\Delta\Delta E$ derived from the ΔE represents the correct relative level. This is a general method of investigation of organic reactions and their transition states *e.g.* the hydrolysis reactions of carboxylates[17] and toluene-*p*-sulphonate.[18] Therefore, the difference in the hydrolysis rate constants of the ring opening and retention for cyclic phosphorus esters may also be determined from the difference in their ΔE, (*i.e.* $\Delta\Delta E$), which can be evaluated by molecular mechanics. The larger the value of $\Delta\Delta E$, the larger the difference in rate constants. The lowest energy conformation of (**1**) is (**1a**) as determined from molecular mechanics program MM2 1985. The possible conformations of the pentaco-ordinated transition state of compound (**1**) are (**1b**), (**1c**), (**1d**), (**1f**), and (**1g**). The steric energies are given in Table 1.

The data in Table 1 indicate that the square pyramids (**1f**) and (**1g**) are more stable than other trigonal bipyramids. Generally, the hydrolysis of phosphorus ester takes place in its trigonal bipyramid conformation in which the leaving group occupies the axial position. When the (**1f**) and (**1g**) convert to the trigonal bipyramid form, by pseudorotation the hydrolysis of (**1**) occurs. The steric energy of the trigonal bipyramid, determines the ring opening rate, equations (1) and (2). The ring retention rate is

$$\Delta E_{ba} = E_{1b} - E_{1a} \qquad (1)$$

$$\Delta E_{ca} = E_{1b} - E_{1a} \qquad (2)$$

determined by ΔE_{ca} and ΔE_{ea} equation (3). The relative rate of

$$\Delta E_{ea} = E_{1e} - E_{1a} \qquad (3)$$

the ring opening and retention is mainly governed by the $\Delta\Delta E$ of $\Delta E_{ca} - \Delta E_{ba}$, *i.e.* $\Delta\Delta E = E_{1c} - E_{1b} = 1.3$ kcal mol^{-1}.* On consideration of the contribution of the conformation of (**1b**), (**1c**), and (**1d**), which are determined by the Boltzmann function $e^{-\Delta\Delta E/RT}$, the ratio of ring opening and retention products is calculated as 97 : 3, which is consistent with the experimental data for the alkaline hydrolysis of compound (**1**).[6]

In the alkaline hydrolysis of compound (**2**) the ring opening rate is 10^6 times faster than the ring retention rate. Similar to compound (**1**), the relative rate of the ring opening and ring retention will be determined by the energy difference between the conformations of the transition states. Based on the molecular mechanics calculations, the most stable conformation of compound (**2**) is (**2a**), the relative conformations of the pentaco-ordinate transition state in the alkaline hydrolysis are (**2b**), (**2c**), (**2d**), (**2e**), (**2f**), and (**2g**). Their steric energies are listed in Table 2.

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* 1 cal = 4.184 J.

Table 3. ΔE and relative data of some cyclic phosphonates.

Compound	Ring size	ΔE/kcal mol^{-1}	$\Delta\Delta E$/kcal mol^{-1}	log k^b	$-\Delta H^{\ddagger}$/kcal mol^{-1a}
(3)	5	3.564	0	5.73	6.92
(4)	6	11.245	7.68	1.42	3.80
(5)	7	13.800	10.330	0.04	2.62
(6)	open chain	13.544	9.98	0.236	2.50

[a] $\Delta H^{\ddagger}$ corresponding to compounds (**9**), (**10**), (**11**), and (**12**) respectively. [b] Measured at 50 °C.

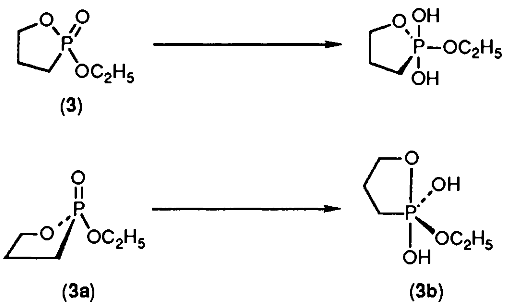
Only conformation (**2b**) is related to the ring-opening process and the conformations (**2c** and **2e**) to the ring-retention process. The energy difference between (**2c**) and (**2b**) ($\Delta\Delta E_{bc}$) is 6.4, and $\Delta\Delta E_{bd}$ is 6.7 kcal mol^{-1}. Therefore, the ratio of the ring opening product to the ring retention product is estimated to be 10^4–10^5 which is consistent with the observed data well.

Effect of Ring Size on the Rate Constant.—Aksnes and coworkers (ref. 21) have reported that in the alkaline hydrolysis of compounds (**3**–**6**) the rate constant decreases with an increase in ring size of the cyclic phosphorus esters. They proposed that the decrease in the rate constant with an increase in ring size is due to the decrease on releasing ring strain energy in the transition states, but no quantitative data are given. In our opinion, the activation enthalpy of alkaline hydrolysis of compounds (**3**), (**4**), and (**5**) is proportional to the difference in the steric energies (ΔE) between the most stable conformations of the tetracoordinated substrate and its pentaco-ordinated transition state.

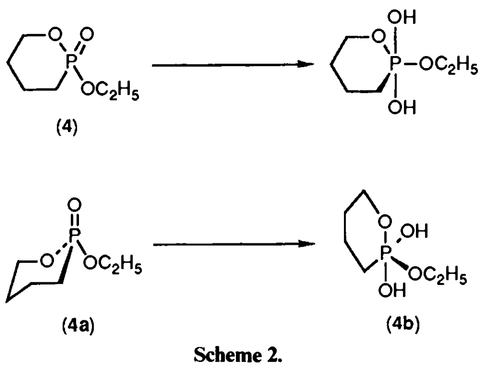
The most stable conformation of compound (**3**) is (**3a**) and the most stable conformation of the ring opening transition state is (**3b**) then $\Delta E_3 = E_{3_b} - E_{3a}$, Scheme 1.

Similarly, for compounds (**4**) and (**5**), Schemes 2 and 3. In comparison with the open chain phosphorus ester, diethyl ethylphosphonate (**6**) is calculated analogously.[14] If compound (**3**) is taken as a reference, then $\Delta\Delta E = \Delta E_n - \Delta E_3$ can be used as a measure of the ring size effect. The ΔE and $\Delta\Delta E$ as well as relative data are shown in Table 3.

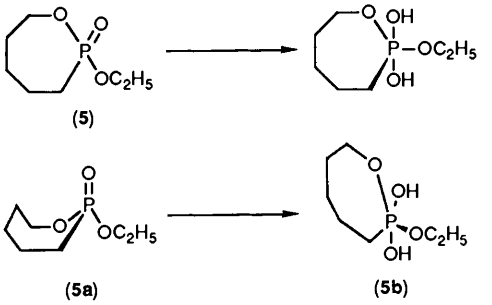
As shown in the Figure, the $\Delta\Delta E$ is linearly correlated with log k. In Table 3, the magnitude of activation enthalpy $(\Delta H^{\ddagger})^{20}$ is very close to that of corresponding phosphonates (**9**)–(**12**), which have the same ring size as compounds (**3**)–(**6**), respectively. During the hydrolysis process, the pentacoordinated transition states of (**9**)–(**12**) are similar to those of (**3**)–(**6**) respectively, as each of the pairs has a similar environment. Therefore, $\Delta H^{\ddagger}$ is also linearly correlated with $\Delta\Delta E$ (see the Figure). It can be concluded that the ring size effect on the hydrolysis rate constant is mainly governed by the steric effect of the ring strain, and this effect can be evaluated, at least semiquantitatively, by molecular mechanics calculations.



Scheme 1.



Scheme 2.



Scheme 3.

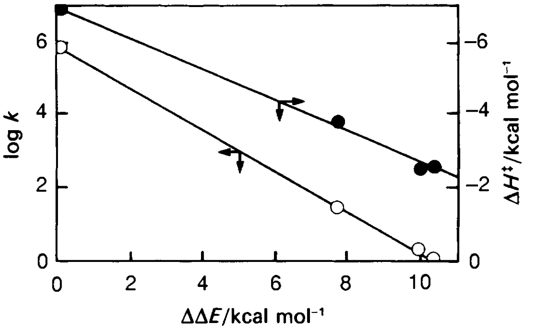
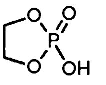
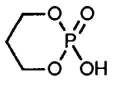


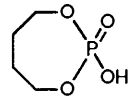
Figure. Relationship between $\Delta\Delta E$ and log$k$ or $\Delta H^{\ddagger}$ for some cyclic phosphorus esters.



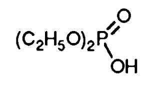
(**9**)



(**10**)



(**11**)



(**12**)

The Effect of an Endocyclic Substituent on the Hydrolytic Rate Constant.—It was found that the hydrolysis rate constant for compound (**8**) was 10^3 lower than that for compound (**7**).[22] The introduction of two methyl groups at the carbon atom adjacent to the phosphorus atom causes remarkable steric hindrance on the hydrolysis process. The change of the steric energy (ΔE_7) for compound (**7**) in the hydrolytic reaction, as estimated by molecular mechanics calculations, is 4.27, while for ΔE_8 is 8.30 kcal mol^{-1}. Therefore, the increase in steric energy caused by two methyl groups in the transition state is 4.03 kcal mol^{-1}. The calculated relative rate of hydrolysis of compounds (**7**) and (**8**) is, therefore, 884:1, which is close to the experimental data reported by Hawes.[23]

(**7**) (**7a**)

(**8**) (**8a**)

Conclusions

The above discussion indicates that molecular mechanics calculations are suitable for the study of the hydrolytic reaction of cyclic phosphorus esters including the structural effect on the ring opening and retention, the ring size as well as *endo*-substituent effect. These structural effects are mainly determined by the steric effect. It is, therefore, reasonable to expect that, molecular mechanics calculations can be used to study the steric effect in organic chemistry in general.

Acknowledgements

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