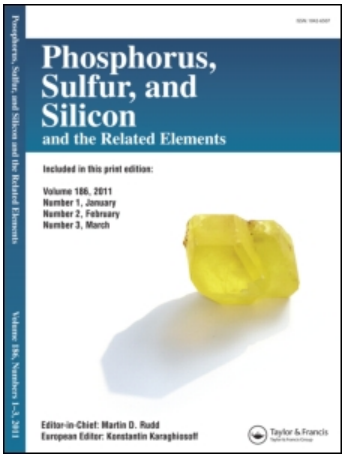

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Ring Strain VS. Solvent Effects in Phosphate Base Hydrolysis

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To determine the factors governing the enhanced reactivity of 5-membered ring phosphates, the lowest activation free-energy profiles for the alkaline hydrolyses of methyl ethylene phosphate (5-MEP), its acyclic analog, trimethyl phosphate (a-TMP), and its 6-membered ring analog, methyl propylene phosphate (6-MPP), have been computed using *ab initio* and continuum dielectric methods. The calculations yield product distributions and activation free energy differences in accord with experiment. They show that solvent stabilization of the 5-membered ring transition state plays a key role in the million-fold enhanced rates of alkaline hydrolysis of 5-MEP relative to its acyclic or 6-membered ring analogs. Furthermore, strain energy calculations show that ring strain contributes partly to the observed rate enhancement of 5-MEP relative to 6-MPP but *not* to that of 5-MEP relative to a-TMP.

Keywords: phosphates; ring strain; solvation; continuum dielectric

INTRODUCTION

Five-membered cyclic phosphate esters hydrolyze in acid or base millions of times faster than their acyclic or 6/7-membered ring analogs[1,2]. This rate acceleration was found to be due mainly to enthalpic rather than entropic effects[3]. Several factors have been suggested to account (in all or partly) for the observed rate enhancement

of 5-membered ring phosphates: These include (i) ring strain in the 5-membered ring ground state[4]; (ii) stereoelectronic effects in the cyclic transition state[5]; (iii) steric crowding in the acyclic transition state[6] and (iv) differential solvation of the cyclic and acyclic transition states[7].

Our aim is to elucidate the driving forces behind the enhanced reactivity of 5-membered ring phospho-esters. To this end, *ab initio* and continuum dielectric methods were used to map out the lowest activation free-energy profiles for the alkaline hydrolyses of 5-MEP, its acyclic analog (a-TMP) and 6-membered ring counterpart (6-MPP)[8,9]. Subsequently, the rate-limiting transition states for each of the three reactions were relocated in solution using two solvation models[9]. Furthermore, strain energies of 5-membered ring species relative to their acyclic and 6-membered ring analogs have been computed to assess the role of ring strain in the observed enhanced rates of ring cleavage[10]. Details of the calculations can be found in ref. 8 to 10.

RESULTS AND DISCUSSION

Reaction Mechanism and Product Distribution

For the 3 reactions studied, the lowest free energy pathway in solution reflects that in the gas phase except that "long-range" ion-dipole intermediates found in the gas phase do not exist in solution (see ref. 9, Figures 1–3). For the alkaline hydrolysis of a-TMP, the lowest free-energy pathway is hydroxide attack at phosphorus, followed by pseudo-rotation and subsequent methoxide elimination with simultaneous intra-molecular proton transfer to yield methanol and dimethyl phosphate (see ref. 9, Scheme 1). In contrast, cyclic 5-MEP and 6-MPP hydrolyze in base via hydroxide attack at phosphorus *concerted* with pseudorotation, followed by ring opening with simultaneous intramolecular proton transfer (see ref. 9, Schemes 2 and 3). The calculations predict product distributions for the base hydrolyses of a-TMP and 5-MEP that are in accord with experiment. However, they do not support previously proposed mechanisms for the two reactions, which result in products with *inversion* of configuration[9] (as opposed to products with *retention* of configuration predicted by the calculations). Further experiments are needed to distinguish between the various proposed mechanisms.

Rate-limiting Transition State

The rate-limiting step for the alkaline hydrolyses of a-TMP, 5-MEP and 6-MPP is not pseudorotation or P–O cleavage but hydroxide attack at the phosphorus atom; i.e., formation of a "long-range" transition state. For all three reactions, there is a significant change in the transition state geometry due to solvent effects, which favor a "late" transition state as the magnitude of the solvation free energy increases with longer $P–O^H$ separation. This trend is expected for other nucleophilic substitution reactions involving a neutral reactant and a small, anionic nucleophile.

The Enhanced Reactivity of 5-MEP relative to a-TMP

Table 1 shows that the activation free energy difference between the alkaline hydrolyses of a-TMP and 5-MEP (8.1 kcal/mol), which agrees with the measured value (7.8±0.6 kcal/mol[3]), stems from greater solvent stabilization of the cyclic transition state relative to its acyclic analog (by 10.7 kcal/mol). The latter is due to dihedral ring constraints yielding a more solvent-exposed hydroxyl group in the cyclic transition state compared to its acyclic counterpart[7].

TABLE 1. Properties of the acyclic (a-TS) and 5-membered cyclic (5-TS) rate-limiting transition states relocated in solution by computing solvation free energies using continuum methods.[a]

Species	$P–O^H$	$\Delta H^{\dagger}_{gas}$	$\Delta G^{\dagger}_{gas}$	ΔG_s(TS)	ΔG_s(GS)	$\Delta G^{\dagger}_{sln}$
a-TS	2.48	−19.5	−8.5	−58.3	−105.0	38.2
5-TS	2.67	−16.8	−7.2	−69.0	−106.2	30.1
a-TS − 5-TS	−0.2	−2.7	−1.3	10.7	1.2	8.1

[a]The zero of energy corresponds to the reactants separated at infinity in the gas-phase. Distance in angstroms and energies in kcal/mol.

The negative $\Delta\Delta H^{\dagger}_{gas}$ (−2.7 kcal/mol, Table 1) and strain energy calculations indicate that ring strain does *not* account for the observed rate acceleration of 5-MEP relative to a-TMP. The strain energies of the 5-membered ring ground state, rate-limiting transition state and pseudorotated intermediate relative to their acyclic counterparts are 6.7, 10.7 and −1.0 kcal/mol, respectively. Thus, the strain energy in 5-MEP is *not* relieved upon forming the rate-limiting transition state, but is relieved instead in the pseudorotated intermediate.

The Enhanced Reactivity of 5-MEP relative to 6-MPP

The activation free energy difference between the alkaline hydrolyses of 6-MPP and 5-MEP (6.6 kcal/mol) is close to the experimental estimate (7.3±0.6 kcal/mol)[3,11]. Table 2 shows that about half of this difference stems from greater solvent stabilization of the 5-membered cyclic transition state relative to its 6-membered ring analog (by 3.5 kcal/mol), while the remaining difference results from more favorable solute-solute interactions in the 5-membered species compared to the respective six-membered ones.

TABLE 2. Properties of the 5-membered (5-TS) and 6-membered (6-TS) ring rate-limiting transition states relocated in solution by computing solvation free energies using the PSGVB[12] program.[a]

Species	P–O[H]	$\Delta H^{\dagger}_{gas}$	$\Delta G^{\dagger}_{gas}$	ΔG_s(TS)	ΔG_s(GS)	$\Delta G^{\dagger}_{sln}$
6-TS	2.43	−16.5	−5.8	−73.9	−110.3	30.6
5-TS	2.54	−19.1	−9.6	−77.4	−111.0	24.0
6-TS − 5-TS	−0.1	2.6	3.8	3.5	0.7	6.6

[a]See footnote to Table 1.

Strain energy calculations suggest that ring strain relief provides part of the contribution to the observed rate difference between 5-MEP and 6-MPP. Relative to the 6-membered ring species, the strain energy in the five-membered ring transition state (1.5 kcal/mol) is less than that in the 5-MEP ground state (4.1 kcal/mol). The decrease in strain energy is not due in as much to the relief of OPO and COP angle strain in 5-MEP upon forming the 5-membered ring transition state but to the poorer ability of the 6-membered cyclic transition state to accommodate strain in the ring angles and dihedrals compared to the 6-MPP ground state. This is supported by the finding that the 6-membered cyclic intermediate has more strain than the corresponding 5-membered ring intermediate (by 2.6 kcal/mol).

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