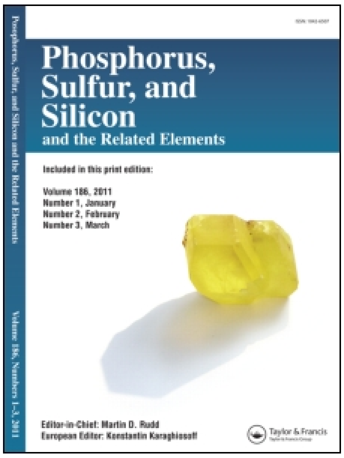

Phosphorus, Sulfur, and Silicon and the Related Elements

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A Comparison of Semi-Empirical and AB Initio Methods on the Hydrolysis of Phosphinates, Phosphonates, and Phosphates

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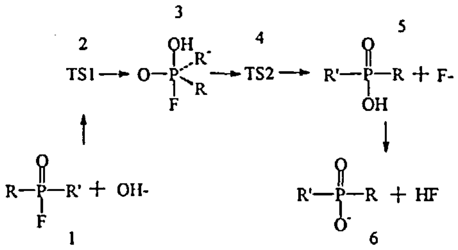
The hydrolysis of phosphorus fluoridates was studied by semiempirical and ab initio methods. The reaction proceeds through a metastable intermediate separated from the reactants and products by transition structures. Both methods gave similar qualitative results; however, the first transition (formation of the trigonal bipyrimid intermediate) occurred earlier and the second (loss of F-) later with semiempirical methods. Including solvation in the calculations is critical. The AMSOL program generated reasonable energies especially when the limitations of the semiempirical Hamiltonian are considered. The Onsanger model was not a significant improvement over calculations on isolated molecules.

Keywords: semiempirical; solvation; hydrolysis; phosphorus; Hartree-Fock

INTRODUCTION

Nucleophilic substitution at phosphorus plays a critical role in several biochemical reactions including the synthesis and degradation of nucleic acids, energy storage and utilization, etc. In addition, enzymes such as acetylcholinesterase can be phosphylated at the active site and thereby lose catalytic activity. In organic chemistry, nucleophilic substitution is the most frequent method for introducing non-carbon substituents. The most common path for nucleic substitution of phosphates under basic conditions involves a pentavalent trigonal bipyrimid intermediate in which the incoming nucleophile and the leaving group are in axial positions.[1] An S_N1 type mechanism, with general base catalysis, is limited principally to compounds having an acidic hydrogen on the substituent adjacent to the phosphorus.[2]

Computational chemistry is ideally suited for studying mechanisms and elucidating reaction pathways because, unlike physical and spectroscopic methods, calculations are not limited to stable structures. Semiempirical methods frequently provide good geometries and relative energies but the Hamiltonian is too truncated for accurate absolute energies. In general, calculations at the Hartree-Fock level of theory with double or triple zeta basis sets produce geometries sufficiently accurate for most applications; however, post HF methods are sometimes needed when the energy differences are small.



R = CH_3, OCH_3
R' = CH_3, OCH_3

Pertubation techniques like Moller-Plesset are currently the most frequently used post HF methods, but are not variational and therefore the lowest energy may not be the most accurate.

In nucleophilic substitution at phosphorus atoms, a negatively charged species reacts with a neutral phosphorus (1) to form and negatively charged intermediate (3) that subsequently dissociates into the product and a negatively charged leaving group (5). The phosphorus compound is able to accommodate the negative charge more effectively than the nucleophile because of the presence of electron buffers like the P=O bond and other electronegative atoms. As a consequence, solvation plays a major role in stabilizing the charge on the nucleophile and the leaving group. This paper examines the substitution of fluoro phosphinates, phosphonates, and phosphates by hydroxide at semiempirical and ab initio levels of theory. Calculations on isolated molecules (i.e., gas phase) and with continuum solvation models provide insight into the importance of including solvation in reactions containing ionic species.

METHODS

Semiempirical calculations were run with the AMPAC 5.0[3] package using the AMSOL[4] SM-2.1 continuum solvation model and the associated AM1 Hamiltonian. Gas phase energies are the AMSOL values without the free energy of solution. An initial guess of the transition structure was identified by extending the length of bond of interest until the maximal energy was obtained. The initial structure was refined into the final transition structure using the TS routine. Force calculations were performed on the stationary points to confirm the presence of a stable compound or transition structure. The AMPAC Graphical User Interface was used to illustrate that the vibration corresponding to the negative frequency was associated with the approach of the nucleophile or departure of the leaving group.

Ab initio calculations were performed using the GAUSSIAN-94[5] series of programs. All structures were fully optimized at the RHF level of theory using the 6-31G(d) basis sets. The minimizations were carried out using the Berny method and the default parameters were used for the integral cut-off and minimization convergence criteria. Frequency calculations were performed to determine the nature of the stationary points. IRC (Intrinsic Reaction Coordinate) calculations were performed to confirm that the transition structures connected the stable structures along the reaction path.

RESULTS

In Table 1, the bond lengths and angles for the forming and breaking bonds are compared. Both semiempirical and ab initio methods give essentially the same values for the phosphinate and phosphonate. The first transition occurs very early with the forming P-OH bond at 2.9Å. The P-F bond lengthens only .02Å from the reactant. The intermediate is almost symmetrical with the P-OH and P-F bonds at 1.7Å and 1.6Å respectively. The second transition occurs very late with the P-F bond almost totally broken at 2.9Å. At the RHF/6-31G(d) level, the first transition occurs later with slightly shorter P-OH bonds and longer P-F bonds. As would be expected, the 2nd transition is earlier with a shorter breaking P-F bond.

The need for solvation is evident in Table 2. In the gas phase, the reactants have the highest energy. The energy of the system drops dramatically as the OH^- approaches reaching a minimum at the intermediate before rising through the 2nd transition to the products. The stabilizing effect of the phosphorus moiety is demonstrated by the difference in the product (5) and the anionic structure (6). With solvation, the transition structures are higher energy than the reactants and products; however, the energy of the intermediate is still below the reactants. If this profile were indicative of the actual reaction in solution, the product would be the trigonal bipyrimid anion. The results with solvation give insight into the relative reactivities of phosphinates, phosphonates, and phosphates. The energies (relative to the reactants) of the two transition structures for the 3 phosphorus compounds are approximately the same. In the intermediates, the phosphate is much more stable than the phosphonate and the phosphinate is least stable. The alkoxy groups stabilize the charge much more effectively in the intermediate than in the transition structures thereby increasing the energy of activation for the 2nd transition structure.

TABLE 1. COMPARISON OF SELECTED PARAMETERS FOR REACTANTS, PRODUCTS, TRANSITION STRUCTURES, AND INTERMEDIATES.

		SM2.1-AM1		RHF/6-31G(d)	
STRUCTURE	PARAMETER	CPC	CPOC	CPC	CPOC
REACTANT	P-F	1.54	1.53	1.572	1.563
TS1	P-F	1.55	1.54	1.617	1.598
TS1	P-OH	2.90	2.95	2.851	2.837
TS1	F-P-OH	172.3	162.9	158.7	164.4
INT	P-F	1.60	1.58	1.743	1.735
INT	P-OH	1.81	1.71	1.770	1.717
INT	F-P-OH	176.1	165.7	167.2	164.4
TS2	P-F	2.91	2.90	2.614	2.569
TS2	P-OH	1.64	1.63	1.669	1.647
TS2	F-P-OH	167.0	169.0	159.1	162.3
PRODUCT	P-OH	1.62	1.60	1.608	1.603

CPC refers to dimethylphosphinofluoridate. CPOC refers to methyl methylphosphonofluoridate. Bond lengths are in angstroms; bond angles in degrees.

Table 2. RELATIVE ENERGIES FROM SEMIEMPIRICAL CALCULATIONS

CALC	REACT	TS1	INT	TS2	PROD	ANIONIC
1S	0	25	5	42	18	-20
2S	0	26	-12	44	18	-26
3S	0	30	-25	52	25	-30
1G	0	-17	-43	-1	21	-64
2G	0	-18	-77	-8	21	-77

Relative Energies are in Kcal/mole relative to the reactants.

Calculation 1S, 2S, 3S refer to the solution phase dimethylphosphinyl fluoride, methyl methylphosphonofluoridate, and dimethyl phosphorofluoridate respectively. The G designation refers to isolated or gas phase calculations.

The results at the RHF/6-31G(d) level (Table 3) are similar to the semiempirical calculations. In the gas phase, the energy drops immediately as the hydroxide approaches the phosphorous fluoridate with only a small hump at the transition structures. The improvement in the calculations by addition of the Onsanger continuum solvation model was minimal.

TABLE 3. RELATIVE ENERGIES FROM RHF CALCULATIONS

CALC	REACT	TS1	INT	TS2	PROD
1G	60.96	23.80	0.00	15.65	50.99
1S	58.47		0.00		51.05
2G	62.27	24.40	0.00	16.15	52.16
3G	64.88	25.52	0.00	17.71	54.71

Relative energies are in Kcal/mole relative to the intermediate.

CONCLUSIONS

The major conclusion is the need for improved solvation models and techniques — particularly for reactions in which charges are developed or lost. In the nucleophilic substitution of the phosphinate with neutral water, no ionic species is generated. At the RHF/6-31G(d) level the energies (relative to the reactants at infinite separation) of TS1, the two metastable intermediates, and TS2 are 32.7, 9.44, 4.61, 21.32 Kcal/mole respectively.[6] The simple continuum models are an improvement over gas phase calculations but cannot provide sufficient charge neutralization to generate accurate energy profiles. Current work with the SCI-PCM method is showing considerable progress.[7]

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