(12) O. L. Chapman, K. Mattes, C. L. McIntosh, and J. Pacansky, *J. Am. Chem. Soc.*, **95**, 6134 (1973).
(13) The non-appearance of an intermediate at 4.2 K could conceivably be caused by a local thermal process utilizing the energy released in the first step, but we expect aromatic lattices to have very high thermal conductivity at 4.2 K. The same situation might not prevail in diatomic or atomic lattices in which local heating might become important.

Robin M. Hochstrasser,* David S. King
Laboratory for Research on the Structure of Matter
and Department of Chemistry
University of Pennsylvania
Philadelphia, Pennsylvania 19174
Received April 22, 1975

Theoretical Calculations of the Hydrolysis Energies of Some "High Energy" Molecules. I. The Phosphoric and Carboxylic Acid Anhydrides

Sir:

In view of a recent proposal by Boyer et al.[1] that much of the free energy change associated with the formation of certain biologically important P-O-P bonds (e.g., that of ATP) occurs when the product is released from the enzyme into the aqueous environment rather than during actual bond formation, we felt it would be timely to reexamine the nature of these and other "high energy" molecules. We have carried out ab initio molecular orbital calculations using a STO-3G basis set[2] on phosphoric acid (H_3PO_4), pyrophosphoric acid ($H_2PO_3OPO_3H_2$), methyl dihydrogen phosphate ($CH_3OPO_3H_2$), acetic anhydride [$(CH_3CO)_2O$], and their hydrolysis products as an approach to the description of the electronic structure of molecules with high group-transfer potential.

Complete geometrical optimization of these molecules would have been prohibitive, so we carried out a limited search,[3] optimizing the geometries at a comparable level for all the compounds involved. First, we examined the energy of H_3PO_4 as a function of the O=P—O—H dihedral angles, $\phi_1 = \phi_2 = \phi_3$, with $R(\mathrm{P{=}O}) = 1.5$ Å, $R(\mathrm{P{-}O}) = 1.7$ Å, and $R(\mathrm{O{-}H}) = 0.99$ Å. Since $\phi = 0$ was the lowest energy, we optimized $R(\mathrm{P{=}O})$ and $R(\mathrm{P{-}O})$ at this angle, and then varied the ϕ's once again, but this time independently, on a 60° grid. The energy minimum is at $\phi_1 = 180$, $\phi_2 = 0$, and $\phi_3 = 0$. Then we carried out calculations on $CH_3OPO_3H_2$ and $H_2O_3POPO_3H_2$ reoptimizing[4] only the P-O and C-O bond distances and bond angles of the P-O-P and C-O-P linkages. Using the optimal geometries of Lathan et al.[5] we calculated the energies for both CH_3OH and H_2O. This enabled us to calculate ΔE values for the prototypal "high" and "low energy" hydrolysis reactions (eq 1 and 2) (see Table I).

$$H_2O_3POPO_3H_2 + H_2O \rightarrow 2H_3PO_4 \tag{1}$$

$$CH_3OPO_3H_2 + H_2O \rightarrow CH_3OH + H_3PO_4 \tag{2}$$

The energies (ΔE) for the hydrolysis of the "high energy" P-O-P bond in reaction 1 and "low energy" C-O-P bond in reaction 2 are calculated to be −2.71 and −0.94 kcal/mol, respectively.

Since the predominant phosphate species in aqueous solution at neutral pH are charged, we also carried out calculations on $^-HO_3POPO_3H^-$, $CH_3OPO_3H^-$, and $H_2PO_4^-$ to study the energetics of reactions 3 and 4.

$$^-HO_3POPO_3H^- + H_2O \rightarrow 2H_2PO_4^- \tag{3}$$

$$CH_3OPO_3H^- + H_2O \rightarrow CH_3OH + H_2PO_4^- \tag{4}$$

Using the minimum energy dihedral angles determined by Newton[6] for the dimethyl phosphate anion, we optimized both the P-OH and P—O⁻ bond lengths in $H_2PO_4^-$ and used these geometrical parameters in $CH_3OPO_3H^-$ and $^-HO_3POPO_3H^-$. We reoptimized only R(P-O) of the POP and POC linkages and R(C-O) for the POC linkage (see Table I). The energies for reactions 3 and 4 are calculated to be −75.3 and +0.7 kcal/mol, respectively.[7] To determine the role of electrostatics in these reactions, we also calculated the energy of hydrolysis of $^-HO_3POPO_3H_2$ (reaction 5),[8] and found it to be +10.2 kcal/mol.

$$^-HO_3POPO_3H_2 + H_2O \rightarrow H_3PO_4 + H_2PO_4^- \tag{5}$$

To test the reliability of these results for a "high energy" bond whose gas phase thermodynamics are known, we calculated the energy of the molecules involved in reaction 6. Using Hess's law and experimental heats of formation,[9] the enthalpy of reaction 6 is found to be −11.6 kcal/mol. Using our calculated total energies for acetic anhydride, acetic acid,[10] and water, the ΔE of reaction 6 is predicted to be −17.2 kcal/mol. Although this agreement is only fair, it is clear that our calculations show a qualitative difference between the acetic anhydride "high energy" bond and those of the neutral and singly charged phosphates. Similarly, the calculations on the pyrophosphate dianion indicate that, in the gas phase, hydrolysis of this molecule is even more exothermic than the carboxylic acid anhydrides.

$$CH_3\overset{\overset{\large O}{\|}}{C}O\overset{\overset{\large O}{\|}}{C}CH_3 + H_2O \rightarrow 2CH_3COOH \tag{6}$$

Table I. Summary of Geometry and Energy Results[a]

Molecule	R(P—OH)	R(P=O)	ϕ	R (C—O)	R (O—H)	θ(POP), deg	R(P—OR)[d]	θ(POC), deg	E_T
H_2O					0.99				−74.96590
CH_3OH				1.433	0.99				−113.54919
H_3PO_4	1.657 (1.57)[b]	1.575 (1.52)[b]	0, 0, 180		0.99				−633.896804
	1.657	1.575	0, 0, 0		0.99				−633.894514
$CH_3OPO_3H_2$	1.657	1.575	0, 0, 0	1.445	0.99		1.655	109.5[f]	−672.472448
	1.657	1.575	0, 0, 180	1.445	0.99		1.655	115.6	−672.478593
$H_2O_3POPO_3H_2$	1.657	1.575	(0, 0, 0; 0, 0, 180)[c]		0.99	117.0	1.685		−1192.823393
$H_2PO_4^-$	1.714	1.607	*e*		0.99				−633.14333
$CH_3OPO_3H^-$	1.714	1.607	*e*	1.440	0.99		1.740	109.5	−671.727694
$^-HO_3POPO_3H^-$	1.714	1.607	*e*		0.99	109.5	1.730		−1191.200828

[a] Distances in angstroms, and energies in hartrees. [b] Experimental values in parentheses; see ref 17. [c] One phosphate group had 0, 0, 0 dihedral angle; the other 0, 0, 180. The conformation with all $\phi = 0$ brought the two P=O bonds too close together. [d] P—O bond length for POP or POC linkage. [e] We used RO—P—O—R' dihedral angles of 60° which are near the calculated optimum angles reported in ref 6 for dimethyl hydrogen phosphate anion. [f] This angle was assumed tetrahedral for only the ϕ = 0, 0, 0 conformation, and optimized for ϕ = 0, 0, 180.

In their recent study of the nature of high energy bonds, George et al.[11] concluded that solvation effects contributed very importantly, perhaps more than intramolecular effects, to the large negative enthalpy (and free energy)[12] of hydrolysis of "high energy" P-O-P bonds. The similarity in our calculated ΔE for reactions 1 and 2 would imply that the known high-energy nature of the former reaction is not entirely due to intramolecular electronic effects. Unfortunately, our minimal basis set calculations are probably not sufficiently accurate to allow one to place great confidence in differences of just a few kilocalories per mole.[13]

A comparison of the calculated hydrolysis energy of $^-HO_3POPO_3H^-$ with $H_2O_3POPO_3H_2$ indicates that, in the gas phase, electrostatic repulsions are important in determining the "high energy" nature of the former molecule. However, the similarity of the experimental enthalpies of hydrolysis of $H_2O_3POPO_3H_2$ and $^-HO_3POPO_3H^-$ in aqueous solution (−7.6 and −6.8 kcal/mol)[11] would imply that these electrostatic effects are diminished either by association with counterions or by the large dielectric constant of water. Our calculated gas phase energy of hydrolysis of $^-HO_3POPO_3H^-$ indicates that its solvation energy should be 209 rather than 134 kcal/mol as estimated by George et al.[14]

In contrast to the probable important contribution of solvation to high energy phosphate bonds, the "high energy" nature of carboxylic acid anhydrides is more clearly a result of intramolecular effects (described by George et al. as "opposing resonance" [15]). The precise role of solvation in other biologically important molecules with high group-transfer potentials and a further characterization of their electronic structure will be subjects of further studies. In addition, we hope that examination of reactions 1-6 with more extended basis sets[16] will yield a more precise measure of their hydrolysis energies.

Acknowledgments. Financial support from USPHS Grant AM 17323 (G.L.K.) and GM-20654 (P.A.K.) is gratefully acknowledged. P.A.K. and G.L.K. are grateful to the USPHS for Career Development Awards GM-70718 (P.A.K.) and AM-00014 (G.L.K.).

References and Notes

(1) P. D. Boyer, R. L. Cross, and W. Momsen, *Proc. Nat. Acad. Sci. U.S.A.* **70,** 2837 (1973).

(2) W. J. Hehre, R. F. Stewart, and J. A. Pople, *J. Chem. Phys.*, **51**, 2657 (1969).

(3) We used the O–H bond length found to be the optimum in STO-3G calculations on H_2O (ref 5) and tetrahedral bond angles around the phosphorus. Based on known phosphate structures, (see *Chem. Soc. Spec. Publ.*, "Tables of Interatomic Distances", 1958 and 1965) these are reasonable approximations.

(4) In the case of $H_2O_3POPO_3H_2$, we considered three dihedral angle combinations. The first with all six dihedral angles (ϕ) = 0, leads to a very short P=O···O=P contact, R(O···O) = 1.9 Å, and consequent high energy; the second with all ϕ(H—O—P=O) = 0° and ϕ(P—O—P=O) = 180°, yielding a C_{2v} structure, was relatively unfavorable with a calculated energy 8.2 kcal/mol above the third structure of C_s symmetry, this structure retained all ϕ(H—O—P=O) = 0° but had one ϕ(P—O—P—=O) angle equal to 0° and the other equal to 180°. The C_{2v} structure was probably relatively high in energy because of the unfavorable alignment of the phosphate dipoles, but studies to elucidate the conformational properties of $H_4P_2O_7$ are continuing.

(5) W. Lathan, L. Curtiss, W. Hehre, J. Lisle, and J. A. Pople, *Prog. Phys. Org. Chem.*, **11,** 175 (1974).

(6) M. D. Newton, *J. Am. Chem. Soc.*, **95,** 256 (1973).

(7) Since anions are poorly represented by single determinant wave functions, one has less confidence in the quantitative accuracy of these energies. However, a recent study by Radom (*Chem. Commun.*, 403 (1974); and L. Radom in "Modern Theoretical Chemistry II. Electronic Structure: *Ab Initio* Methods", H. F. Schaefer, Ed., Plenum Press, New York, N.Y., 1975) shows that isodesmic reacts may be reasonably represented for certain anions.

(8) The geometrical parameters for $^-HO_3POPO_3H_2$ were chosen as follows: (1) for the negative end of the molecule optimum values for $H_2PO_4^-$ were used; (2) for the neutral end, the optimum values for H_3PO_4 were used; (3) for the POP linkage, one P–O bond length was taken from $H_4P_2O_7$ and the other from $H_2P_2O_7^{2-}$. The POP angle was taken from $H_4P_2O_7$.

(9) J. D. Cox and G. Pilcher, "Thermochemistry of Organic and Organo-Metalic Compounds", Academic Press, London and New York, 1970.

(10) We used the acetic acid geometry deduced from microwave spectra (W. J. Tabor, *J. Chem. Phys.*, **27,** 974 (1957) except for R(O–H) = 0.99 Å to be consistent with the water O–H bond. We then optimized the C–OH bond lengths in acetic acid and C–O–C bond length and COC angle in acetic anhydride.

(11) P. George, R. J. Witonsky, M. Trachtman, C. Wu, W. Donvart, L. Richman, F. Shurayh, and B. Lentz, *Biochim. Biophys. Acta*, **223,** 1 (1970).

(12) Reference 11 has found that *both* the solution phase free energy and enthalpy of hydrolysis are more negative for the P–O–P compounds than P–O–C by about 4 kcal/mol.

(13) W. J. Hehre, R. Ditchfield, L. Radom, and J. A. Pople, *J. Am. Chem. Soc.*, **92,** 4796 (1970). These authors have studied a series of bond separation reactions involving molecules containing only C, N, O, F, and H and have found that although most chemical trends are correctly reproduced, the mean error in the energies relative to known experimental values at the STO-3G level is 5.8 kcal/mol. We know of no comparable study involving second-row atoms.

(14) It should be pointed out that George et al. emphasized that their entries in Table V were lower bounds for the solvation energy and our calculations show this is most clearly the case when the products have more charge separation than the reactants. Even though a minimal basis set will exaggerate the exothermicity of this reaction, we feel its magnitude is correctly represented.

(15) "Opposing resonance" means the products have a larger number of contributing resonance structures than the reactants.

(16) All of the reactions studied here are examples of isodesmic reactions which should be well-treated at the single determinant level.

(17) *Chem. Soc., Spec. Publ.*, "Tables of Interatomic Distances", 1958 and 1965.

David M. Hayes, George L. Kenyon, Peter A. Kollman*
Department of Pharmaceutical Chemistry
School of Pharmacy, University of California
San Francisco, California 94143
Received March 27, 1975

9-Isocyanopupukeanane, a Marine Invertebrate Allomone with a New Sesquiterpene Skeleton[1]

Sir:

An observation by Johannes,[2] that the nudibranch *Phyllidia varicosa* Lamarck, 1801 secretes a strong and unusually smelling, heat-stable, volatile substance, lethal to fish and crustaceans, has led us to the isolation of this metabolite from *P. varicosa* and also from its prey, a sponge, *Hymeniacidon* sp. This secretion, which protects the delicate, shell-less, brightly colored opisthobranch mollusk from its predators, and which at the same time is the allomone of the browser-prey relationship, has the structure of a tricyclic sesquiterpene isocyanide with a new, rearranged isoprenoid skeleton (**1**).

Locating and netting the relatively rare *P. varicosa* by SCUBA and maintaining the mollusks in aquaria proved to be difficult. By gently squeezing and rinsing 20 animals with sea water we gradually accumulated sufficient mucus for purification by vacuum distillation of the wet salty secretion, followed by extraction of the distillate with methylene chloride, TLC on alumina (methylene chloride-hexane, 15:85, R_f 0.6), thus yielding 20 mg of a mobile oil with the typical odor of the animal and lethal to fish. We characterized this metabolite as an isocyanide (ν_{max} 2120 cm^{-1}; thermal isomerization to nitrile, ν_{max} 2250 cm^{-1}; acid hydrolysis to formamide, ν_{max} 1685 cm^{-1}) possessing a sesquiterpenoid ($C_{16}H_{25}N$; highest m/e 205, prominent losses of Me_2CH, Me; isopropyl doublet of doublets and tertiary methyls in NMR) skeleton, which clearly differed from a sponge-derived bicyclic isocyanosesquiterpene which we were studying.[3]

Luckily one of us (B.J.B.), while diving off Pupukea on the north shore of Oahu, observed *P. varicosa* feeding on an