

the total energy to drop *below* that for the calculated equilibrium zwitterionic structure. Shorter NH distances (from 1.12 to 1.21 Å) were then considered, with  $\theta$ ,  $r$ , and  $\alpha$  being optimized for each point. This procedure yielded a very small barrier ( $\sim 0.5$  kcal/mol) at an NH distance of 1.18 Å ( $H\cdots O = 1.41$  Å). The calculations thus indicate that the gas-phase zwitterion most likely corresponds at best to a very shallow potential energy minimum with respect to proton transfer, and its expected lifetime would be of the order of a vibrational time scale ( $10^{-14}$ – $10^{-13}$  s) at most.<sup>24</sup> In view of the shallowness of the barrier it is not even clear that a vibrational state would be contained within the local minimum which defines the zwitterion.

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## References and Notes

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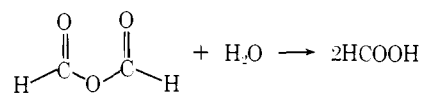
## Theoretical Calculations of the Hydrolysis Energies of Some "High-Energy" Molecules. 2. A Survey of Some Biologically Important Hydrolytic Reactions

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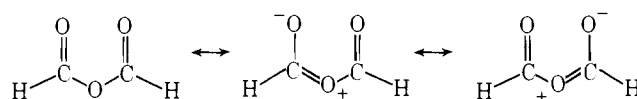
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**Abstract:** We present ab initio calculations on most of the major classes of hydrolytic reactions of high-energy molecules of importance in biological processes. Although intramolecular (opposing resonance and electrostatic) effects play an important role in determining the energy of hydrolysis in some of these reactions, it is concluded that in those hydrolyses of most importance in energy storage and transduction ( $ATP \rightarrow ADP + \text{orthophosphate}$  and  $\text{phosphocreatine} + ADP \rightarrow \text{creatine} + ATP$ ), relative solvation energies of reactants and products are by far the most important factors in determining these energies. We applied simple reaction field equations to estimate solvation energies. By doing so, we are able to reproduce the fact that phosphoguanidinium and pyrophosphate ions have similar free energies of hydrolysis in  $H_2O$ , despite the huge calculated difference between the corresponding energies of hydrolysis in the gas phase.

Biologically important compounds with large negative free energies of hydrolysis at physiological pH have been described as "high-energy" compounds. Because of their importance in processes fundamental to the maintenance of life, these compounds have received much attention from both experimentalists and theoreticians. One of the first to consider these reactions from a theoretical viewpoint was Kalckar,<sup>2</sup> who suggested that "opposing resonance" played an important role in the large negative free energy of hydrolysis of high-energy compounds. For example, in the hydrolytic reaction



there are three important resonance structures for the anhydride reactant,



**Table I.** Geometries and Total Energies of Molecules Studied (For each molecule there is a corresponding figure which shows the particular bond eclipses the C-D bond;  $\phi = 180^\circ$  means atoms A and D are trans.)

Molecule	Bond lengths, Å										
	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	R <sub>4</sub>	R <sub>5</sub>	R <sub>6</sub>	R <sub>7</sub>	R <sub>8</sub>	R <sub>9</sub>	R <sub>10</sub>	R <sub>11</sub>
H <sub>3</sub> PO <sub>4</sub> (1) <sup>a</sup>	1.575	1.657	0.99								
H <sub>2</sub> PO <sub>4</sub> <sup>-</sup> (2) <sup>b</sup>	1.714	1.607	0.99								
HPO <sub>4</sub> <sup>2-</sup> (3) <sup>c</sup>	1.771	1.618	0.99								
H <sub>4</sub> P <sub>2</sub> O <sub>7</sub> (4) <sup>d</sup>	1.575	1.657	0.99	1.685							
H <sub>3</sub> P <sub>2</sub> O <sub>7</sub> <sup>-</sup> (5) <sup>e</sup>	1.575	1.657	0.99	1.685	1.730	1.607	1.714	0.99			
H <sub>2</sub> P <sub>2</sub> O <sub>7</sub> <sup>2-</sup> (6) <sup>f</sup>	1.714	1.730	0.99	1.607							
H <sub>2</sub> O (7) <sup>g</sup>	0.99										
CH <sub>3</sub> OH (8) <sup>h</sup>	0.991	1.095	1.092	1.433							
CH <sub>3</sub> OPO <sub>3</sub> H <sub>2</sub> (9) <sup>i</sup>	1.575	1.657	0.99	1.655	1.445	1.09					
CH <sub>3</sub> OPO <sub>3</sub> H <sup>-</sup> (10) <sup>j</sup>	1.714	1.740	1.607	0.99	1.44	1.09					
HCOOH (11) <sup>k</sup>	1.104	1.214	1.386	0.991							
NH <sub>3</sub> (12) <sup>l</sup>	1.033										
HCONH <sub>2</sub> (13) <sup>m</sup>	1.105	1.218	1.403	1.013	1.014						
CH <sub>3</sub> COOH (14) <sup>n</sup>	1.380	1.245	1.497	1.09	0.99						
CH <sub>3</sub> (CO)O(CO)CH <sub>3</sub> (15) <sup>o</sup>	1.09	1.497	1.245	1.414							
CH <sub>2</sub> =C(OH)COOH (16) <sup>p</sup>	1.09	1.33	1.36	0.99	1.46	1.22	1.36	0.99			
Pyruvic acid (enol)											
CH <sub>2</sub> =C(OH)COO <sup>-</sup> (17) <sup>q</sup>	1.09	1.33	1.36	0.99	1.46	1.26					
Pyruvate anion (enol)											
CH <sub>3</sub> COCOOH (18) <sup>r</sup>	1.09	1.52	1.22	1.46	1.22	1.36	0.99				
Pyruvic acid (keto)											
CH <sub>3</sub> COCOO <sup>-</sup> (19) <sup>s</sup>	1.09	1.52	1.22	1.46	1.26						
Pyruvate anion (keto)											
CH <sub>3</sub> COOCH <sub>3</sub> (20) <sup>t</sup>	1.09	1.497	1.245	1.38	1.43	1.09					
CH <sub>3</sub> COSCH <sub>3</sub> (21) <sup>u</sup>	1.09	1.497	1.245	1.78	1.82	1.09					
CH <sub>3</sub> SH (22) <sup>v</sup>	1.09	1.82	1.33								
CH <sub>3</sub> COOPO <sub>3</sub> H <sub>2</sub> (23) <sup>w</sup>	1.09	1.497	1.245	1.386	1.675	1.575	1.657	0.99			
Acetyl phosphoric acid											
CH <sub>3</sub> COOPO <sub>3</sub> H <sup>-</sup> (24) <sup>x</sup>	1.09	1.497	1.245	1.386	1.714	1.607	1.714	0.99			
CH <sub>3</sub> COOPO <sub>3</sub> <sup>2-</sup> (25) <sup>y</sup>	1.09	1.497	1.245	1.386	1.771	1.618					
CH <sub>2</sub> =C(OPO <sub>3</sub> H <sub>2</sub> )(COOH) (26) <sup>z</sup>	1.09	1.33	1.46	1.36	1.22	0.99	1.43	1.657	1.575	1.657	0.99
Phosphoenolpyruvic acid											
CH <sub>2</sub> =C(OPO <sub>3</sub> H <sub>2</sub> )(COO) <sup>-</sup> (27) <sup>aa</sup>	1.09	1.33	1.46	1.26	1.26		1.43	1.657	1.575	1.657	0.99
CH <sub>2</sub> =C(OPO <sub>3</sub> H <sup>-</sup> )(COOH) (28) <sup>bb</sup>	1.09	1.33	1.43	1.714	1.607	1.714	0.99	1.46	1.22	1.36	0.99
CH <sub>2</sub> =C(OPO <sub>3</sub> H)(COO) <sup>2-</sup> (29) <sup>cc</sup>	1.09	1.23	1.43	1.714	1.607	1.714	0.99	1.46	1.26	1.26	
CH <sub>2</sub> =C(OPO <sub>3</sub> )(COOH) <sup>2-</sup> (30) <sup>dd</sup>	1.09	1.33	1.43	1.771	1.618	1.46	1.22	1.36	0.99		
CH <sub>2</sub> =C(OPO <sub>3</sub> )(COO) <sup>3-</sup> (31) <sup>ee</sup>	1.09	1.33	1.43	1.771	1.618	1.46	1.26	1.26			
Guanidinium cation (32) <sup>ff</sup>	1.37	1.037									
Phosphoguanidinium cation (33) <sup>gg</sup>	1.37	1.037	1.37	1.734	1.575	1.657	0.99				
Phosphoguanidinium zwitterion (34) <sup>hh</sup>	1.37	1.037	1.37	1.734	1.607	1.714	0.99				
Phosphoguanidinium anion (35) <sup>ff</sup>	1.37	1.037	1.37	1.734	1.037	1.618					
Metaphosphate PO <sub>3</sub> <sup>-</sup> (36) <sup>jj</sup>	1.543										

<sup>a</sup> Pseudo-*D*<sub>3</sub> symmetry about P=O assumed; two O-H bonds are cis and one is trans to the P=O bond;  $\phi_1 = \phi_2 = \phi(\text{O}=\text{POH}) = 0^\circ$ ;  $\phi_3(\text{O}=\text{POH}) = 180^\circ$ . The optimization of the dihedral angles is discussed in ref 7. <sup>b</sup> A *C*<sub>2</sub> axis of symmetry bisects  $\phi_1$  and  $\phi_2$ .  $\phi_1(\text{HOPOH}) = \phi_2(\text{HOPOH}) = 60^\circ$ . The optimization of the dihedral angles is discussed in ref 7. <sup>c</sup> Assume pseudo-*C*<sub>3</sub> symmetry around the P-OH bond.  $\phi(\text{OPOH}) = 0^\circ$  gives an energy minimum. <sup>d</sup> Pseudo-*C*<sub>3</sub> symmetry around each P=O is assumed. We considered three dihedral angle combinations. The first with all six dihedral angles  $\phi = 0^\circ$  leads to a very short P=O...O=P contact.  $R(\text{O}...O) = 1.9 \text{ \AA}$ , and consequent high energy; the second with all  $\phi(\text{HOP}=\text{O}) = 0^\circ$  and  $\phi(\text{POP}=\text{O}) = 180^\circ$ , yielding a *C*<sub>2v</sub> structure, was relatively unfavorable with a calculated energy 8.2 kcal/mol above the third structure symmetry. This structure retained all  $\phi(\text{HOP}=\text{O}) = 0^\circ$  but had one  $\phi(\text{POP}=\text{O})$  angle equal to  $0^\circ$  and the other equal to  $180^\circ$ . The *C*<sub>2v</sub> structure was probably relatively high in energy because of the unfavorable alignment of the phosphate dipoles. <sup>e</sup> A pseudo-*C*<sub>3</sub> axis around P=O and a *C*<sub>2</sub> axis bisecting  $\theta_4$  and  $\theta_5$  are assumed. The geometrical parameters for HO<sub>3</sub>POPO<sub>3</sub>H<sub>2</sub> were chosen as follows: (1) for the negative end of the molecule optimum values for H<sub>2</sub>PO<sub>4</sub><sup>-</sup> were used; (2) for the neutral end, the optimum values for H<sub>3</sub>PO<sub>4</sub> were used; (3) for the POP linkage, one P=O bond length was taken from H<sub>4</sub>P<sub>2</sub>O<sub>7</sub> and the other from H<sub>2</sub>P<sub>2</sub>O<sub>7</sub><sup>2-</sup>. The POP angle was taken from H<sub>4</sub>P<sub>2</sub>O<sub>7</sub>.  $\phi_1(\text{HOP}=\text{O})$ ,  $\phi_2(\text{O}=\text{POP}) = 180^\circ$ ;  $\phi_3(\text{OPOH}) = 60^\circ$ ;  $\phi_4(\text{HOPOP}) = 60^\circ$ . <sup>f</sup> See ref 7 regarding the optimization of this geometry.  $\phi_1(\text{OPOH}) = \phi_2(\text{HOPOP}) = \phi_3(\text{HOPOP}) = \phi_4(\text{OPOH}) = 60^\circ$ . <sup>g</sup> Optimized at the STO-3G level in ref 12. <sup>h</sup> The staggered conformation with *C*<sub>s</sub> symmetry is assumed. We use the STO-3G optimized geometry in ref 12. <sup>i</sup> The C-O bond is a pseudo-*C*<sub>3</sub> symmetry axis. The methyl C-H bonds are staggered with respect to the P-O bond.  $\phi_1(\text{HOP}=\text{O})$ ,  $\phi_2(\text{O}=\text{POC}) = 180^\circ$ . <sup>j</sup> The C-O bond is a pseudo-*C*<sub>3</sub> symmetry axis. The methyl hydrogens are staggered with respect to the P-O bond.  $\phi_1(\text{OPOH}) = 60^\circ$ ,  $\phi_2(\text{OPOCH}_3) = 60^\circ$ . <sup>k</sup> The geometry was optimized at the STO-3G level by Del Bene et al., see ref 13. The molecule is planar. <sup>l</sup> *C*<sub>3v</sub> symmetry assumed. Geometry optimized in ref 12. <sup>m</sup> Geometry optimized for planar formamide at the STO-3G level in ref 13. <sup>n</sup> The C=O bond eclipses one of the methyl C-H bonds. <sup>o</sup> *C*<sub>s</sub> symmetry;  $\phi_1(\text{O}=\text{COC}) = 0^\circ$ ;  $\phi_2(\text{COC}=\text{O}) = 180^\circ$ . <sup>p</sup> Planar; conformation is that shown in the figure; standard bond lengths and angles have been used. <sup>q</sup> See footnote p. <sup>r</sup> *C*<sub>s</sub> symmetry; conformation is that shown in the figure; standard bond lengths and angles have been used.

conformation used in the calculations. Explicit reference to dihedral angles will use the following convention:  $\phi(\text{ABCD}) = 0^\circ$  means the A-B

Bond angles, deg											<i>E</i>	<i>E</i>	<i>E</i>
$\theta_1$	$\theta_2$	$\theta_3$	$\theta_4$	$\theta_5$	$\theta_6$	$\theta_7$	$\theta_8$	$\theta_9$	$\theta_{10}$	$\theta_{11}$	STO-3G, hartrees	STO-3G*, hartrees	4-31G, hartrees
116.6	109.5										-633.91344	-634.28187	-641.05663
95.9	130.6										-633.16552	-633.55779	-640.51828
109.5	109.5										-632.12526		
116.6	117.0	109.5									-1192.85405	-1193.58726	-1206.18899
116.6	109.5	117	95.9	130.6	109.5						-1192.11157	-1192.87265	-1205.64121
109.5	95.9	130.6	109.5								-1191.19257		
100											-74.76590		-75.90324
103.8	130.4	108.1	107.7								-113.54919		-114.86716
116.6	109.5	115.6	109.5								-672.49370	-672.86238	-680.02454
130.6	95.9	109.5	109.5	109.5							-671.74727		-679.47661
125.9	110.4	104.8									-186.21788		-188.46988
104.2											-55.45542		-56.09829
124.3	111.4	121.6	120.1								-166.68821		-168.67733
119.5	109.5	116.2	107.8								-244.80424		-227.46208
125	119.5	109.5	116.2								-374.61515		-378.98521
120	120	120	120	120	120	120					-335.97824		
120	120	120	120	120							-335.23724		
109.5	120	120	120	120	120						-336.01034		
109.5	120	120	120								-335.26799		
109.5	119.5	116.2	120	109.5							-263.38105		
109.5	119.5	116.2	120	109.5							-582.69905	-582.76793	
109.5	120										-432.86798	-432.93468	
116.6	116.6	116.6	117.7	124.3	116.2	109.5	109.5				-783.74532	-784.10729	-792.59280
109.5	95.9	130.6	117.7	116.2	124.3	109.5					-783.01247		
109.5	116.2	117.7	124.3	109.5							-782.01534		
120	120	120	120	120	120	120	116.6	116.6	116.6	109.5	-894.91973		
120	120	120	120	120	120	120	116.6	116.6	116.6	109.5	-894.17264		
130.6	95.9	109.5	120	120	120	120	120	120	120		-894.18893		
130.6	95.9	109.5	120	120	120	120	120	120			-893.32715		
120	120	120	120	120	120	120	109.5				-893.18377		
120	120	120	120	120	120	109.5					-892.20078		
120	120										-201.95785		
120	120	120	120	116.6	116.6	116.6	109.5				-760.92024		
120	120	120	120	95.9	130.6	109.5					-760.31064		
120	120	120	120	109.5							-759.45565		
120											-558.11289		-564.56610

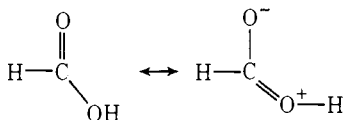
<sup>s</sup> Same geometry as **18** except for the -COOH group which now has the proton removed. <sup>t</sup>  $C_s$  symmetry;  $\phi_1(\text{HCC}=\text{O}) = 0^\circ$ ,  $\phi_2(\text{O}=\text{COC}) = 0^\circ$ ,  $\phi_3(\text{COCH}) = 0^\circ$ . The  $\text{CH}_3\text{COOH}$  bond lengths and angles were used for the  $\text{CH}_3\text{CO}$  part of methyl acetate and the methanol geometry for  $\text{OCH}_3$ . <sup>u</sup> The geometrical parameters for the  $\text{CH}_3\text{CO}$  fragment are from  $\text{CH}_3\text{COOH}$ ; for the - $\text{SCH}_3$  fragment they are from methanethiol (**22**); the  $\text{OC}-\text{SCH}_3$  bond length is from an electron diffraction study of  $\text{CH}_3\text{COSH}$ . See ref 14. The molecule has  $C_s$  symmetry and is in the conformation shown in the figure. <sup>v</sup> The methyl hydrogens are staggered with respect to the S-H bond. The structure is from a microwave study. See ref 15. <sup>w</sup>  $C_s$  symmetry; methyl C-H eclipses C=O, C=O eclipses O-P, and C-O is trans to P=O. The geometries of the acetyl and phosphate groups are from acetic acid and  $\text{H}_3\text{PO}_4$ , respectively. <sup>x</sup> Methyl C-H eclipses C=O, C=O is trans O-P, and C-O is trans to P-OH.  $\phi(\text{OPOH}) = 300^\circ$ . The geometries of the acetyl and phosphate groups are from acetic acid and  $\text{H}_2\text{PO}_4$ , respectively.  $\text{R}_4$  is from the acetyl phosphate optimization. <sup>y</sup> The geometry of the  $\text{CH}_3\text{COO}^-$  group is the same as in acetyl phosphate. The phosphate moiety has the structure of the  $\text{HPO}_4^{2-}$  anion. <sup>z</sup>  $C_s$  symmetry; the conformation is that shown in the figure for phosphoenolpyruvate. The phosphate moiety has the geometry determined for  $\text{H}_3\text{PO}_4$ . Similarly, the pyruvate moiety has the geometry assigned previously to pyruvic acid. <sup>aa</sup> Same structure as **26** except for the carbonyl group which is now deprotonated. <sup>bb</sup>  $\text{H}_2\text{PO}_4^-$  attached to pyruvic acid enol. The molecule has a plane of symmetry except for the phosphate proton which is twisted  $60^\circ$  out of the plane. The conformation is that shown in the figure. <sup>cc</sup> Same structure as **28** except for the carboxyl group which is now deprotonated. <sup>dd</sup>  $\text{HPO}_4^{2-}$  attached to pyruvic acid enol. The molecule has a plane of symmetry and has the conformation shown in the figure. <sup>ee</sup> Same structure as **30** except for the carboxyl group which is now deprotonated. <sup>ff</sup> STO-3G optimized geometrics by Kollman et al. See ref 16. <sup>gg</sup>  $\text{H}_3\text{PO}_4$  attached to guanidinium cation. The molecule has a plane of symmetry and is in the conformation shown in the figure. <sup>hh</sup> Conformation is that shown in the figure. The phosphate hydrogen is  $60^\circ$  out of the molecular plane. The geometry is that of an  $\text{H}_2\text{PO}_4^-$  attached to the guanidinium cation. The P-N bond length is taken from **33**. <sup>ii</sup> Conformation is shown in the figure. The geometry is that of an  $\text{HPO}_4^{2-}$  attached to the guanidinium cation. The P-N bond length is taken from **33**. <sup>jj</sup> Geometry was optimized by using a "double zeta" Gaussian basis set. The molecule has  $D_{3h}$  symmetry.

Table II. Calculated Gas-Phase Reaction Energies

Reaction	$\Delta E$ STO-3G, kcal/mol	$\Delta E$ STO-3G*, kcal/mol	$\Delta E$ 4-31G, kcal/mol	$\Delta H$ (exptl), kcal/mol
(1) $H_4P_2O_7 + H_2O \rightarrow 2H_3PO_4$	-4.34	-6.64	-13.20	-7.6 (soln) <sup>c</sup>
(2) $H_3P_2O_7^- + H_2O \rightarrow H_3PO_4 + H_2PO_4^-$	-0.93	-0.70	-19.10	-7.3 (soln) <sup>c</sup>
(3) $H_2P_2O_7^{2-} + H_2O \rightarrow 2H_2PO_4^-$	-75.23		-70.98	-6.8 (soln) <sup>c</sup>
(4) $CH_3OPO_3H_2 + H_2O \rightarrow H_3PO_4 + CH_3OH$	-1.90	-1.74	+2.50	-4.4 (soln) <sup>d</sup>
(5) $CH_3OPO_3H^- + H_2O \rightarrow H_2PO_4^- + CH_3OH$	-0.97		-3.50	-2.5 (soln) <sup>d</sup>
(6) $CH_3(CO)O(CO)CH_3 + H_2O \rightarrow 2CH_3COOH$	-17.21		-22.41	-11.6 (gas) <sup>a</sup>
(7) $H(CO)NH_2 + H_2O \rightarrow HCOOH + NH_3$	-12.05		+7.78	+6.6 (gas) <sup>a</sup>
(8) $CH_3COOPO_3H_2 + H_2O \rightarrow CH_3COOH + H_3PO_4$	-4.05	-8.10	-14.23	~-8 to -10 (soln) <sup>e</sup>
(9) $CH_3COOPO_3H^- + H_2O \rightarrow CH_3COOH + H_2PO_4^-$	+5.40			-8.6 (soln) <sup>c</sup>
(10) $CH_3COOPO_3^{2-} + H_2O \rightarrow CH_3COOH + HPO_4^{2-}$	+32.47			
(11) $^+C(NH_2)_2NHPO_3H_2 + H_2O \rightarrow C(NH_2)_3^+ + H_3PO_4$	+9.32			
(12) $^+C(NH_2)_2NHPO_3H^- + H_2O \rightarrow C(NH_2)_3^+ + H_2PO_4^-$	+96.11			
(13) $^+C(NH_2)_2NHPO_3^{2-} + H_2O \rightarrow C(NH_2)_3^+ + HPO_4^{2-}$	+212.37			
(14) $CH_3COOCH_3 + H_2O \rightarrow CH_3COOH + CH_3OH$	+4.03			-0.1 (gas) <sup>a</sup> (+4.6 ethyl, gas phase <sup>b</sup> )
(15) $CH_3COSCH_3 + H_2O \rightarrow CH_3COOH + CH_3SH$	-4.56	-3.20		
(16) $CH_2=C(OPO_3H_2)COOH + H_2O \rightarrow CH_2=C(OH)COOH + H_3PO_4$	-3.80			
(17) $CH_2=C(OPO_3H_2)COOH + H_2O \rightarrow CH_3COCOOH + H_3PO_4$	-23.94			-14.3 (soln) <sup>c</sup>
(18) $CH_2=C(OPO_3H_2)COO^- + H_2O \rightarrow CH_2=C(OH)COO^- + H_3PO_4$	-7.62			
(19) $CH_2=C(OPO_3H_2)COO^- + H_2O \rightarrow CH_3COCOO^- + H_3PO_4$	-26.88			
(20) $CH_2=C(OPO_3^-H)COOH + H_2O \rightarrow CH_2=C(OH)COOH + H_2PO_4^-$	+6.95			
(21) $CH_2=C(OPO_3^-H)COOH + H_2O \rightarrow CH_3COCOOH + H_2PO_4^-$	-13.20			-12.2 (soln) <sup>c</sup>
(22) $CH_2=C(OPO_3H)COO^{2-} + H_2O \rightarrow CH_2=C(OH)COO^- + H_2PO_4^-$	-68.84			-8.8 (soln) <sup>c</sup>
(23) $CH_2=C(OPO_3H)COO^{2-} + H_2O \rightarrow CH_3COCOO^- + H_2PO_4^-$	-88.10			
(24) $CH_2=C(OPO_3)COOH^{2-} + H_2O \rightarrow CH_2=C(OH)COOH + HPO_4^{2-}$	+8.83			
(25) $CH_2=C(OPO_3)COOH^{2-} + H_2O \rightarrow CH_3COCOOH + HPO_4^{2-}$	+28.97			
(26) $CH_2=C(OPO_3)COO^{3-} + H_2O \rightarrow CH_2=C(OH)COO^- + HPO_4^{2-}$	-122.88			
(27) $CH_2=C(OPO_3)COO^{3-} + H_2O \rightarrow CH_3COCOO^- + HPO_4^{2-}$	-142.14			-6.0 (soln) <sup>c</sup>
(28) $PO_3^- + H_2O \rightarrow H_2PO_4^-$	-54.38		-33.82	

<sup>a</sup> See ref 18. <sup>b</sup> See ref 19. <sup>c</sup> See ref 6. <sup>d</sup> See ref 6; used value for hydrolysis of glucose phosphate. <sup>e</sup> See ref 32.

whereas in the products, there are four, two from each molecule:



Thus, opposing resonance (e.g., the inability of a single central oxygen to satisfy the electron demand of two C=O groups as well as when each C=O group can draw electrons from its own -O-) tends to stabilize the products relative to the reactants. Hill and Morales<sup>3</sup> pointed out that although opposing resonance was of crucial importance in most high-energy compounds, electrostatic repulsions were very important in the large negative free energies of hydrolysis of ATP, ADP, and phosphoenolpyruvate.

In  $\pi$  electron molecular orbital theory, the effect associated with opposing resonance can be estimated from the orbital energies, and, in the 1950's,  $\pi$  electron calculations by Pullman and Pullman<sup>4</sup> led to their conclusion that both electrostatic repulsions and opposing resonance played important roles in the hydrolyses of ATP, ADP, acyl phosphates, and phosphoenolpyruvate; these calculations were not successful, however, in providing a rationale for the "high-energy" nature

of the phosphoguanidines, phosphocreatine, and phosphoarginine. Approximately a decade later, Boyd and Lipscomb<sup>5</sup> carried out extended Hückel calculations on phosphate-containing high-energy compounds and also concluded that both opposing resonance and electrostatic repulsions contribute importantly to the large negative free energies of hydrolysis of these compounds.

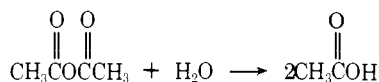
In a landmark paper, George et al.,<sup>6</sup> analyzing the thermodynamics of hydrolysis of different pH forms of pyrophosphate, acetyl phosphate, and phosphoenolpyruvate, concluded that intramolecular effects such as opposing resonance and electrostatic repulsions were of secondary importance; they suggested that differences in solvation energy of reactants and products were the predominant free-energy contributions to the large negative free energies of hydrolysis of these compounds.

In an earlier communication employing minimal basis ab initio methods,<sup>7</sup> we noted that intramolecular effects (opposing resonance) were more important in the carboxylic acid anhydrides than the phosphoric acid anhydrides. We also noted the very large size of electrostatic repulsions in the gas-phase hydrolyses of such dianions as  $^-HO_3POPO_3H^-$ . In this study we survey many of the compounds whose large negative free energies of hydrolysis have been discussed by Mahler and

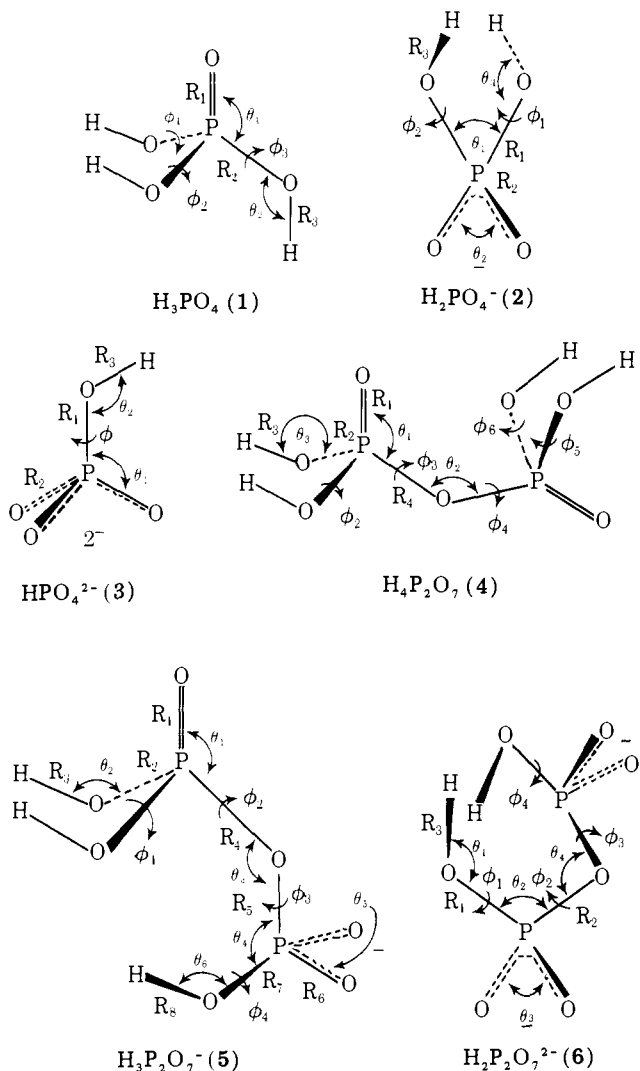
Cordes:<sup>8</sup> phosphoric acid anhydrides, acetyl phosphates, phosphoguanidines, enol phosphates, thiol esters, and amino acid esters. We calculate reaction energies and electronic structures of these compounds with different basis sets. We attempt to determine the relative contributions of intramolecular (opposing resonance and electrostatic) and intermolecular (solvation) effects in causing the large negative free energies of hydrolysis of these compounds.

### Computational Details

The ab initio calculations reported here were carried out using Gaussian 70 and Gaussian 74 with STO-3G (minimal),<sup>9</sup> STO-3G\* (minimal plus "d" functions),<sup>10</sup> and 4-31G (split level shell) basis sets.<sup>11</sup> The STO-3G\* basis set included a single set of d functions ( $x^2$ ,  $y^2$ ,  $z^2$ ,  $xy$ ,  $xz$ , and  $yz$ ) with an exponent of 0.39 on P and on S. Complete geometry optimization would have been too costly, so limited optimizations were carried out. We attempted to optimize both reactants and products, however, at a consistent level. For example, in the hydrolysis of acetic anhydride,



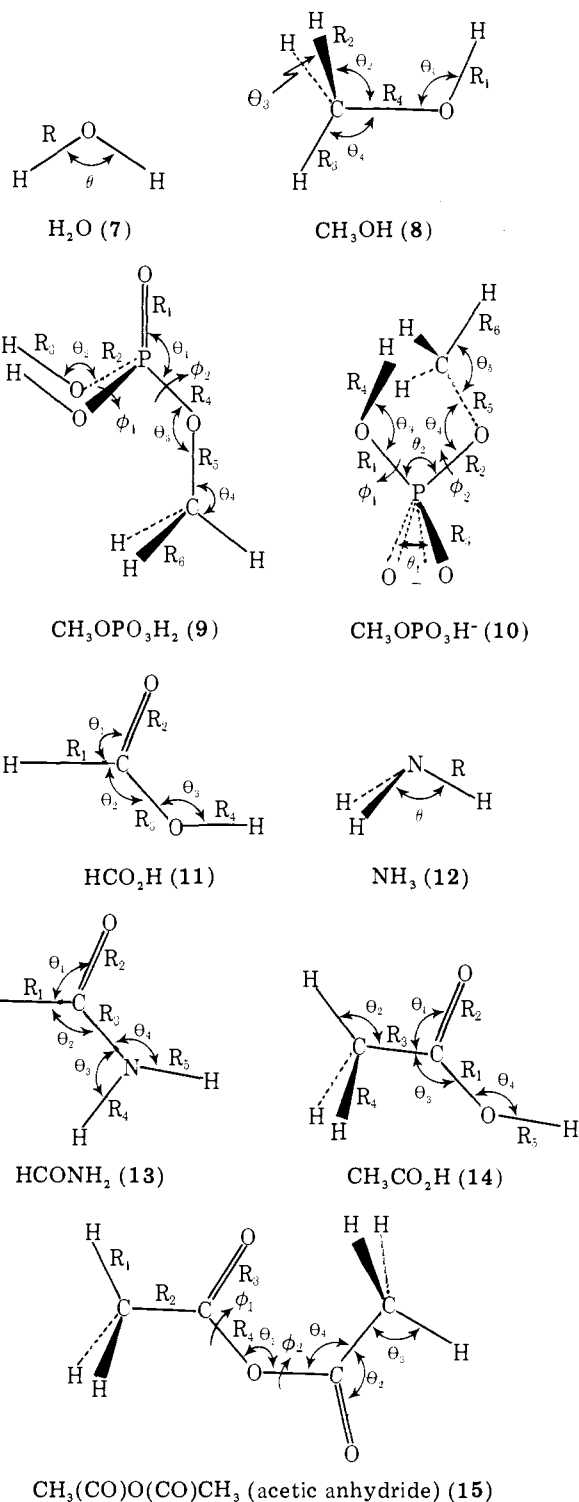
we used identical C-H and O-H bond lengths and  $\text{CH}_3\text{C}(\text{O})$  units in both reactants and in products, optimizing  $R(\text{CO})$ ,  $\theta(\text{COC})$ , and  $\phi(\text{O}=\text{COC})$  in the anhydride and  $R(\text{CO})$  in acetic acid. The total energies of the molecules considered and the geometrical parameters are summarized both in Table I and in the accompanying drawings (1-36).

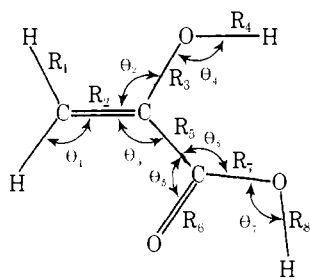
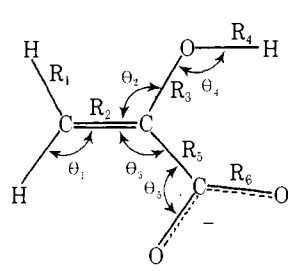
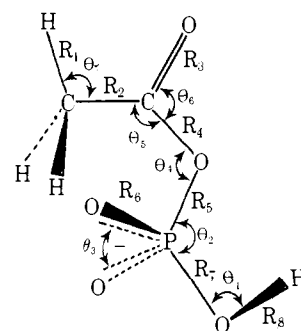
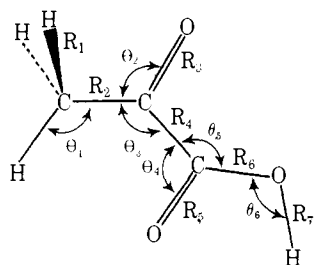
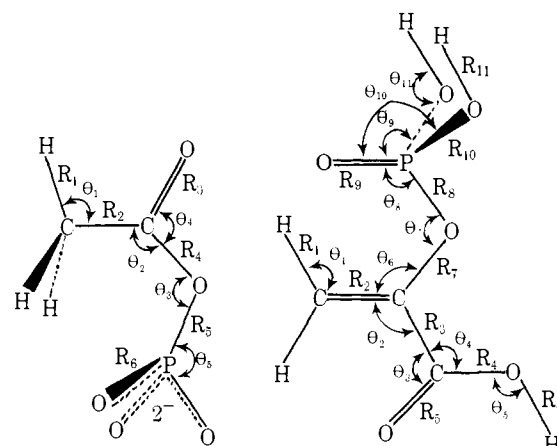
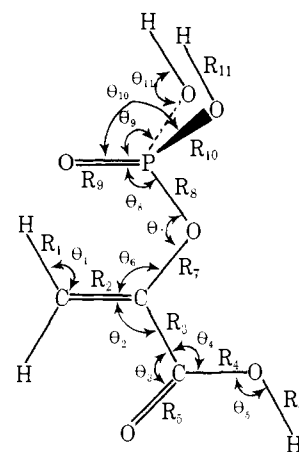
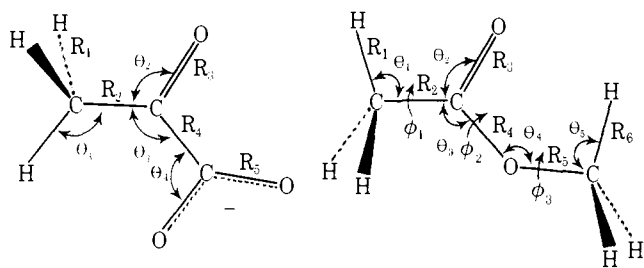
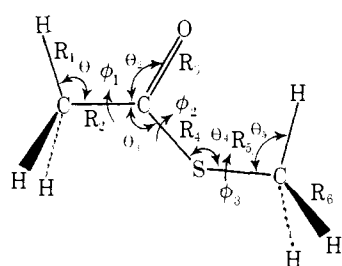
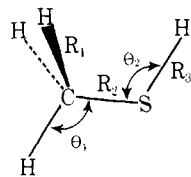
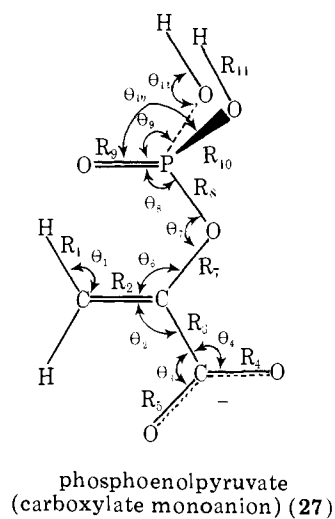
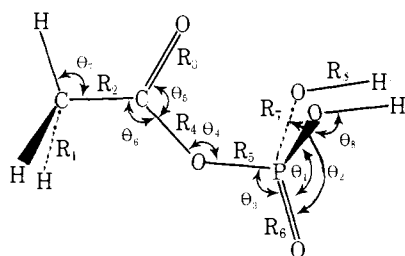


### Results and Discussion

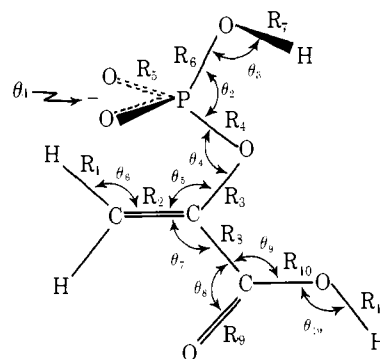
Table II summarizes the calculated reaction energies ( $\Delta E_0$ ) as well as available experimental reaction enthalpies ( $\Delta H_{298}$ ). Most of the reactions considered here are isodesmic (same number and types of bonds in reactants and products); thus the difference between  $\Delta H_{298}$  and  $\Delta E_0$ , which should mainly come from zero-point energy differences for these gas-phase reactions, is expected to be very small.<sup>20</sup> In any case, we do not expect this difference to exceed approximately 1-2 kcal/mol.

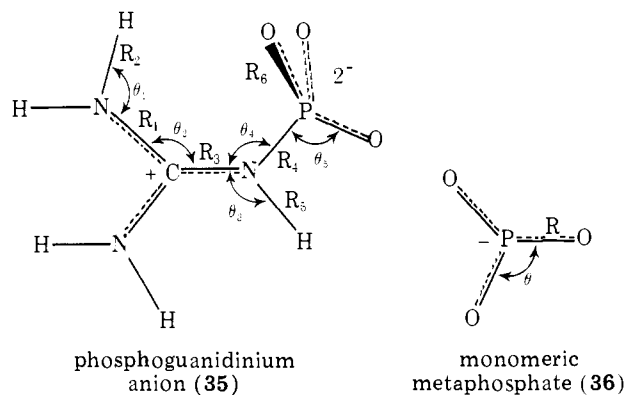
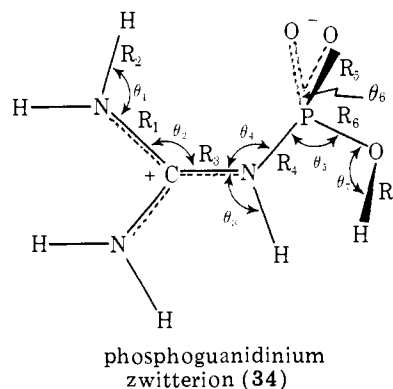
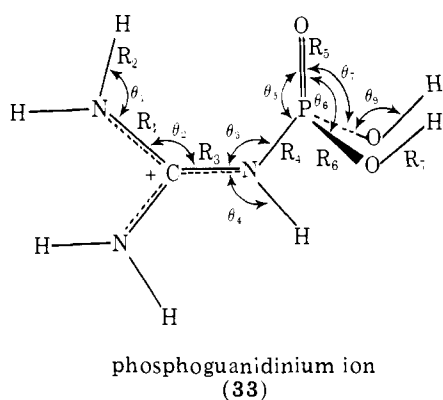
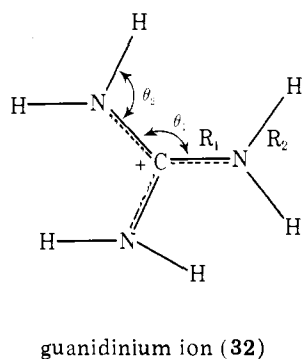
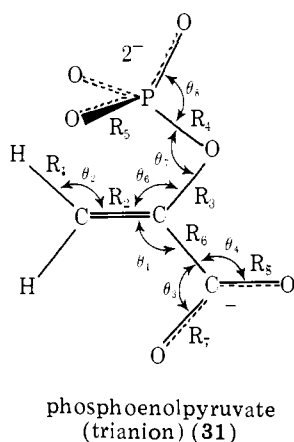
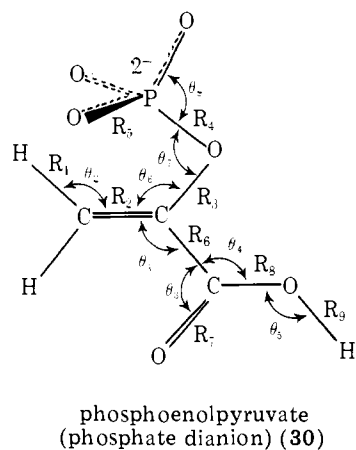
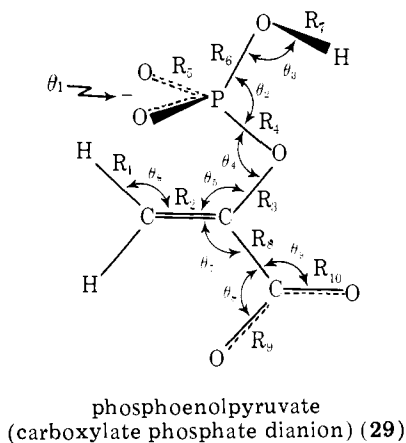
Although the standard definition of "high-energy" molecules are those with large negative free energies ( $\Delta G$ ) of hydrolysis, in virtually all of the cases considered here the enthalpy parallels the free energy and thus is an appropriate index



pyruvic acid  
(enol form) (16)pyruvate anion  
(enol form) (17)acetyl phosphate  
monoanion (24)pyruvic acid  
(keto form) (18)acetyl phosphate  
dianion (25)phosphoenolpyruvic  
acid (26)pyruvate anion  
(keto form) (19)CH<sub>3</sub>OC(O)CH<sub>3</sub> (20)CH<sub>3</sub>SC(O)CH<sub>3</sub> (21)CH<sub>3</sub>SH (22)phosphoenolpyruvate  
(carboxylate monoanion) (27)

acetyl phosphoric acid (23)

phosphoenolpyruvate  
phosphate monoanion (28)



of a high-energy molecule. For example, in aqueous solution, the difference in the free energies of hydrolysis of  $\text{H}_4\text{P}_2\text{O}_7$  and glucose 6-dihydrogen phosphate is 4.3 kcal/mol and the difference in the enthalpies of hydrolysis is 3.2 kcal/mol<sup>6</sup> (the P-O-P hydrolysis having the more negative  $\Delta H$  and  $\Delta G$  of hydrolysis). Only for the very highly charged  $\text{P}_2\text{O}_7^{4-}$  is the  $\Delta H$ (hydrolysis) very different from  $\Delta G$ (hydrolysis), presumably due to the release of tightly bound water to the highly charged ion ( $\Delta S = +22$  eu for this hydrolysis).

Below we discuss the results in Table II in some detail, separating our discussion (as have the previous workers in this field) into the various classes of high-energy molecules.

**Phosphoric Acid Anhydrides.** We first wish to compare the energies of hydrolysis of the "high-energy" P-O-P bond with those of the "standard" or "low-energy" P-O-C bond, and this is done in reactions 1-5. For the reactions involving neutral molecules (reactions 1 and 4), the differences between the energies of hydrolysis of P-O-C and P-O-P are 2.4, 4.9, and 15.7 kcal/mol with the STO-3G, STO-3G\*, and 4-31G basis sets, respectively. The STO-3G basis set underestimates polarity and the 4-31G basis set overestimates it,<sup>21</sup> so it is not necessarily the case that the correct answer can be extrapolated from these results; rather, the hydrolysis energy difference is likely to be between 2.4 and 15.7 kcal/mol if we assume that a major contribution to the hydrolysis energy is the relief of intramolecular electrostatic repulsion. When we now compare reactions 2 and 5 involving a singly ionized phosphate, we see that the calculated difference in hydrolysis energies varies from 0 to 15.6 kcal/mol. A reasonable explanation of why reactions 2 and 5 are calculated to be more endothermic than the corresponding 1 and 4 with the STO-3G basis set is the stabilization of the anion in the larger molecule by charge delocalization (or conversely, the destabilization which comes about by trying to localize the negative charge on one of the product molecules).<sup>22</sup> With the 4-31G basis set, the opposite trend is observed, reactions 2 and 5 being calculated to be more *exothermic* than reactions 1 and 4. The likely reasons for this are the rather large partial negative charges on the oxygens in this basis set and the resulting intramolecular electrostatic repul-

sion. This repulsion is apparently dominant over the delocalization stabilization noted above.

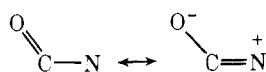
Reaction 3 has a very large negative energy of hydrolysis ( $\Delta E \sim -70$  kcal/mol) due to the charge-charge repulsion between the ends of the molecule ( $\text{H}_2\text{P}_2\text{O}_7^{2-}$ ). Since in most biological environments each phosphate group is (at least) singly ionized, solvation must play a substantial role in the observed  $\Delta H$  for this reaction in aqueous solution ( $\Delta H = -6.8$  kcal/mol).<sup>6</sup>

Thus, in our view, the most important difference between "low-energy" P-O-C linkages and "high-energy" P-O-P linkages is that the latter contain a substantial electrostatic repulsion dampened by solvation effects. As noted by Hill and Morales,<sup>3</sup> in the largely nonaqueous environment of an enzyme, this electrostatic repulsion will be substantially greater than that in water. This will contribute to a lowering of the activation energy for enzyme-catalyzed P-O-P hydrolysis and make molecules such as ATP easily *usable* energy sources.

Although "opposing resonance" may play a role in P-O-P vs. P-O-C hydrolysis comparisons, it is substantially smaller than that observed in carboxylic acid anhydrides (see below) and probably is not responsible for differentiating the "high-energy" P-O-P hydrolyses 1-3 from the "low-energy" P-O-C hydrolyses 4 and 5.

**Carboxylic Acid and Amide Hydrolyses.** As prototypal hydrolysis reactions where resonance effects are of clear importance, we studied the energies of hydrolysis of both acetic anhydride and formamide, where gas-phase enthalpies of reaction are available. Both basis sets overestimate the exothermicity of the anhydride reaction, but each finds the carboxylic acid anhydride resonance effect to be at least  $\sim 10$  kcal/mol more important than the phosphoric acid anhydride resonance (assuming electrostatic repulsion contributes similarly in both cases).

The amide resonance appears to be poorly represented at the minimal (STO-3G) level, and this is the apparent reason why the calculated  $\Delta E$  for reaction 7 is in such poor agreement with experiment. The relative H-bonding abilities<sup>23</sup> of the C=O and N-H in formamide are reversed in the 4-31G compared to STO-3G basis sets, and that is apparently also a reflection of the poorer description of the



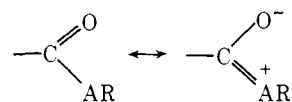
resonance by the minimal basis set.

**Acetyl Phosphate, Acetate, and Thioacetate.** Reaction 8 suggests that the role of resonance in causing the "high-energy" nature of the acetyl phosphate C-O-P bond is *comparable* to that found for the P-O-P bond in  $\text{H}_4\text{P}_2\text{O}_7$  (reaction 1). However, since there is no large electrostatic repulsion in this case, a major cause of the ease of hydrolysis of acetyl phosphate may well be the intramolecular opposing resonance effect.

The  $\Delta E$  values calculated for reactions 9 and 10 are apparently dominated by the ability to delocalize the negative charge in the reactant compared to the product. Because these are minimal basis set calculations, we feel they probably exaggerate the magnitude of this effect. It is unlikely to be completely spurious, however, and again suggests an important role for solvation in determining the nature of the acetyl phosphate "high-energy" bond. Opposing resonance would cause a negative  $\Delta E$  for reaction 10. Since our calculated value is positive, one must conclude that water stabilizes the *product* more than the reactant in order for  $\Delta H$  hydrolysis in solution to be its observed  $-8.6$  kcal/mol.

Although we do not have comparative solution phase  $\Delta H$  values for reactions 14 and 15, the available thermodynamic parameters for the hydrolysis of nonhighly charged compounds suggest that the relative free energies parallel the relative

enthalpies.<sup>6</sup> Thus, our calculations which find a more negative  $\Delta E$  for thioacetate than acetate hydrolysis of  $\sim 9$  kcal/mol are qualitatively consistent with the observation that the free energy of hydrolysis of thioacetate (a model for acetyl coenzyme-A) is  $\sim 3$  kcal/mol more negative than that of acetate. This difference in  $\Delta E$  is presumably predominantly a resonance effect; i.e., the resonance stabilization from

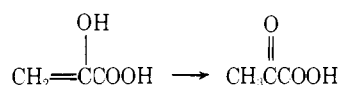


is 3 kcal/mol greater for A = O than for A = S.

**Phosphoguanidines.** The N-P bonds in both phosphocreatine and phosphoarginine are considered to be of a high-energy nature. As is evident from reactions 11-13, however, in this type of molecule (especially reactions 12 and 13) there is a large intramolecular attraction in the gas phase; a much more substantial solvation of the products than reactants is required to make these reactions exothermic in aqueous solution. This reaction is in interesting contrast to the pyrophosphate reaction and this may have physiological implications. For example, phosphocreatine would be expected to be kinetically much more stable than ATP, and thus would be an appropriate molecule for use in energy storage. ATP would have a lower activation barrier to cleavage and thus would be a more appropriate molecule in energy transduction and energy use, such as in the processes of muscle action.<sup>24</sup>

One might speculate that the  $\text{CO}_2^-$  group of both phosphoarginine and phosphocreatine is in an extended conformation in aqueous solution,<sup>25</sup> but, when bound to the arginine and creatine kinases, respectively, it is "forced" into a conformation which increases  $\text{CO}_2^- \cdots \text{PO}_3^{2-}$  repulsions and, thus, facilitates N-P bond cleavage.

**Phosphoenolpyruvate.** The hydrolysis reactions for the various ionization states of phosphoenolpyruvate are described in reactions 16-27. All reactions suggest a substantial contribution to the "high-energy" nature of this compound due to the energy gain from enol  $\rightarrow$  keto tautomerism



in the product, in agreement with the  $\pi$  calculations of Pullman and Pullman.<sup>4</sup> In those reactions where both the phosphate and carboxylate are charged (reactions 22, 23, 26, and 27), the solvation energy must be crucial in dampening the large negative  $\Delta H$  calculated in the gas phase to its solution value of  $-6$  to  $-12$  kcal/mol.<sup>6</sup>

There are interesting comparisons among reactions 16, 18, and 20 (or 17, 19, and 21). Reaction 18 is more exothermic than 16, presumably because of internal electrostatic effects between the  $\text{CO}_2^-$  and the phosphate oxygens. Reaction 20 is more endothermic than 16, however, presumably because of the inductive stabilization of  $\text{PO}_3\text{H}^-$  by the pyruvic acid moiety.

**Hydration of Monomeric Metaphosphate.** Although reaction 28 is not a hydrolysis reaction like 1-27, a recent study by Guthrie implicating the metaphosphate ion in phosphate exchange reactions has suggested that the experimental  $\Delta G$  of reaction 28 is  $-27 \pm 2$  kcal/mol.<sup>26</sup> Loew<sup>17</sup> has compared the electronic structure of  $\text{PO}_3^-$  and  $\text{NO}_3^-$  and suggested reasons for the relative instability of  $\text{PO}_3^-$ , so we decided to quantify this lack of stability by evaluating the  $\Delta E$  for reaction 28. Since there is a single negative charge in reactants and products, one might not expect a very large solvation effect on this reaction. The more reliable 4-31G calculations find a  $\Delta E$  of ca.  $-30$  kcal/mol, in reasonable agreement with the experimental *free* energy. Despite the uncertainties associated with comparing



Table III. Solvation Energy Estimates

Molecule	Cavity radius, Å	Solvation energy ( $-\Delta E$ ) <sup>a</sup>
H <sub>2</sub> PO <sub>4</sub> <sup>-</sup> (2)	3.0	55
HPO <sub>4</sub> <sup>2-</sup> (3)	3.0	219
C(NH <sub>2</sub> ) <sub>3</sub> <sup>+</sup> (32)	2.9	57
C(NH <sub>2</sub> ) <sub>2</sub> <sup>+</sup> NHPO <sub>3</sub> <sup>2-</sup> (35)	4.1	40
CH <sub>2</sub> =C(COO <sup>-</sup> )(OPO <sub>3</sub> H <sup>-</sup> ) (29)	4.2	149
CH <sub>3</sub> C(O)COO <sup>-</sup> (19)	3.8	43
H <sub>2</sub> P <sub>2</sub> O <sub>7</sub> <sup>2-</sup> (6)	4.0	164
CH <sub>3</sub> C(O)(OPO <sub>3</sub> <sup>2-</sup> ) (25)	4.0	164
CH <sub>2</sub> =C(COO <sup>-</sup> )(OPO <sub>3</sub> <sup>2-</sup> ) (31)	4.2	335
H <sub>2</sub> O (7)	1.4	9
CH <sub>3</sub> COOH (14)	3.0	1

<sup>a</sup> In kcal/mol; estimated using the reaction field equation (see text),  $\epsilon = 80$ ; for H<sub>2</sub>O and CH<sub>3</sub>COOH we used the dipolar equation<sup>28</sup>  $-\Delta E = [(\epsilon - 1)/(2\epsilon + 1)] (\mu^2/a^3)$ ,  $\mu$  = dipole moment = 1.85 D for H<sub>2</sub>O and 1.75 D for CH<sub>3</sub>COOH.

solution-phase  $\Delta G$  with gas-phase  $\Delta H$ , our calculated values are close enough to Guthrie's to support the reasonableness of his value for  $\Delta G$ , which was not a directly measured number, but which was inferred from kinetic arguments.

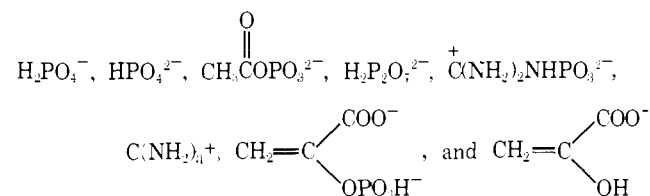
Although no *direct* measure of the heat of hydration of PO<sub>3</sub><sup>-</sup> is available, the heat of hydration of the isoelectronic SO<sub>3</sub> can be estimated from known thermochemical data<sup>27</sup> to be about -24 kcal/mol.

**Estimates of Solvation Energies.** Because there are likely to be large solvation energy effects associated with the hydrolytic reactions discussed above when there are charge separations in going from reactant to product, we have qualitatively estimated the reaction field stabilization (in H<sub>2</sub>O) for a number of the ions considered in this study, using the reaction field equation (for solvation of ions):<sup>28</sup>

$$-\Delta E = \frac{\epsilon - 1}{2\epsilon} \frac{q^2}{a}$$

where  $\epsilon$  is the solvent dielectric constant,  $q$  is the solute charge, and  $a$  is the cavity radius of the solute. The results are sensitive to the cavity radius  $a$ , so one must not interpret the precise values in a quantitative fashion. The results of such an analysis are instructive, however, as we shall see below.

Table III contains the results of the solvation estimates for



These molecules are not spherical, but we estimated the cavity radii by the following procedure. Take the central atom (the P in H<sub>2</sub>PO<sub>4</sub><sup>-</sup> and HPO<sub>4</sub><sup>2-</sup>, the phosphoryl N in phosphoguanidinium, the C in guanidinium, the central carbon in pyruvic acid, and the phosphoryl O in both phosphoenolpyruvate and acetyl phosphate), determine the distance to the furthest (nonhydrogenic) atom from it, and add the van der Waals radius for that atom.<sup>29,30</sup>

Evaluating the solvation effect for the reactions described in Table II in which there is charge separation, we can see that even the very crude solvation model we used brings the calculated solvation energies into the same range as the experimental ones, with the calculated values usually being too exothermic (Table IV).<sup>31</sup> Reaction 27 shows the largest deviation from experiment. This reflects the crudeness of the

Table IV. Solvation Effect on Reactions with Charge Separation

Reaction	$\Delta E$ (gas phase) <sup>a</sup>	$\Delta E$ (H <sub>2</sub> O) <sup>b</sup>	$\Delta H$ (exptl) <sup>c</sup>
(3)	-75	-2	-7
(10)	+32	-15	-6
(12)	+96	-7	(-9) <sup>d</sup>
(13)	+212	-15	(-9) <sup>d</sup>
(23)	-88	-21	-9
(27)	-142	-44	-6

<sup>a</sup> In kcal/mol, using STO-3G energies from Table II. <sup>b</sup> In kcal/mol, estimated using the reaction field equation (see text). <sup>c</sup> In kcal/mol, from ref 6, unless otherwise indicated. <sup>d</sup> Free energies of hydrolysis from ref 8; by examination of the many  $\Delta G$  and  $\Delta H$  values in ref 6, it is likely that  $\Delta G$  and  $\Delta H$  values of hydrolysis are similar in both sign and magnitude.

model and the extreme sensitivity of this calculation to the cavity radius chosen in the calculation. For example, changing the cavity radius  $a$  from 4.2 to 4.0 Å for phosphoenolpyruvate would lead to calculated solution  $\Delta E$  values of -12 and -23 kcal/mol for reactions 23 and 27, respectively.

The point that should be emphasized here, however, is that even this crude model is able successfully to rationalize (reproduce) the fact that the enthalpies of hydrolysis of pyrophosphate (reaction 3) and phosphoguanidinium (reaction 13) are comparable, despite the large difference in sign and magnitude for the gas-phase  $\Delta E$  values.

### Caveats and Conclusions

Because there are often large basis set dependencies as well as limited geometry optimizations in the studies reported here, we must stress that most of our calculated  $\Delta H$  values may be in substantial absolute error ( $\pm 10$  kcal/mol). We do feel, however, that most *trends* will be successfully reproduced. For the solution-phase hydrolysis reactions involving no charge separation we calculate the following trend in reaction energies in order of increasing exothermicity: C-O-P(alkyl phosphate) < P-O-P(pyrophosphate) ~ acetyl phosphate < phosphoenolpyruvate. The solution-phase exothermicities of the four linkages above are -4.4, -7.1, -8.6, and -14.2 kcal/mol.<sup>6</sup> The corresponding experimental free energies are -5.2, -9.5, -9.9, and -15.2.<sup>6,32</sup>

Of the examples of important hydrolytic bonds in biological systems noted in Mahler and Cordes,<sup>8</sup> we have discussed the major classes of bonds of high hydrolytic free energy except acetyl adenylate and acetyl imidazole. These molecules are too large for us to examine with extended (4-31G) basis sets and the poor representation of the hydrolysis of formamide by STO-3G caused us not to study these. However, they are cases where opposing resonance is likely to be of more importance than for the phosphoric acid anhydrides.

We conclude in agreement with George et al.<sup>6</sup> that for biologically important high-energy compounds in which there is no charge separation, the key energy terms are the large intramolecular electrostatic terms strongly modulated by solvation effects. As emphasized by George et al.,<sup>6</sup> the intramolecular electrostatic effects are not the "key" to the high-energy nature because  $\Delta G$  does not become more exothermic the larger the ionization state of pyrophosphate. Our calculations emphasize this point even more strongly because we find that for the hydrolysis of phosphocreatine, solvation effects change an intrinsically very "low-energy" N-P bond ( $\Delta G$  and  $\Delta H$ ,  $\gg 0$ ) to a high-energy bond ( $\Delta G$ ,  $\Delta H$  ca. -10 kcal/mol). The only prototypal high-energy reaction dominated by a resonance effect is the hydrolysis of acetic anhydride, although the enol-keto tautomerization of pyruvate is apparently the predominant factor in the very exothermic heat of hydrolysis of phosphoenolpyruvate.

Although these calculations have not been able to describe quantitatively the enthalpies of these biologically important hydrolysis reactions, for most of the charged molecules they do give more precise estimates of the  $\Delta H$  values than have been heretofore available. Thus, they provide an interesting testing ground for theoretical models which include more sophisticated treatments of solvation effects: to calculate correctly  $\Delta H$ (hydrolysis) in solution for charged forms of both pyrophosphate and phosphocreatine.

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- (30) Phosphoenolpyruvate was an exception; for it we use the average distance from the phosphoryl oxygen to the five ( $3\text{P}\cdots\text{O}^{2-}$  and  $2\text{C}\cdots\text{O}^{2-}$ ) oxygens.
- (31) Note that a reaction field model correctly models the heat of vaporization of  $\text{H}_2\text{O}$  ( $\Delta H \sim 10$  kcal/mol)<sup>27</sup> but not that of acetic acid ( $\Delta H \sim 10$  kcal/mol).<sup>27</sup>
- (32) For acetyl phosphate, we are quoting the free energy and enthalpy of hydrolysis of the anion  $\text{CH}_3\text{COOPO}_3\text{H}^-$ , since no experimental values of  $\text{CH}_3\text{COOPO}_3\text{H}_2$  were reported. However, by analogy with  $\text{H}_4\text{P}_2\text{O}_7$  vs.  $\text{H}_3\text{P}_2\text{O}_7^-$ , whose enthalpies of hydrolysis are  $-7.6$  and  $-7.3$  kcal/mol, respectively, we expect this difference to be small.

## Theoretical Model for the Conversion of an Even $\pi$ Orbital to an Odd $\pi$ Orbital System and Its Implication to Vision

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**Abstract:** A computer program based on PPP molecular orbital approximations is used to calculate the conversion of an even  $\pi$  orbital system to an odd  $\pi$  orbital system. The model is based on an even system of 12 atoms that goes to an odd system of 11 and is selected to represent the conversion of *N*-retinylidene-*n*-butylamine to the *N*-retinylidene-*n*-butylammonium cation. The conversion is brought about by gradually increasing the charge on nitrogen ( $Z_p$ ) that is used to polarize the  $\pi$  electrons. In the calculations, the increase in  $Z_p$  is accounted for by continuously adjusting orbital occupancy and the coulomb integral  $\alpha_N$ . As  $Z_p$  changes, the following output parameters are examined: excitation energy, wave function geometry, eigenvalues of wave functions, bond orders, electron density, and resonance energy. The output parameters are completely consistent with conversion from even to odd as the value of  $Z_p$  goes to unity. The eigenvectors reveal that the first  $\pi$  orbital is transformed from a molecular orbital to an atomic orbital centered over nitrogen. Also the first unoccupied MO is transformed from antibonding to nonbonding. The overall changes in the  $\pi$  system are related to the chromophoric molecule in visual pigments.

Retinal in its 11-cis configuration is the chromophore molecule that condenses with visual proteins in a Schiff base linkage to form visual pigments. Retinal absorbs at approximately 380 nm, yet it condenses with specific visual proteins to form pigments with  $\lambda_{\text{max}}$  values from 440 to 575 nm. Ren-

dering a satisfactory explanation of this so-called bathochromic shift has been a problem of considerable difficulty. Most recently explanations are based on the effect of the counter negative charge on the positively charged organic cation and also on the effect of twisting about essential single bonds. At-