this work yields $k_1 = k_R$ and, hence, $\Delta G_1^{\ddagger} = \Delta G_R^{\ddagger}$.

(4) We predict that the anti form **30** can be experimentally detected if appropriate substituents are incorporated at the CH_2 bridge.

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Supplementary Material Available: Three tables containing geometries of **10–12** and **15–26** (4 pages). Ordering information is given on any current masthead page.

Ab Initio Studies of Molecular Structures and Energetics. 1. Base-Catalyzed Hydrolysis of Simple Formates and Structurally Related Reactions

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Abstract: Molecular structures, conformations, and thermodynamic properties of the orthoformate anionic molecules produced by the interaction of hydroxy or methoxy ions with formic acid or methyl formate have been determined by ab initio computations. These substances are the accepted intermediates, or models thereof, in the hydrolysis of esters, both in basic solution and by enzymes. The simplest of these orthoformate ions—$[HCO(OH)_2]^-$, formed from formic acid and a hydroxyl ion—and some related compounds were examined in a series of good-quality basis sets and, like the other orthoformates studied, were proven to be stable compounds rather than transition-state molecules. Energies were computed at the SCF and MP2 levels of approximation, with and without addition of diffuse basis functions. Theoretical corrections for nuclear motion were computed and used to obtain values of ΔH°_{298} for a series of reactions including the postulated steps in base-catalyzed and enzymatic hydrolyses. The stable conformers were found to correspond to the hydrogen of an OH (or OCH_3) group being adjacent or opposed to the lone oxygen, with both adjacent being the more stable. A modified Fourier expansion of the OH and OCH_3 torsional potentials indicated that the conformers of the $[HCO(OH)_2]^-$ and $[HCO(OH)(OCH_3)]^-$ structures are stabilized by monopolar electrostatic forces rather than by stereoelectronic effects.

Recent rapid advances in computational techniques and resources have made possible the application of rigorous ab initio theoretical methods to the study of an ever-widening array of fundamental chemical problems. The ab initio approach, which is thus currently supplanting the simpler approximate ones, has the important property that no prior experimental data is required in its implementation, making it a practical and reliable tool especially suited for interesting compounds that are difficult to isolate. Of course the history of wildly unreliable quantum calculations makes it obligatory for the present-day investigator to demonstrate that his approach is as appropriate for little-known structures as it is for well-characterized, related molecules. This may be done by comparison with experiment and, by employing an often overlooked feature of the ab initio approach, the intercomparison of results computed at various levels of approximation.[1] The study presented here, dealing with anions of organic orthoacids and esters—structures that have been widely invoked as intermediates in ester hydrolysis—is a particularly useful example of both these aspects of the ab initio method and philosophy.

From the interpretation of kinetic experiments and other experimental data, the base-catalyzed hydrolysis of organic esters and peptides has been shown to involve an orthoacid derivative (a monoesterified orthoacid anion, $[R'CO(OR)(OH)]^-$, for ester hydrolysis) produced by nucleophilic attack on the carbonyl carbon atom. Because the tricoordinated carbonyl carbon atom of the ester becomes tetracoordinated in its orthoacid derivative, the latter is sometimes called a "tetrahedral intermediate" and is usually assumed to be thermodynamically less stable than its precursors or successors in the hydrolysis process.

Enzymatic hydrolyses of esters also appear to proceed through such intermediate structures.[2] Thus, hydrolytic enzymes such as the serine esterases and proteases exhibit a strongly basic group (i.e., a serine residue) which is considered to act as a substituent in a "tetrahedral intermediate". Another such intermediate is involved in a subsequent step in which water is taken up prior to disengagement of the substrate. In one or both steps the enzyme is believed to exhibit a topology that maximizes its binding to several sites in the intermediate. Hence knowledge of the molecular structure of these intermediates provides indirect (template) information about the enzyme active site and the structural requirements for binding to the site by other compounds, such as inhibitors.

Gas-phase reactions between esters and strong bases have been the subject of detailed experimental studies[3-5] employing mass spectroscopy and ion-cyclotron resonance. To date these have provided no direct evidence of the existence of tetrahedral intermediates. In fact it has recently been suggested, based on this type of data, that these tetracoordinate intermediates are not even stable species in the gas phase but rather transition states.[4] Also there is apparently no experimental information about their structural parameters.

Some prior theoretical investigations have been reported concerning the structure and properties of this type of intermediate species. These fall into two groups: (a) early studies[6,7]—employing

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a simple STO basis set and with little or no optimization of the molecular structure—of the interaction of esters with HO^- ions and (b) more recent studies,[8-10] some involving larger basis sets, of the interaction of a molecule containing a peptide bond (formamide) with HO^- or CH_3O^- as models of the enzymatic hydrolysis of polypeptides. These have all indicated the existence of a stable tetracoordinate species, although other aspects of the overall reaction have remained elusive and are the subject of current research.[11]

The majority of prior quantum-chemical studies have dealt with structures and properties in the gas phase, as we also shall do here. Although it seems likely that relative energies are appreciably different in aqueous solutions, it may be argued that the gas phase is probably a better approximation to an enzyme active site, from which water is largely excluded. Also recent calculations,[9] involving both molecular-mechanical and quantum-mechanical computations, indicate that an aqueous environment has little effect on structures or on the number and positions of energy minima. Hence computations that presuppose gas-phase species appear to be the most appropriate at present.

In this paper we report a systematic study of the simplest prototype molecules occurring in the base-catalyzed or enzymatic hydrolysis of esters. For base catalysis in solution, it is generally thought that the pertinent steps are

$$\mathrm{R'C{=}O(OR) + HO^- \rightleftharpoons R'CO^-(OR)(OH) \rightleftharpoons} \\ \mathrm{R'C{=}O(OH) + RO^- \rightarrow R'CO_2^- + ROH} \quad (1)$$

and, for the enzymatic hydrolysis,

$$\mathrm{R'C{=}O(OR) + EO^- + H_2O \rightleftharpoons R'CO^-(OE)(OR) + H_2O \rightarrow} \\ \mathrm{R'C{=}O(OE) + RO^- + H_2O \rightarrow} \\ \mathrm{R'C{=}O(OE) + ROH + HO^- \rightleftharpoons} \\ \mathrm{R'CO^-(OE)(OH) + ROH \rightarrow R'C{=}O(OH) + ROH + EO^-} \quad (2)$$

where R′ and R are organic groups and EO^- stands for a deprotonated serine residue of the enzyme. The three intermediate model compounds, $R'CO^-(OR)(OR'')$, on which this study is focused correspond to R′ = H in each of three cases: R = R″ = H for the simplest one, which was studied the most thoroughly; R = CH_3 with R″ = H for another; and R = R″ = CH_3 for the last one.

Method

All calculations reported here were carried out with the GAUSSIAN 82 program.[12] Molecular structures were optimized employing the default analytical-gradient procedure this program contains. The simplest orthoformate anion, $[HCO(OH)_2]^-$, as well as pertinent smaller molecules were studied in a series of basis sets: 4-31G,[13] 4-31G*,[14] 6-311G,[15] 6-311G*,[15] 4-31+G,[16] and 4-31+G*.[14,16] Here the * implies a 5-fold set of d functions on all carbon and oxygen atoms and the + represents the addition of a very diffuse sp set on each of these two atoms. The diffuse basis functions consisted of s and p primitive Gaussians with exponents suggested by Chandrasekhar et al.[16] For the $[HCO(OH)_2]^-$ ionic molecule, the geometrical structures employed with the 4-31+G basis set were those optimized in the 6-311G* (and also in the 4-31G) basis. Those for the 4-31+G* basis were optimized in the 4-31G* basis. The structures of the $[HCO(OCH_3)OH]^-$ and $[HCO(OCH_3)_2]^-$ intermediates were computed in the 4-31G basis, and this structure was employed in computing the energy with the 4-31+G basis. Throughout this study each methyl group was constrained to exhibit the same C–H bond distance and OCH bond angle for all three of its hydrogens. Otherwise all of the geometric parameters were optimized, with each optimization step involving minimization of the molecular SCF energy. An approximation to the total energy including electron correlation was computed with second-order Møller–Plesset perturbation theory,[17,18] MP2, including all valence-orbital excitations, and with the structure previously having been optimized in the SCF approximation.

The complete set of vibrational frequencies required to compute the zero-point and thermal corrections to the energy in order to obtain enthalpies at 25 °C were computed by using the GAUSSIAN 82 procedures based on analytically derived force constants. Since vibrational frequencies computed by an SCF method tend to be somewhat high, these corrections are estimated to be as much as 10% too large. The translational correction of $^3/_2RT$ plus an additional factor of RT to represent the pressure–volume term was employed in the energy corrections presented in Table III. These were added to the energy of each species in order to obtain its enthalpy.

Comparison of Results in Different Basis Sets with Experiment

All of the geometrically optimized molecules discussed herein (including the various conformers) exhibit an increase in energy when any bond distance, bond angle, or torsional angle is incrementally increased or decreased, either singly or in concert. This means that these molecules are stable structures. It seems fairly certain from the first and second derivatives of the energy with respect to deformation that these calculated structures, except perhaps for some torsional angles concerned with internal rotation of a few of the molecules, will persist with little change upon going from the gas to the aqueous phase. For the orthoformates $[HCO(OH)_2]^-$, $[HCO(OCH_3)(OH)]^-$, and $[HCO(OCH_3)_2]^-$ these findings in all of the basis sets used show that these compounds should not be classed as transition states, which by definition must exhibit at least one negative energy change with some incremental variation of the molecular geometry.

Molecular Geometries. The remainder of this section is devoted to showing that comparison of ab initio results computed in a series of basis sets gives valuable information concerning the physical meaningfulness of the calculations for molecules relevant to the present study. Let us first consider the optimized geometries of those molecules of interest for which there are reasonably accurate experimental values. These data are presented in Table I, where bond distances and angles calculated in the various basis sets are compared with experiment.[19] In general the agreement between the values corresponding to a particular bond distance are quite good, lying within several hundredths of an angstrom, but only being within several degrees for certain bond angles. In particular, the incorporation of d orbitals into the basis set is needed to reduce the HOM angles (M = C or H) to values near the experimental ones. For M = P, our previous observations[20] also indicated similar difficulties in getting a properly small value for the angle about

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Table I. Computed Bond Lengths and Angles[a] in Several Basis Sets for Gaseous Compounds with Reported Experimental Geometries

	basis set				
parameter	4-31G	4-31G*	6-311G	6-311G*	exptl value[b]
		Water–H_2O			
H–O	0.9505	0.9486	0.9455	0.9394	0.958 (eq)
∠HOH	111.23	105.35	111.88	107.53	104.5
		Methanol–CH_3OH			
C–H	1.0804	1.0846			1.094 (eff)
C–O	1.4300	1.3976			1.425
O–H	0.9505	0.9474			0.945
∠HCH[c]	109.03	108.42			108.6
∠COH	112.61	108.74			108.5
		trans-Formic Acid—$H^0CO^0(O^1H^1)$			
C–O^0	1.2003	1.1791	1.2016	1.1757	1.202 (eff)
C–H^0	1.0723	1.0825	1.0722	1.0847	1.097
C–O^1	1.3419	1.3203	1.3417	1.3207	1.343
O^1–H^1	0.9560	0.9555	0.9505	0.9452	0.972
∠O^0CO^1	124.61	125.05	124.27	124.93	124.6
∠H^0CO^0	124.95	124.73	124.95	124.77	124.1
∠CO^1H^1	114.87	108.50	114.53	109.49	106.3
		Methyl Formate–$H^0C^0O^0(O^1C^1H_3{}^m)$			
C^0–O^0	1.2034				1.200 (sub)
C^0–H^0	1.0740				1.101
C^0–O^1	1.3335				1.334
O^1–C^1	1.4478				1.437
H^m–C^1	1.0761				1.086
∠$O^0C^0O^1$	124.94				125.9
∠$C^0O^1C^1$	119.79				114.8
∠HC^1H^c	110.49				110.7

[a] Bond lengths in Å and angles in deg. [b] All values are obtained from microwave and other gas-phase spectroscopic methods.[19] The abbreviations in parentheses refer to the way the data were interpreted: eq stands for equilibrium distances between nuclear positions; eff means that the geometrical parameters were adjusted to give best fit to effective ground-state rotational constants; sub means that the parameters were determined by Kraitchman's equations. [c] Average over the three angles.

a bridging oxygen atom, the unshared pairs of which may be presumed to be difficult to describe without d participation. Not surprisingly, better agreement with experiment for most bond angles appears to be found when d orbitals are included, since these "polarizing" functions allow more freedom of angular orientation. These findings indicate that at least for these kinds of compounds appreciable improvements in bond distances and angles are not to be obtained by employing larger atom-optimized basis sets; instead, some subtle improvements seem to be needed in the choice of polarizing functions.

SCF Energies and Conversion to Enthalpies at 25 °C. The SCF and MP2 energies calculated for use in this study are listed in Table II. In this tabulation the reference state for each system is the set of isolated electrons and nuclei at 0 K. The practical value of these calculated energies can be ascertained by considering the chemical reactions between the molecules of Table II for which experimental enthalpies are available.[21,22] For each such reaction, the reaction enthalpies as measured and as computed with different electronic approximations may be intercompared. Since the thermodynamic data[21] for nearly all of these molecules for which heats of formation are reported are available only for 25 °C, the corrections of Table III for nuclear motion (including zero-point and thermal vibrations, rotation, translation, and the PV term) have been applied to each reaction to convert the computed value of ΔE_0 to $\Delta H^\circ{}_{298}$.

Reaction Enthalpies. The comparison with experiment and between basis sets for some reactions of molecules and of ions involved in the hydrolysis processes studied herein are given in Tables IV and V, respectively.

Reaction i of Table IV describes the conversion of the cis to the trans conformer of formic acid.[23] The calculated energies for this reaction obtained with the various basis sets (with and without MP2 electron correlation) agree with each other within 1.0 kcal/mol, except for the 4-31+G basis with MP2, a value which lies only 0.5 kcal/mol below this small range. Reaction ii of Table IV describes the formation of formic acid from carbon monoxide and water, a process involving extensive redistribution of the electrons, associated with a change in coordination number of the carbon from 1 to 3 and the loss of an H–O bond coupled with a gain of an H–C and an O–C bond. Therefore, the range from the highest to the lowest computed value of $\Delta H^\circ{}_{298}$ is considerably larger than the range found for eq i so that it becomes important to select the basis set that would have been most appropriate to use if only one calculation (including geometrical optimization) had been employed. Obviously, it would not have been the 4-31+G basis set, with or without the MP2 correction. On the other hand reaction iii represents the overall hydrolysis of methyl formate, a process involving no changes in coordination numbers and no gains or losses of any particular bond. For this reaction the computed energies for the 4-31G basis with and without the MP2 correction agree within 1 kcal/mol with the experimental value. Note that these nonionic reactions using MP2 or basis sets larger than 4-31G do not consistently give improved agreement with the reported experimental values.

The reactions of Table V involve ionic species and are numbered so as to be a continuation of Table IV. Reactions iv–vi correspond to dissociation of a neutral molecule into a proton and an anionic molecule. Since anions are swollen (because the total electron charge is greater than the nuclear), the basis set employed to describe them should allow for their larger radii. Chandrasekhar et al. have shown[16] that for the special case of protonation reactions (including those listed here, iv–vi) this may be neatly accomplished simply by adding a diffuse sp set of primitive Gaussian functions to the basis set. The energy data of eq iv–vi show the diffuse 4-31+G and 4-31+G* basis sets as giving considerably lower values (generally coming much closer to the experimental number) than the excessively high ones obtained with the other basis sets. However, the diffuse sets in conjunction with the MP2 approximation generally overcompensate. The energy errors of the basis sets without diffuse s and p functions reflect the apportionment of the anionic swelling around the molecule. For example, the difference δ_{l-e}, between the theoretical enthalpy in the 4-31G basis with MP2 and the experimental value is 27.6 kcal/mol for the ionization of water to give the hydroxy anion, in which the ionic charge must be strongly localized on the oxygen atom. For the ionization of methanol to give methoxide (in which there is some charge delocalization), δ_{l-e} = 26.6 kcal/mol; while for the ionization of formic acid to give an anion in which there is 50/50 charge resonance between the two oxygen atoms, δ_{l-e} = 4.6 kcal/mol. However, it should be emphasized that the same principles apply to other types of reactions involving anions. Thus, for example, for the reaction of a hydroxy ion with carbon monoxide to give the formate ion, δ_{l-e} is 22.8 kcal/mol. Note also that these energy differences are all positive values as would be expected from the unsuitability of the 4-31G basis set for energies of anions with localized negative charge.

Since, with respect to the enthalpies, reaction viii = vi − v, reaction ix = iii − iv + v, and reaction x = vi − iv, the values of δ_{l-e} for reactions viii–x may be similarly obtained additively.

Geometry of the Orthoformate Ionic Molecules

The $[HCO(OH)_2]^-$ anion (R = R″ = H) is the simplest intermediate species in reactions such as the first step of eq 1 and hence is useful as a reference system in checking the accuracy of computed results for systems of this type. Its structure was

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Table II. Energies (in hartrees) for Formation from Electrons and Nuclei (with no Nuclear Motion) of Geometrically Optimized Gaseous Molecules[a] in Several Extended Basis Sets

	basis set					
molecule	4-31G	4-31G*	6-311G	6-311G*	4-31+G[b]	4-31+G*
HO^-	−75.229 79	−75.242 30	−75.342 47	−75.353 28	−75.290 16[c]	−75.303 41
with MP2 corr	−75.354 31	−75.426 07	−75.482 69	−75.555 66	−75.445 59	−75.516 25
H_2O	−75.908 64	−75.932 88	−76.010 96	−76.032 40	−75.918 07[c]	−75.942 79
with MP2 corr	−76.035 99	−76.117 20	−76.149 60	−76.234 36	−76.051 42	−76.133 16
CO	−112.552 36	−112.622 97	−112.699 49	−112.769 48		−112.629 97
with MP2 corr	−112.763 68	−112.900 02	−112.925 61	−113.072 10		−112.910 76
CH_3O^-	−114.218 41	−114.264 16			−114.252 27	−114.297 49
with MP2 corr	−114.439 25	−114.578 50			−114.492 86	−114.628 44
CH_3OH	−114.870 82	−114.917 72			−114.878 99	−114.925 77
with MP2 corr	−115.085 89	−115.225 37			−115.101 01	−115.239 64
HCO_2^-	−187.901 98	−187.989 67	−188.150 87	−188.235 43	−187.929 86[c]	−188.023 63
with MP2 corr	−188.244 24	−188.467 20	−188.522 18	−188.758 83	−188.288 70	−188.519 25
trans-HCO(OH)	−188.475 62	−188.572 47	−188.719 80	−188.811 87	−188.482 18[c]	−188.583 17
with MP2 corr	−188.815 10	−189.044 81	−189.084 15	−189.327 96	−188.826 71	−189.063 32
cis-HCO(OH)	−188.464 63	−188.562 49	−188.709 28	−188.801 94	−188.472 23	−188.573 46
with MP2 corr	−188.804 77	−189.035 08	−189.074 32	−189.318 49	−188.818 14	−189.053 36
$HCO(OCH_3)$	−227.442 72				−227.452 68	
with MP2 corr	−227.871 47				−227.891 59	
$[HCO(OH)_2]^-$	−263.793 68	−263.898 05	−264.146 15	−264.242 09	−263.827 31[c]	−263.938 82
with MP2 corr	−264.255 36	−264.565 05	−264.648 27	−264.972 81	−264.313 21	−264.632 12
$[HCO(OH)(OCH_3)]^-$	−302.757 14				−302.791 82	
with MP2 corr	−303.311 26					
$[HCO(OCH_3)_2]^-$	−341.718 07				−341.748 36	
with MP2 corr	−342.365 20					

[a] Except for *cis*-HCO(OH), these data refer to the most stable conformer. [b] The molecular geometry for the 4-31+G basis set was optimized in another basis set, 6-311G*, for all of the structures for which an energy is reported for this basis, and 4-31G, for the other structures. [c] In order to obtain proper ΔE values for certain equations, the energy in the 4-31+G basis had to be calculated for the 4-31G as well as the 6-311G* geometry. The 4-31+G data corresponding to the 4-31G geometry are for HO^- −75.289 90, with MP2 −75.446 73; H_2O, −75.919 07, with MP2 −76.053 40; CO, −112.558 77, with MP2 −112.774 91; *trans*-HCO(OH), −188.485 61, with MP2 −188.834 52; HCO_2^-, −187.932 68, with MP2 −188.296 35; and $[HCO(OH)_2]^-$, −263.832 38.

Table III. Computed Energy Corrections due to Zero-Point plus Thermal Motions[a]

species	energy
CO	5.4
HO^-	6.9
H_2O	16.4
HCO_2^-	16.3
trans-HCO(OH)	25.3
cis-HCO(OH)	25.1
CH_3O^-	26.4
CH_3OH	37.0
$[HCO(OH)_2]^-$	35.2
$HCO(OCH_3)$	45.3
$[HCO(OCH_3)(OH)]^-$	55.1
$[HCO(OCH_3)_2]^-$	75.0[b]

[a] In kcal/mol, computed in 4-31G basis by assuming a temperature of 298.15 K. [b] Value estimated by extrapolation.

optimized in each of four basis sets of increasing complexity, 4-31G, 4-31G*, 6-311G, and 6-311G*, and the resulting molecular geometries are presented in Table VI. A search for other rotational isomers was carefully carried out, using the default geometrical-optimization procedure of GAUSSIAN 82, in two basis sets, 4-31G and 6-311G*, and an additional conformer was found only when employing the 6-311G* basis. Structural parameters of the resulting isomer, which is higher in energy than the more stable one by 4.0 kcal/mol, are shown in parentheses in Table VI.

From inspection of Table VI, we see that a greater change in all of the molecular parameters results from addition of polarizing d orbitals than from going from the 4-31G to the larger 6-311G basis set. For each parameter, about the same change was found in going from 4-31G to 4-31G* as from 6-311G to 6-311G*, but this change was quite different from parameter to parameter, being largest for the ∠COH. This is another example of the need for d-orbitals to give a proper description of the angle about a bridging oxygen atom, as mentioned above in the discussion of Table I. A Mulliken population analysis of the electronic distribution of the more stable $[HCO(OH)_2]^-$ structure as computed (at the 4-31G structure) in a minimal Slater representation—the only kind of basis set for which Mulliken populations are directly meaningful—shows that the lone oxygen (O^0) has a relatively high charge of −0.60ϵ (where +1ϵ is the charge of one proton), as compared to a charge of −0.38ϵ on each of its two OH oxygens. In the more stable conformer of HCO(OH), a charge of −0.23ϵ resides on the carbonyl oxygen and −0.28ϵ on the OH oxygen. This information plus the C^0–O^0 bond distance of Table VI, as compared to the other C-O distances of this table and of Table I, indicates that structurally this lone oxygen of $[HCO(OH)_2]^-$ may formally be considered as being negatively ionized by loss of a proton from orthoformic acid.

Table IV. Comparison between Calculated and Experimental Enthalpies (in kcal/mol) for Three Reactions[a] not Involving Ionic Species

cis-HCO(OH)(g) → *trans*-HCO(OH)(g) (i)			
exptl	−3.9[b]		
4-31G	−6.7	MP2	−6.3
4-31G*	−6.1	MP2	−5.9
6-311G	−6.4	MP2	−6.0
6-311G*	−6.0	MP2	−5.7
4-31+G	−6.0	MP2	−5.2
4-31+G*	−5.9	MP2	−6.0
$CO(g) + H_2O(g) \rightarrow HCO(OH)(g)$ (ii)			
exptl	−6.3		
4-31G	−5.7	MP2	−6.2
4-31G*	−6.9	MP2	−13.8
6-311G	−2.4	MP2	−2.1
6-311G*	−2.8	MP2	−10.0
4-31+G[c]	−1.4	MP2	−0.4
4-31+G*	−3.0	MP2	−8.7
$HCO(OCH_3)(g) + H_2O(g) \rightarrow HCO(OH)(g) + CH_3OH(g)$ (iii)			
exptl	+3.1		
4-31G	+3.7	MP2	+4.1
4-31+G[c]	+5.1	MP2	+6.5

[a] Except for *cis*-HCO(OH), these data refer to the most stable conformers. [b] See ref 23 for the microwave study giving this value and for a review of other quantum-chemical calculations. [c] For all of the entries in the equation, the 4-31+G computations were done using 4-31G optimized geometries. For 4-31+G entries without the *c* superscript, the geometrical optimization was done by using the 6-311G* basis set.

Table V. Comparison between Calculated and Experimental Enthalpies (in kcal/mol) for Several Reactions[a] Involving Ionic Species

$H_2O(g) \rightarrow H^+(g) + HO^-(g)$ (iv)			
exptl	+391.3		
4-31G	+417.1	MP2	+418.9
4-31G*	+424.4	MP2	+424.8
6-311G	+410.6	MP2	+409.6
6-311G*	+417.2	MP2	+417.0
4-31+G	+385.1	MP2	+371.3
4-31+G*	+392.3	MP2	+378.2
$CH_3OH(g) \rightarrow H^+(g) + CH_3O^-(g)$ (v)			
exptl	+379.2		
4-31G	+399.4	MP2	+405.8
4-31G*	+400.1	MP2	+395.9
4-31+G[b]	+383.3	MP2	+371.6
4-31+G*	+384.2	MP2	+373.5
$HCO(OH)(g) \rightarrow H^+(g) + HCO_2^-(g)$ (vi)			
exptl	+345.2		
4-31G	+351.6	MP2	+349.8
4-31G*	+357.3	MP2	+354.1
6-311G	+348.6	MP2	+344.2
6-311G*	+353.3	MP2	+348.7
4-31+G	+338.2	MP2	+329.2
4-31+G*	+342.7	MP2	+333.0
$CO(g) + HO^-(g) \rightarrow HCO_2^-(g)$ (vii)			
exptl	-52.4		
4-31G	-71.2	MP2	-75.2
4-31G*	-74.1	MP2	-84.5
6-311G	-64.3	MP2	-67.5
6-311G*	-66.7	MP2	-78.3
4-31+G[b]	-48.7	MP2	-42.9
4-31+G*	-52.6	MP2	-53.9
$HCO(OH)(g) + CH_3O^-(g) \rightarrow HCO_2^-(g) + CH_3OH(g)$ (viii)			
exptl	-34.0		
4-31G	-47.8	MP2	-47.6
4-31G*	-42.8	MP2	-41.9
4-31+G	-45.1	MP2	-42.4
4-31+G*	-41.5	MP2	-40.5
$HCO(OCH_3)(g) + HO^-(g) \rightarrow HCO(OH)(g) + CH_3O^-(g)$ (ix)			
exptl	-9.0		
4-31G	-14.0	MP2	-18.4
4-31+G[b]	+2.4	MP2	+6.4
$HCO(OH)(g) + HO^-(g) \rightarrow H_2O(g) + HCO_2^-(g)$ (x)			
exptl	-46.1		
4-31G	-65.5	MP2	-69.1
4-31G*	-67.1	MP2	-70.7
6-311G	-62.0	MP2	-65.4
6-311G*	-62.7	MP2	-68.2
4-31+G	-46.5	MP2	-41.8
4-31+G*	-49.6	MP2	-45.2

[a] These data refer to the most stable conformers. [b] For all of the entries in the equation, the 4-31+G computations were done by using 4-31G optimized geometries. For 4-31+G entries without the *b* superscript, the geometrical optimizations were done using the 6-311G* basis set.

The structural parameters of the methyl hydrogen orthoformate anion, $[HCO(OCH_3)(OH)]^-$, are presented in Table VII as calculated in the 4-31G basis. Since this orthoformate is the intermediate in the aqueous hydrolysis of methyl formate, the first data column of this table is devoted to its predecessors, methyl formate and water, and the last data column to the products, formic acid and methanol, with the structural parameter that is equivalent between reactants, intermediate, and products given on the same line. The main changes in going from reactants to intermediate and from intermediate to products that appear in this table are related to the tetracoordination of the central carbon atom (C^0) of the intermediate as compared to tricoordination in the pertinent reactant and product molecules and to the anionic form of the intermediate. Due to these factors, (a) the bond distances in the intermediate are consistently larger than in the reactants or products and (b) the bond angles centered on the C^0 carbon appropriately change between those of trigonal-planar and those of tetrahedral geometries, as usually distorted. In addition,

Table VI. Geometrical Parameters[a] Calculated for the More Stable Conformer of the Dihydrogen Orthoformate Anion, $[H^0C^0O^0(O^1H^1)_2]^-$, in Four Basis Sets

parameter	4-31G	4-31G*	6-311G	6-311G*
C^0–O^0	1.3102	1.2775	1.3191	1.2794 (1.2581)[b]
C^0–H^0	1.0886	1.1043	1.0852	1.1024 (1.1099)
C^0–O^1	1.4677	1.4421	1.4626	1.4410 (1.4624)
C^0–$O^{1'}$[c]				(1.4525)
H^1–O^1	0.9549	0.9503	0.9492	0.9407 (0.9396)
H^0–$O^{1'}$[c]				(0.9412)
$\angle H^0C^0O^0$	118.69	117.97	118.46	117.84 (117.41)
$\angle H^0C^0O^1$	103.40	103.24	103.73	103.44 (102.11)
$\angle H^0C^0O^{1'}$[c]				(104.80)
$\angle O^1C^0O^0$	111.94	112.36	111.65	112.16 (113.46)
$\angle O^{1'}C^0O^0$[c]				(113.74)
$\angle O^1C^0O^1$[d]	106.34	106.56	106.67	106.74 (103.75)
$\angle H^1O^1C^0$	104.83	100.37	105.35	101.78 (101.49)
$\angle H^{1'}O^{1'}C^0$[c]				(105.84)
tor $\angle H^1O^1C^0O^0$[e]	±14.79	±12.48	±15.27	±13.58 (−20.44)
tor $\angle H^{1'}O^{1'}C^0O^-$[c,e]				(156.96)

[a] Bond lengths in Å, angles in deg. [b] Values in parentheses refer to the less stable conformer. [c] The primed superscript refers to the OH group pointed away from the lone oxygen (O^0) in the less stable conformer. [d] The bond angle $\angle O^1C^0O^1$ refers to the OC^0O angle involving the oxygens of both OH groups. [e] Dihedral angles between H–O–C^0 and O–C^0–O^0 planes. The OH groups in the molecule are rotated in opposing directions.

Table VII. Geometrical Parameters[a] for the Stable Species in the $HCO(OCH_3) + H_2O \rightleftharpoons HCO(OH) + CH_3OH$ Hydrolysis Reaction

parameter	$HCO(OCH_3)$ + H_2O	$[HCO(OCH_3)(OH)]^-$ intermediate	$HCO(OH)$ + CH_3OH
C^0–O^0	1.2034	1.3028	1.1932 (1.2003)
C^0–H^0	1.0740	1.0875	1.0801 (1.0723)
C^0–O^1	1.3335	1.4773	
C^0–O^2		1.4739	1.3458 (1.3419)
H^1–O^1			0.9505[c]
H^2–O^2	0.9505[b]	0.9544	0.9507 (0.9560)
O^1–C^1	1.4478	1.4143	1.4300[c]
H^m–C^1	1.0761	1.0839	1.0804[c]
$\angle H^0C^0O^0$	124.43	118.38	122.83 (124.95)
$\angle H^0C^0O^1$	110.63	104.79	
$\angle H^0C^0O^2$		100.58	114.62 (110.44)[c]
$\angle O^1C^0O^0$	124.94	111.22	
$\angle O^2C^0O^0$		115.49	122.55 (124.61)
$\angle O^1C^0O^2$		104.87	
$\angle H^2O^2C^0$		104.51	116.66 (114.87)
$\angle H^1O^1C^1$			112.61[c]
$\angle C^1O^1C^0$	119.79	115.23	
$\angle H^mC^1O^1$	108.43	109.79	109.91[c]
tor $\angle H^2O^2C^0O^0$[d]		4.05	0.00 (180.00)
tor $\angle C^1O^1C^0O^0$[e]	0.00	−43.28	
tor $\angle H^mC^1O^1C^0$[f]	59.67, 180.00, 300.32	34.37, 154.71, 274.03	
$\angle H^1O^2H^2$	111.23[b]		
tor $\angle H^mC^1O^1H^1$[g]			60.41, 180.00, 299.59

[a] Computed in 4-31G basis. Bond lengths in Å, angles in deg. The superscripts designating the molecular locations of the atoms refer to the intermediate as follows: $[H^0C^0O^0(O^1C^1H_3{}^m)(O^2H^2)]^-$. Values in parentheses with respect to *trans*-formic acid. [b] Values for water, all others in this column for methyl formate. [c] Values for methanol, all others in this column for formic acid. [d] Dihedral angle between the H^2–O^2–C^0 and O^2–C^0–O^0 planes. The OH and OCH_3 groups are rotated in opposing directions. [e] Dihedral angle between the C^1–O^1–C^0 and O^1–C^0–O^0 planes. [f] Methyl torsional angles. First H is adjacent to C–O^0, rotated away from the OH. [g] Dihedral angle between H^m–C^1–O^1 and C^1–O^1–H^1 planes.

Table VIII. Geometrical Parameters[a] of the Reactants and Intermediate in the Reaction $HCO(OCH_3) + OCH_3^- \rightleftharpoons HCO(OCH_3)_2^-$

parameter	$HCO(OCH_3)$ + OCH_3^-	$HCO(OCH_3)_2^-$ intermediate
$C^0{-}O^0$	1.2034	1.2944
$C^0{-}H^0$	1.0740	1.0891
$C^0{-}O^1$	1.3335	1.5080
$C^0{-}O^2$		1.4590
$O^1{-}C^1$	1.4478	1.4109
$O^2{-}C^2$	1.3613[b]	1.4162
$H^m{-}C^1$	1.0761	1.0852
$H^m{-}C^2$	1.1219[b]	1.0831
$\angle H^0C^0O^0$	124.43	117.56
$\angle H^0C^0O^1$	110.63	103.83
$\angle H^0C^0O^2$		101.54
$\angle O^1C^0O^0$	124.94	113.94
$\angle O^2C^0O^0$		116.19
$\angle O^1C^0O^2$		101.65
$\angle C^1O^1C^0$	119.79	116.67
$\angle C^2O^2C^0$		115.24
$\angle H^mC^1O^1$	108.43	110.09
$\angle H^mC^2O^2$	115.72[b]	109.68
tor $\angle C^1O^1C^0O^0$ [c]	0.00	-21.79
tor $\angle C^2O^2C^0O^0$ [c]		-45.35
tor $\angle H^mC^1O^1C^0$ [d]	59.67, 180.00, 300.32	24.15, 145.27, 264.14
tor $\angle H^mC^2O^2C^0$ [d]		28.86, 149.10, 268.62

[a] Computed in the 4-31G basis. Bond lengths in Å, angles in deg. [b] Values for methoxy, all others in this column for methyl formate. [c] Dihedral angle between the C–O–C and O–C–O^0 planes. Both methyl carbon atoms in the intermediate rotate in the same direction. [d] Methyl torsional angles. Note that in methyl formate the methyl hydrogens are staggered with respect to the carbonyl oxygen, whereas in both methyl groups of the intermediate the positive methyl-hydrogen torsion of one hydrogen is nearly compensated by the negative carbon torsional angle, thereby causing this hydrogen to be in close proximity to the carbonyl oxygen.

(c) the methyl group goes from a staggered to an eclipsed orientation with respect to the lone oxygen, O^0, when passing from the reagents or products to the intermediate.

In Table VIII are listed the computed parameters of the third and most complex intermediate species described herein, the dimethyl orthoformate anion $[HCO(OCH_3)_2]^-$, which corresponds formally to the species formed by the interaction of methyl formate with a methoxy anion. This is the simplest model compound for the first intermediate in eq 2 involving the interaction of an ester with a serine esterase (symbolized by one of the methoxy groups). The same three processes, (a)–(c), are found in this case as well. In addition the changes between reactants and intermediate are seen to be very similar to those given in Table VII.

Internal Rotation of the Orthoformate Ionic Molecules

Optimized Conformers. Searches employing geometrical optimizations for all three of the anionic molecules $[HCO(OH)_2)]^-$, $[HCO(OH)(OCH_3)]^-$, and $[HCO(OCH_3)_2]^-$ demonstrate that there is more than one stable conformer for each. Those geometrical parameters that differ the most between the conformers of each structure are presented in Table IX, along with the energy differences from the most stable conformer to the other ones of a particular species. These parameters consist of the torsional angle describing the rotation about the bond between the carbon atom of the formyl moiety and the pertinent bridging oxygen atom, as well as the distance between the lone (ionized) oxygen and the nearest hydrogen of an OH or OCH_3 moiety. In this project and in work on phosphorus oxyacids[20] and their esters,[24] we find that the OH or OCH_3 hydrogens are attracted toward the lone oxygen and that the lone O···H distance is a more readily understood parameter than are the respective torsion angles. As can be seen in Table IX for the 4-31G basis set, the lone O···H distance for the closely lying OH hydrogen is ca. 2.2 Å and for the closely lying OCH_3 hydrogen ca. 2.3 Å. The energy difference between the conformers of an orthoformate structure is also quite small, being generally 4 kcal/mol or less. In each case energy barriers between conformations correspond to torsional angles of approximately ±120°.

Table IX. Torsional Angles, Nonbonding Distances (Å), and Energy Differences (kcal/mol) for the Conformers of the Orthoformate Anions Studied

tor $\angle O^0COH$	tor $\angle O^0COC$	$O^0\cdots H{-}O$ dist	$O^0\cdots H{-}C$ dist	ΔE
		$[HCO(OH)_2]^-$ Orthoformate Anion		
14.8, -14.8		2.24, 2.24		0
13.5, -13.5[a]		2.15, 2.15		0
156.9, -19.8[a]		3.00, 2.19		4.0
		$[HCO(OCH_3)(OH)]^-$ Orthoformate Anion		
4.0	-43.3	2.21	2.33	0
21.8	179.3	2.28	3.87	3.9
154.4	-28.5	3.06	2.27	4.2
		$[HCO(OCH_3)_2]^-$ Orthoformate Anion		
	-21.8, -45.4		2.20, 2.33	0
	34.7, 179.5		2.35, 3.81	2.6

[a] Data in this line obtained with a 6-311G* basis set. Other data obtained with a 4-31G basis set.

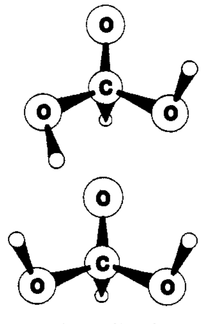

Figure 1. Stable conformers of the dihydrogen orthoformate anion, as computed in the 6-311G* basis and reproduced to scale, in order of increasing energy from bottom to top.

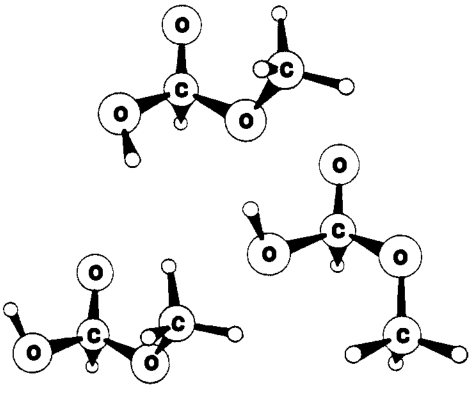

Figure 2. Three stable conformers of methyl hydrogen orthoformate anion, as computed in the 4-31G basis and reproduced to scale, in order of increasing energy from bottom to top.

Figure 1 depicts accurate computed representations of both of the two stable conformers of the $[HCO(OH)_2]^-$ ionic molecule. In the conformer of lower energy (the two-up orientation) the pair of OH groups are adjacent to the lone oxygen (O^0 in the table) but slightly rotated away from it in opposite directions; while in the other conformer (one up/one down) one OH is similarly positioned and the other is opposite to the lone oxygen and slightly rotated away from the O–C axis of this oxygen in the opposite direction from the other OH group.

The $[HCO(OCH_3)(OH)]^-$ structure exhibits a similar gross geometrical arrangement of its conformers, of which there are three because in the one-up/one-down combination the methoxy group can either be up or down. These conformers are presented in Figure 2.

For the $[HCO(OCH_3)_2]^-$ structure there are two conformers, of which the one-up/one-down arrangement is quite similar to

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[24] Van Wazer, J. R.; Ewig, C. S. *J. Am. Chem. Soc.*, in press.

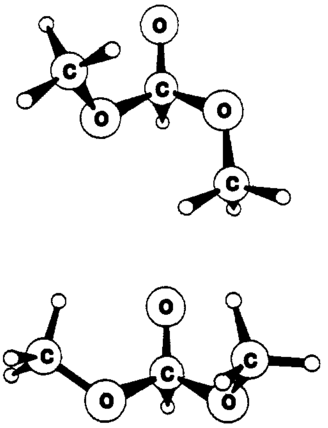

Figure 3. Stable conformers of dimethyl orthoformate anion, as computed in the 4-31G basis and reproduced to scale, in order of increasing energy from bottom to top.

that of the other orthoformate ionic molecules but the two-up arrangement differs in that the pair of methoxy groups lie to the same side of the lone oxygen. The structures of these two conformers are shown in Figure 3.

Analysis of Torsional Potentials. It is also of wide interest to determine why these intermediate species exhibit their particular conformations and this has been the subject of considerable learned speculation.[25] One way of attempting to ascertain the factors that lead to a preferred molecular conformation has been suggested by Radom et al.[26] They proposed that the potential energy as a function of torsional angle τ be expanded in a Fourier series, which we shall write as

$$V(\tau) = V_0 + V_1 \cos(\tau) + V_2 \cos(2\tau) + V_3 \cos(3\tau)$$

In this series, the coefficients V_1, V_2, and V_3 may then be associated with different physical effects giving rise to the variation in V. As we have pointed out previously,[20] in this type of expansion there is no reason that the first two types of effects should necessarily be aligned with the molecular framework, so it may be more accurate to employ the more general expansion

$$V(\tau) = V_0 + V_1 \cos(\tau + \alpha_1) + V_2 \cos 2(\tau + \alpha_2) + V_3 \cos 3(\tau) \quad (3)$$

where α_1 and α_2 are relative phases that may be included in the fit to the torsional potential.

V_1 and V_2 have been referred to respectively as "dipole–dipole" and stereoelectronic terms.[26] But it is more useful to define V_1 simply as a dipolar term, since it clearly reflects the periodicity of the interaction either of a monopole with a dipole or between two dipoles. Similarly V_2 is a quadrupolar term and has the periodicity of the interaction between a quadrupole and either a monopole or another quadrupole. The interaction of a monopole with another monopole, such as an internal hydrogen bond, is a mixture of the two preceding types of terms with $V_1{:}V_2 = 2{:}1$. Probably the best known origins of V_2 terms are stereoelectronic or hyperconjugation effects. The component of the torsional energy about a bond to a tetrahedrally coordinated atom given by V_3 represents steric repulsion. (Hence α_3 exhibits a value of zero if τ is set to zero when atoms or groups are adjacent, and thus α_3 need not be included in eq 3.)

Table X. Coefficients of the Torsional Potentials[a] for the $[HCO(OH)_2]^-$ and $[HCO(OCH_3)(OH)]^-$ Intermediates

basis	group	V_1	V_2	V_3	α_1	α_2	barrier
		Internal Rotation of $[HCO(OH)_2]^-$					
4-31G	OH	−4.11	−1.92	0.33	−34.87	5.55	10.5
4-31G*		−3.69	−1.94	0.37	−30.21	6.43	9.7
6-311G		−4.06	−1.91	0.42	−31.61	5.13	10.3
6-311G*		−3.64	−1.86	0.45	−29.02	6.31	9.5
		Internal Rotation of $[HCO(OCH_3)(OH)]^-$					
4-31G	OH	−3.52	−2.97	0.38	−13.48	4.01	10.8
	OCH_3	−3.86	−1.87	1.89	18.90	27.06	11.0

[a] Defined in the text. V_1, V_2, V_3, and barrier in kcal/mol, α_1 and α_2 in deg.

Torsional Potential for $[HCO(OH)_2]^-$. From the optimized structural parameters in the appropriate basis set, the total SCF energy of the $[HCO(OH)_2]^-$ structure was computed for rigid rotations of one OH group of 60°, 120°, 180°, 240°, and 300° in each of the basis sets 4-31G, 4-31G*, 6-311G, and 6-311G*. The resulting energies were then fit to eq 3, defining $\tau = 0°$ when the hydrogen is adjacent to the lone oxygen. The findings are shown in the upper part of Table X, in which it can be seen that the results obtained with the four basis sets are remarkably similar. The dominant term in each case is V_1, which stabilizes a conformation in which the hydrogen is adjacent to the lone oxygen, as might be expected from the attraction of a positive charge on the hydrogen ($+0.12\epsilon$) to a large negative charge (-0.62ϵ) on the oxygen. The V_2 term is also significant and stabilizes a conformation in which the hydrogen is adjacent to the lone oxygen, but it is only half as large as V_1 and has a positive phase. (The signs of α_1 and α_2 may of course be exchanged depending on which OH group is to be rotated.) Note that the energy is almost exactly of the form $V_1{:}V_2 = 2{:}1$, showing the existence of predominantly monopolar intramolecular forces. The steric component V_3 is much smaller and, as might be expected, is positive, thereby destabilizing the conformation with the hydrogen adjacent to the lone oxygen. The barrier to rotation through 360°, i.e., the difference between the maximum and minimum torsional energies, is quite large in each basis set, ranging from 9.5 to 10.5 kcal/mol. Reoptimizing the energy with respect to other structural parameters at the top of the barrier has relatively little effect on the barrier height. For example, in the 6-311G* basis it decreases from 9.5 to roughly 8.8 kcal/mol. Therefore it appears that large monopolar intramolecular forces maintain the $[HCO(OH)_2]^-$ molecule in this conformation.

Torsional Potential for $[HCO(OCH_3)(OH)]^-$. It is also possible to use this procedure to estimate the magnitudes of the effects that give rise to the preferred conformation of the $[HCO(OCH_3)(OH)]^-$ anionic molecule. The torsional angle of both the OH and OCH_3 groups were separately increased in steps of 60° as all other structural parameters were held constant. The resulting SCF energies were then fit by means of eq 3. The results are presented in the lower part of Table X, where there are seen to be some striking similarities with the values shown in the first row of data (corresponding to the $[HCO(OH)_2]^-$ structure). The V_1 term is again the most important, both V_1 and V_2 being relatively large and negative, thus stabilizing a conformation in which the OH and OCH_3 groups are adjacent to the lone oxygen. Also the energy is roughly of the form $V_1{:}V_2 = 2{:}1$ for rotation of not only the OH but also the OCH_3 group. As might be expected, the steric term, V_3, of the OCH_3 group is much larger than that of the OH and tends to destabilize the orientation in which this group is adjacent to the lone oxygen. Again there is quite a large barrier to rotation through 360° that tends to hold both groups in place at the preferred conformation.

Torsional Potential for $[HCO(OCH_3)_2]^-$. The coefficients of the torsional potential were not computed for the $[HCO(OCH_3)_2]^-$ structure, since the methyl groups in the equilibrium conformation are rotated in the same direction, bringing them into close proximity, as can be seen from Figure 3. Since a strong steric interaction between the two torsional angles is anticipated, this should make a one-dimensional analysis based on eq 3 inappropriate.

Calculated Enthalpies for the Hydrolysis Steps

The enthalpies, ΔH°_{298}, computed for the gaseous reactions that can be considered as representing various steps in eq 1 and 2 are listed in Table XI, the equations of which are numbered so as to

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[25] For example, see: Deslongchamps, P.; Atlani, P.; Fréhel, D.; Malaval, A. *Can. J. Chem.* **1972**, *50*, 3405–3408. For a comprehensive review: Kirby, A. J. *The Anomeric Effect and Related Stereoelectronic Effects at Oxygen*; Springer-Verlag: Berlin, 1983.

[26] Radom, L.; Hehre, W. J.; Pople, J. A. *J. Am. Chem. Soc.* **1972**, *94*, 2371–2381.

Table XI. Enthalpies (kcal/mol) for Formation of Hydrolysis Intermediates and for a Decomposition of Methyl Formate[a]

$HCO(OH)(g) + HO^-(g) \rightarrow [HCO(OH)_2]^-(g)$ (xi)			
4-31G	-52.4	MP2	-50.9
4-31G*	-49.3	MP2	-56.1
6-311G	-49.6	MP2	-48.1
6-311G*	-45.3	MP2	-53.0
4-31+G	-29.5	MP2	-17.1
4-31+G*	-29.8	MP2	-30.0
$HCO(OH)(g) + CH_3O^-(g) \rightarrow [HCO(OCH_3)(OH)]^-(g)$ (xii)			
4-31G	-36.2	MP2	-32.3
4-31+G[b]	-30.5		
$HCO(OCH_3)(g) + HO^-(g) \rightarrow [HCO(OCH_3)(OH)]^-(g)$ (xiii)			
4-31G	-50.2	MP2	-50.7
4-31+G[b]	-28.0		
$HCO(OCH_3)(g) + CH_3O^-(g) \rightarrow [HCO(OCH_3)_2]^-(g)$ (xiv)			
4-31G	-32.4	MP2	-30.9
4-31+G[b]	-23.9		
$HCO(OCH_3)(g) + HO^-(g) \rightarrow HCO_2^-(g) + CH_3OH(g)$ (xv)			
Exptl	-43.0		
4-31G	-62.9	MP2	-65.5
4-31+G[b]	-43.4		

[a] These data refer to the most stable conformers and the equations are numbered to follow those of Table V. [b] For all of the entries in the equation, the 4-31+G computations were done by using 4-31G optimized geometries. When the 4-31+G entry is not associated with a *b* superscript, the geometry was optimized in the 6-311G* basis set.

be a continuation of Tables IV and V. Note that, for all except the first of the reactions of Table XI, values for only three types of results are reported: those obtained with the 4-31G basis (with and without the MP2 correction) and 4-31+G bases (SCF values only). The pertinent energy data are contained in Table II and the nuclear-motion corrections in Table III.

Internal Criterion for Choosing the Appropriate Basis Set. In order to determine whether or not addition of a very diffuse function to the basis set should give a consistently improved approximation to the correct ΔH°_{298} value, we have employed as criterion the absolute value of the difference $|\delta_{(G-G+)}|$ in kilocalories per mole between the enthalpies calculated in the 4-31G and the 4-31+G bases as obtained from Table II (in both cases using data based on the 4-31G optimized geometries). These differences are presented in Table XII, along with some pertinent Mulliken atomic charges from STO-3G computations on the 4-31G-optimized geometries to show the amount of localization of the anionic charge for representative molecules. Note in Table XII that the unionized molecules have low values of $|\delta_{(G-G+)}|$, 4–7 kcal/mol, whereas the anionic molecules exhibit much higher ones, 19–38 kcal/mol.

Not surprisingly, the largest value of $|\delta_{(G-G+)}|$ in Table XII is 37.7 kcal/mol for the HO^- anion, which also exhibits the greatest negative charge on its O (-0.80ϵ) and a negative charge of -0.20ϵ on the H, although the charge on unionized OH hydrogens is usually around $+0.20\epsilon$. For the formate anion, HCO_2^-, for which $|\delta_{(G-G+)}|$ equals 19.3 kcal/mol, the charge on each of the O's is -0.52ϵ, thus lying between the charge of ca. -0.35ϵ for a bridging oxygen in a neutral molecule and the charge of -0.80ϵ for the oxygen of a hydroxyl ion. However, for this ionic molecule there is a charge of -0.12ϵ on the formyl hydrogen, as compared to $+0.08\epsilon$ for this hydrogen in the unionized acid.

One could imagine that in an anion having an increased number of nearby oxygen atoms on which to distribute the charge, the value of $|\delta_{(G-G+)}|$ might be quite low; but this is not the case for the orthoformate anions, as shown in the last three lines of Table XII. The values of $|\delta_{(G-G+)}|$ for these molecules range from 19.0 kcal/mol for the dimethyl derivative to 24.3 kcal/mol for the dihydroxyl. For all of them the charge is about -0.60ϵ on the lone oxygen, about -0.40ϵ on the OH and -0.34ϵ on the OCH_3 oxygens. On the basis of this information and the data of Table V (particularly eq viii–x), we conclude that (a) $|\delta_{(G-G+)}|$ varies roughly linearly with the localization of the negative charge and (b) the diffuse basis sets are the preferred ones to use from Table XI, giving values of ΔH°_{298} that are the most physically meaningful.

Free Energy Calculated Theoretically. It seems from the 4-31+G and 4-31+G* values of the first four reactions of Table XI that the gaseous "tetrahedral" intermediates shown as being formed in these reactions are stable by more than about 10 kcal/mol (and perhaps by 20–30 kcal/mol) with respect to the reactants or products of the aqueous hydrolysis processes as depicted in eq 1 and 2, and we surmise that this relative stability of the gas-phase intermediates also would be found for essentially any ester being hydrolyzed, i.e., for most values of R, R′, and R″ in these equations. Using the same computed vibrational-spectral data on which Table III was based, we calculated the $T\Delta S$ term needed to obtain the ΔG from the ΔH computed for the formation of the $[HCO(OCH_3)(OH)]^-$ intermediate from methyl formate and the hydroxy anion. The resulting ΔG°_{298} was found to lie +10 kcal/mol above the ΔH value ($\Delta G^\circ_{298} = -18$ kcal/mol, using the 4-31+G basis set).

Energy Diagrams for Hydrolysis. The relative energy levels (ΔH°_{298} computed in the 4-31+G basis set) for the steps of the ester-hydrolysis reactions of eq 1 (base catalyzed) and eq 2 (enzymatically catalyzed) are shown in Figures 4 and 5, respectively. In Figure 5, the deprotonated serine group of the enzyme, symbolized in ionized form by EO^-, is simulated by a CH_3O^- group.

Recomputing the energy of the more stable conformer of $[HCO(OH)_2]^-$ in the 4-31G basis as the length of the C–O bond of one OH group was increased from equilibrium to infinity showed no barrier between this orthoformate ionic molecule and the reactants from which it could form. This agrees with the findings of Umeyama and Nakagawa,[6] who studied this interaction employing an STO-3G basis. As a result of this finding, and similar ones by Lien et al.[7] and Scheiner et al.,[10] we decided not to investigate the parts of the ester-hydrolysis energy surface lying between the schematic plateaus of Figures 4 and 5.

Extrapolation of Experimental Aquation Energies. From the available experimentally based thermodynamic data[21] some information may be obtained about the enthalpy $\Delta H_{(g\rightarrow aq)}$ of the process Q(g) → Q(aq), for Q being the kind of ion or neutral molecule involved in this study. For the H^+ ion $\Delta H_{(g\rightarrow aq)}$ is -367.2 kcal/mol due to its affinity to the water lattice, and for HO^- it is -21.3 kcal/mol. For carbon monoxide, water, methanol, formic

Table XII. Basis-Set Enthalpy Differences (4-31G - 4-31+G, kcal/mol) and Mulliken Charge Assignments for Selected Molecules

		Mulliken charge on					
molecule or ion	$|\delta_{(G-G+)}|$[a]	H^O[b]	H^m	H^C	lone O	bridg O^H[c]	bridg O^C
HO^-	37.7	-0.20			-0.80		
H_2O	6.5	+0.19				-0.38	
CH_3O^-	21.2		-0.10		-0.65		
CH_3OH	4.7	+0.20	+0.07			-0.32	
HCO_2^-	19.3			-0.12	-0.52		
trans-HCO(OH)	4.1	+0.23		+0.08	-0.26	-0.32	
$[HCO(OH)_2]^-$	24.3	+0.12		-0.06	-0.62	-0.40	
$[HCO(OCH_3)(OH)]^-$	21.8	+0.12	+0.02	-0.05	-0.60	-0.41	-0.34
$[HCO(OCH_3)_2]^-$	19.0		+0.04	-0.05	-0.58		-0.34

[a] $\delta_{(G-G+)}$ stands for ΔH°_{298} calcd in 4-31G basis minus ΔH°_{298} calcd in 4-31+G basis. [b] H^O corresponds to the charge (in units of one electron) on the OH hydrogen, H^m to the average charge on the methyl hydrogens, and H^C to the charge on the formyl hydrogen H^0 of the $H^0C^0O^0$ group. [c] Bridg O^H refers to the charge (in units of one electron) on the oxygen of an OH group, and bridg O^C to the charge on the methoxy oxygen.

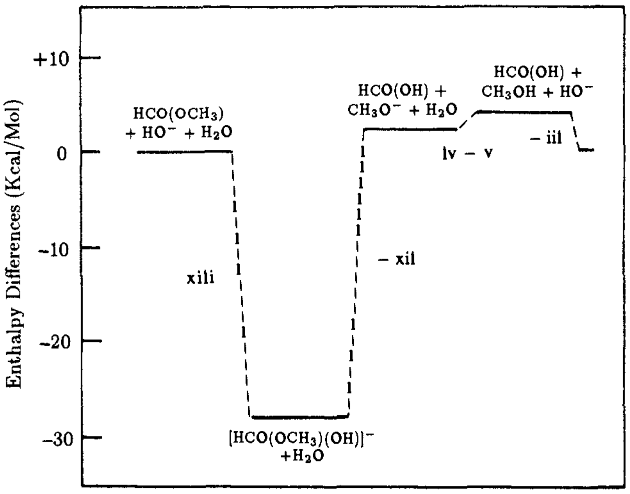

Figure 4. Energy-level diagram for the gas-phase basic hydrolysis of methyl formate. The lower-case Roman numerals refer to equations in Tables IV, V, and XI, with all values corresponding to 4-31+G computed enthalpies.

acid, acetic acid, and methyl formate $\Delta H_{(g \rightarrow aq)}$ is respectively −2.5, −10.5, −13., −11.2, −12.8, and −8.0 kcal/mol, with only a few hundredths of a kilocalorie per mole difference between the un-ionized (m = 1) and ionized (m = 1) aqueous acids. Although the experimental value of ΔH for eq iv and vi of Table V (both involving an H^+) would shift from +391.3 to +13.4 and from +345.2 to −0.03 kcal/mol by going from a gaseous to an aqueous system at 298 K, we find that the ΔH for eq ii, iii, vii, and x of Tables IV and V would shift from −6.3 to −4.5, +3.1 to −0.5, −52.4 to −17.8, and −46.1 to −13.4 kcal/mol, respectively. Extrapolating to the data of Figures 4 and 5, we think that going to an aqueous phase from the gas phase would stabilize the plateaus involving HO^- ions by about 10 kcal/mol relative to the other plateaus, which would otherwise approximately keep their respective positions. In other words, in Figure 4 the intermediate might be destabilized by about 10 kcal/mol with respect to the precursors and successor in the overall hydrolysis processes so that although they would not lie above their neighbors in an energy-level diagram, the free energy may allow for equilibrium with them.

Discussion

Molecular Geometry. The data of Table I show that even the relatively small 4-31G* basis set gives values of the molecular geometry that are comparable in accuracy to those obtained by high-resolution microwave and other precision spectroscopic methods for these systems. Indeed comparison of the structures defined in various ways shows that the accuracy is such that the interpretational procedure employed by the spectroscopist becomes important (hence the reference to the reported procedure in the last column of Table I). Nowadays, in comparing ab initio geometries with experimental ones, the exact definition of the term "internuclear distance" must be considered.

Hydrolysis Intermediates. Our results also show that all three of the orthoformate anionic molecules that we have studied as hydrolysis intermediates are stable, approximately tetrahedral, and not transition states. We have described several structural features that they all share, most notably that a hydrogen of each OH or OCH_3 group prefers a conformation adjacent to the lone oxygen. This, plus the Fourier coefficients, suggests that the conformational energy is dominated by monopolar, presumably electrostatic, attraction to this negatively charged oxygen. Increasing the size of either R or R″ in the model-compound formula given immediately below eq 2 (vide supra) lowers by only a few kilocalories per mole the energy of the reaction to form the intermediate. Thus at the SCF approximation in the 4-31+G basis, the energy of adding HO^- to formic acid is −29.5 kcal/mol and to methyl formate −28.0. Adding OCH_3^- to formic acid corresponds to −30.5 kcal/mol and to methyl formate to only −23.9 kcal/mol.

Some qualitative features of these reactions are also exhibited by simpler ones. For example, Williams et al. have reported[27] that employing a 4-31G basis for the reaction $HO^- + H_2CO \rightarrow [H_2CO(OH)]^-$ an approximately tetrahedral species is formed that is more stable than the reactants by 52 kcal/mol. In this case the length of the lone oxygen C–O bond is 1.325 Å, that of the C–(OH) bond is 1.516 Å, and the hydrogen atom of the OH group is adjacent to the lone oxygen. These are clearly similar to the results shown in Table VI.

The qualitative features of the orthoformate anions have a noteworthy biological implication. Phosphatic compounds that block esterase enzymes[1,28] are believed to enhance their binding to the enzyme active sites through structures[29] that mimic those of hydrolysis intermediates. Thus both species exhibit an approximately tetrahedral coordination about the reactive-site phosphorus or carbon atom. Also, as shown above, bond lengths to this carbon in the orthoformate are considerably longer than in the analogous ester, being considerably closer to, but somewhat shorter than, those to the phosphorus of the blocking agents. Thus similarities not only in bond angles but also in bond lengths about the reactive site may contribute to the efficacy of the inhibition process, the somewhat longer but less polar P–O bonds (as compared to the intermediate's C–O bonds) serving to augment the binding of the inhibitor to the substrate.

To our knowledge the structure of only one of these three intermediate species has been studied previously. Lien et al.[7] studied $[HCO(OCH_3)(OH)]^-$ in a minimal STO-3G basis set with partial structure optimization. Although their results agree with the qualitative finding that this intermediate is stable and possesses an approximately tetrahedrally coordinated carbon, they reported a different stable conformation. This conformation, which was assumed prior to optimization of other structural parameters, is characterized by the OCH_3 group opposed to the lone oxygen, thus corresponding to our first higher energy conformer. Based on their results they stated the conclusion, which is supported by our findings, that the structure of this anionic molecule is stabilized by a strong internal hydrogen bond. However, we found that the OCH_3 group also is stabilized in an orientation adjacent to the lone oxygen by such attraction. Lien et al. found six stable conformers, whereas our results indicate the existence of only three. This is in accord with our earlier observation[20] that minimal STO basis sets tend to give only an upper limit on the number of stable conformers. Also at variance with our findings is their reaction-energy diagram in which the intermediate is shown lying well above the reactants and products (even though their quantum calculations must have shown the opposite).

Stereoelectronic Effect. There has been a great deal of interest in recent years in the structures, particularly the conformations, of tetrahedral intermediates as predicating the course of ester hydrolysis reactions.[25,30] Although a comprehensive treatment of this extensive body of prior work is beyond the scope of the present paper, we note that there are three basic premises that these models have presupposed, premises that may be compared with our computed results: (a) The intermediate is assumed to be of relatively high energy compared to both products and reactants and thus to approximate a transition state. However, we have found that the intermediate has a lower not higher energy in the gas phase and a structure that is definitely not a transition state. This has also been noted in connection with the formamide + HO^- reaction in the gas phase by Alagona et al.[8] and Weiner et al.[9] The latter employed molecular mechanics to show that the same qualitative conclusions should apply in aqueous solution as in the gas phase. (b) The conformation has been assumed to

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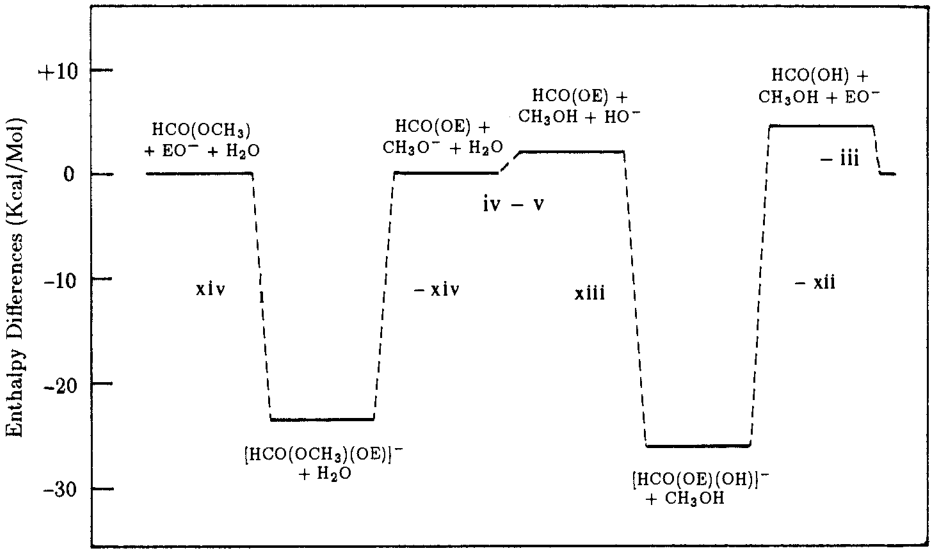

Figure 5. Energy-level diagram for the gas-phase "enzymatic" hydrolysis of methyl formate, with the serine group of the enzyme symbolized in ionic form by EO^- and simulated by a CH_3O^- anion. The lower case Roman numerals refer to equations in Tables IV, V, and XI, with all values corresponding to 4-31+G computed enthalpies.

be governed by stereoelectronic factors, particularly the "anomeric effect".[25,31] This is based on the postulate that lone-pair orbitals on the oxygen atoms of the OH or OR groups contribute to an orbital which is primarily an antibonding component of the bond to another oxygen. Thus when the lone pair is antiperiplanar to this oxygen, the conformation is stabilized. The exact directionality of the lone pair is not precisely predetermined, since its components which are of σ or π character are of similar energy and may mix freely. Thus the directionality is generally to be determined post hoc. However we have shown that the barrier to internal rotation of both OH and OCH_3 groups is about 10 kcal/mol, which would require an extraordinarily large and directionally specific lone-pair effect. An energy difference this large is more characteristic of an internal hydrogen bond—an interpretation supported by our observation (also made by Lien et al.) that in the $[HCO(OCH_3)(OH)]^-$ species the C–O–H bond angle is quite small in the lowest energy conformation (hydroxyl hydrogen adjacent to the lone oxygen) compared to the magnitude of this angle in other conformers or in related compounds. Hence we conclude that the argument for a stereoelectronic effect in determining the conformations of the intermediates is thus far not substantiated.

Finally (c) it has been assumed that a C–O bond antiperiplanar to the lone pair on another oxygen atom is weaker than when the bond is in a different orientation. Our results only partially support this view. For example, in the case of $[HCO(OCH_3)(OH)]^-$, in the conformation with the OH opposed to the lone oxygen and thus with its lone pair antiperiplanar to the oxygen of the OCH_3, the C–(OCH_3) bond length is increased by over 0.05 Å while the C–(OH) bond length decreases by 0.003. In the conformation with the CH_3 group opposed to the lone oxygen, the C–(OH) bond length is increased by 0.012 while the C–(OCH_3) increases by only 0.005. However, as seen from Table VI, in the $[HCO(OH)_2]^-$ structure both C–O bond lengths increase. In $[HCO(OCH_3)_2]^-$ essentially no such change in bond lengths is seen. We conclude that this type of interaction, if present, is not consistently indicated by variations in bond lengths or any of the other structural parameters we have studied.

Thermodynamic Stability of the Intermediates. Another aspect of the properties of tetrahedral intermediates which should be emphasized is their thermodynamic stability with respect to both reactants and hydrolysis products, even though the free intermediate is apparently never isolated or observed. In enzymatic hydrolysis there appears to be little need for an active site to lower the energy of such an intermediate further, as the common terminology "transition-state stabilization" would imply. A more useful description might invoke immobilization of the intermediate, with the free energy of the hydrolysis process—chiefly the entropy contribution—being altered by the presence of the enzyme. In the case of base-catalyzed hydrolysis in aqueous solutions, Weiner et al.[9] have recently shown that, at least in the case of the hydrolysis of formamide, the effect of the solvent is to lower the energies of the products more than that of the intermediate. This stabilization makes the intermediate less stable with respect to reactants, as well as driving the reaction forward to completion. Since there are strong similarities between that reaction and the base-catalyzed hydrolysis of esters, the same explanation is likely to apply to the systems we have studied as well. Indeed as discussed above aquation of the orthoformate intermediates should reduce their stability relative to products and reactants by about 10 kcal/mol.

Finally, in gas-phase reactions such as methyl formate with HO^- studied by ion cyclotron resonance and mass spectroscopy, tetrahedral intermediates have not been observed, with the reaction products, aside from those resulting from proton abstraction from alkyl groups, consisting of only HCO_2^- and CH_3OH.[3-5] These products are predicted by our calculations, presented in Table V eqs. viii and ix and Table XI eq xiii and xv, which show them to be more stable than the intermediate by 15 kcal/mol and more stable than the other anticipated products, HCO(OH) and CH_3O^-, by 45 kcal/mol. Since the HO^- ions in these gas-phase experiments are produced by bombardment of water molecules by energetic (5–6 eV) electrons, they are quite "hot" so that, if the intermediate is formed, it will probably fall apart quickly into the observed, thermodynamically more stable reaction products because of its excessive internal energy.[32] Hence this type of experimental data as well is consistent with our conclusions concerning the stability of the orthoformate intermediate species.

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Registry No. HCO(OH), 64-18-6; $[HCO(OH)_2]^-$, 102575-27-9; $[HCO(OCH_3)(OH)]^-$, 102575-28-0; $[HCO(OCH_3)_2]^-$, 102575-29-1.

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