Stereochemistry of the α-Hydroxycarboxylic Acids and Related Systems

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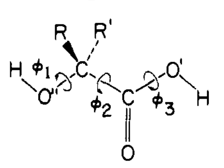
Abstract: The conformational energetics of three α-hydroxycarbonyl systems (glycolic acid, the glycolate anion, and glycolaldehyde) have been investigated using ab initio molecular orbital theory at the 4-31G level. The major aim of the study was to ascertain the role of intramolecular factors in the planarity or near-planarity of the carbon-oxygen framework observed in the α-hydroxycarboxyl moiety of a large number of crystalline α-hydroxy acids and carboxylates, irrespective of the conformation of the α-hydroxy group. The calculations for the isolated species show that the equilibrium conformations correspond to internally hydrogen-bonded structures. Departures from equilibrium obtained by rotating the α-hydroxyl group are calculated to cost appreciably less energy than distortions which destroy the planarity of the carbon oxygen framework, a result consistent with the data for the molecules in the crystalline state, where stronger intermolecular hydrogen bonding takes precedence over internal hydrogen bonding. The conformational energetics of the isolated species are discussed in detail, and the nature of the internal hydrogen bonding is analyzed in terms of energy and charge density criteria and by comparison with related intermolecular hydrogen-bonded systems.

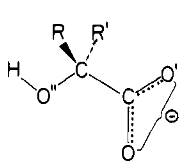
I. Introduction

Since the earliest three-dimensional x-ray crystal structure determinations of the tartaric acids and tartrates, it was recognized that the three oxygen and two carbon atoms of the α-hydroxycarboxylic acid or carboxylate moiety form a characteristically planar or nearly planar group.[1] During the subsequent 20 years, more than 20 crystal structures have been reported containing molecules or ions of type I or II, respectively, all of which show this conformational feature in varying degrees. They include the prototype glycolic acid (R, R′ = H),[2] the tartaric acids,[3] tartronic acid,[4] citric acid,[5] and numerous crystal structures of glycolates,[6] tartrates,[7] gluconates,[8] and citrates.[9]



$\phi_1 = \phi_2 = \phi_3 = 0°$

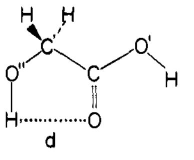
I



$\phi_1 = \phi_2 = 0°$

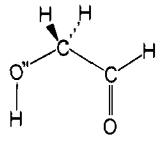
II

These crystal structures have a variety of packing and intermolecular hydrogen bonding patterns, and it seems unlikely that they are all such as to place the same conformational constraint on the α-hydroxycarboxylic acid or carboxylate group. It is appropriate therefore to seek an explanation in terms of the intrinsic properties of the molecules or ions themselves. Unfortunately no structural data are available for the isolated species I or II, but gas-phase microwave[10] and infrared[11] data have been obtained for the related system III, the prototype carbohydrate, glycolaldehyde. Again a planar framework is found, with $\phi_1 = 180°$ and $\phi_2 = 0°$ as shown in III (the analogous conformation of glycolic acid is displayed as structure Ia).[12] This suggests that intramolecular hydrogen bonding[13] may be a primary factor in the stabilization of the planar conformation in the isolated species. The theoretical calculations available for the various conformations of III support this view.[14]



$\phi_1 = 180°, \phi_2 = \phi_3 = 0°$

Ia



$\phi_1 = 180°, \phi_2 = 0°$

III

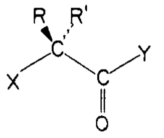
On the other hand, inspection of the crystal structural data shows that such intramolecular hydrogen bonding is rarely observed. The values of $|\phi_1|$ span a wide range from ~0 to ~173°, as determined in most cases by the intermolecular hydrogen bonding. Yet the values of ϕ_2 are all close to 0°, and bear no obvious relationship to those of ϕ_1. This indicates that there may be other intrinsic molecular properties that restrict rotation about the C–C bond, such as hyperconjugative effects and interactions between electron lone pairs or bond dipoles.

The purpose of this paper is to analyze the known conformational data for the species I, II, and III and related systems and to compare them with the results of ab initio molecular orbital calculations, carried out at the 4-31G level,[15] in the hope of discovering the role, if any, that intramolecular energetics plays in the observed persistence of the planar conformation in the crystalline state.

In the course of this analysis we shall pay particular attention to the characterization of intramolecular hydrogen bonding.

II. General Background

Before examining the experimental data and theoretical results for I, II, and III in greater detail, we broaden the scope of this study by noting that these molecules can be viewed as specific examples of a more general class of carbonyl systems, IV, for which a great amount of conformational data is available, both experimental and theoretical. The discussion is confined to various acetyl derivatives (R, R′ = H), with Y taken as H, CH_3, or an electronegative group (OH or a halogen). We first deal with the simplest case, acetaldehyde (X,



$\phi_2 = 0°$

IV

Y = H), which is characterized by an equilibrium conformation with one of the methyl CH bonds trans staggered relative to the aldehyde CH bond ($\phi_2 = 0°$).[18] The alternative statement of this situation, namely that a methyl CH bond prefers to eclipse the CO double bond, appears to be at odds with expectations based on steric interactions, although perhaps not so if the CO double bond is interpreted as two bent single bonds, which would then bear a more acceptable gauche relationship to the methyl CH bond. At any rate simple arguments from perturbation theory[19] based on the π and π^* CO bond orbitals and the corresponding π-type orbitals formed from the methyl CH bond orbitals can rationalize the observed equilibrium angle ($\phi_2 = 0°$). Theory[14,16,20] and experiment[18] both indicate a threefold rotational barrier of ~1 kcal/mol. The situation is formally the same when the substituent Y is changed to an electronegative group (e.g., NH_2 or OH), although the rotational barrier is appreciably smaller (0.3-0.4 kcal/mol).[14]

Perturbing the methyl group of acetaldehyde with an electronegative group X can have several conformational consequences. The hyperconjugative interactions between the methyl and carbonyl groups will clearly be affected, and no definitive prediction of the preferred conformation based on these interactions above seems possible. Other effects may be expected to dominate; e.g., nonbonded repulsion between the electrons of X and those of O and Y, or dipole-dipole interactions among the CX, CO, and CY bonds, which would be expected to favor $\phi_2 = 180°$ if Y were H or CH_3. Indeed, gas-phase infrared[21] and microwave[22] data for α-halo aldehydes and acetones (X = F, Cl, Br; Y = H or CH_3) indicate a large equilibrium value for ϕ_2 (estimated at $\gtrsim 150°$ for X = Cl), although another isomer with $\phi_2 \sim 0°$ was also detected. This rotational isomerism is observed in the condensed phase (liquid, solution, solid) as well. Molecular orbital calculations for fluoroacetaldehyde (X = F, Y = H)[16c] indicate an energy separation of ~4 kcal/mol between the $\phi_2 = 0°$ and $\phi_2 = 180°$ isomers. In contrast to the ketones and aldehydes, the α-haloacetyl halides (X, Y = F, Cl, Br) are found to prefer the $\phi_2 = 0°$ isomer by 1-2 kcal/mol over a second isomer with $\phi_2 \gtrsim 150°$, reflecting a delicate balance between the orientation of the CX, CY, and CO bonds.[23,24] The same qualitative ordering is observed in the liquid. In the related molecule 2-fluoroacetic acid (Y = OH) the energy separation of the two isomers is somewhat smaller (0.6 kcal/mol), possibly due to internal hydrogen bonding in the $\phi_2 = 180°$ isomer (with $\phi_3 = 180°$; see structure I).[25]

If the substituent X is changed from a halogen atom to an electronegative group like OH or NH_2, then an additional degree of the conformational freedom is introduced, and for appropriate values of ϕ_1 and ϕ_2 the group can at least formally serve as a proton donor in an intramolecular hydrogen bond, with either the carbonyl oxygen or an electronegative group Y acting as the proton acceptor. A third H-bonded conformation would have a carboxylic group (Y = OH) serving as proton donor to the electronegative α substituent ($\phi_1 = 0°$, $\phi_2 = 180°$, $\phi_3 = 180°$), as discussed above for the case of 2-fluoroacetic acid.

It is interesting to compare the acetyl halides with the structurally similar species I (both have electronegative X and Y groups), since the former systems demonstrate that preference for $\phi_2 = 0$ can occur in the absence of any possibility of intramolecular hydrogen bonding, both in the gas and liquid phase. The halogen derivatives also suggest that rotational isomerism might be observable for I and III. With molecules of the latter type having been placed in the general context of species IV, we now turn to a detailed discussion of their properties. Further interest is provided by the relationship of I and III to their isoelectronic counterparts obtained from replacing OH by NH_2 in the α position. Calculations for these amino derivatives have been carried out by Vishveshwara and Pople.[26]

III. Structural Details

Values of the conformational angles ϕ_1 and ϕ_2 and the H-bond distance d (see structure Ia) from the crystal structures are given in Table I. The standard deviations on ϕ_2 are of the order of 0.5°. Those on ϕ_1 are up to ten times greater unless a neutron diffraction study has been made, in which case they are comparable. Values of ϕ_3 for the undissociated acids are in almost all cases very close to 0°.[27]

In the majority of the structures $|\phi_2|$ is less than 10°, making the carbon and oxygen atoms close to coplanar, with the hydroxyl and carbonyl oxygen cis. A $|\phi_2|$ value of 10° corresponds to a displacement of the hydroxyl oxygen from the carboxylate plane by ~0.25 Å. The sole example of rotational isomerism (cf. Section II) is provided by the monoclinic form of *meso*-tartaric acid, where in one half of the molecule the hydroxyl and carbonyl oxygens are trans (i.e., $\phi_2 \sim 180°$).[3b] Aside from this exceptional case the largest observed value of $|\phi_2|$ is 19°, in tartronic acid.[4] The clustering of ϕ_2 values near 0° is consistent with the known conformations of the related halogen derivatives discussed in the previous section. However, in the case of I, II, and III additional stabilization of the $\phi_2 = 0°$ conformation might be obtained from internal H bonding (with $\phi_1 = 180°$ and $d \sim 2.0$ Å), even though such a conformation would involve eclipsing of the O″H and CC bonds. For example, structure III is observed for glycolaldehyde,[10] and the previously mentioned calculations indicate that the equilibrium conformation ($\phi_1 = 180°$, $\phi_2 = 0°$) lies 7.2 kcal/mol below the alternative open, staggered structure with $\phi_1 = 0°$ and $\phi_2 = 0.°$.[14] A short-range hydrogen-bond interaction undoubtedly makes some contribution to this energy difference, but one must assess the importance of other factors such as barriers to rotation, and dipole-dipole and other nonbonded interactions.

In spite of our expectations with regard to intramolecular H-bonded structures we find in fact only two unambiguous examples of such a conformation from the crystal data for molecules of the type I and II. They occur in sodium D-tartrate dihydrate, where $\phi_1 = 173°$, $\phi_2 = 8°$, and $d = 2.04$ Å,[7a] and in potassium gluconate monohydrate (form A), where $\phi_1 = 146°$, $\phi_2 = 6°$, and $d = 2.12$ Å.[8] The latter is a neutron diffraction study, which shows that this hydrogen bond is bifurcated, half intra- and half intermolecular, with an intermolecular O···H distance of 1.98 Å. Less definitive examples are from the x-ray studies of tartronic acid,[4] and the anhydrous and monohydrate citric acid structures,[5] where the intra- and intermolecular H···O distances are 2.23 and 3.02, 2.29 and 2.15, and 2.29 and 2.03 Å, respectively. The persistence of $\phi_2 \sim 0°$ even when ϕ_1 is close to 0° is noteworthy in that this latter orientation of the O″H bond directs the hydroxyl lone pairs toward the carbonyl oxygen in a situation where the two oxygens are separated by only 2.7 Å and thus appears to be slightly within the normal nonbonded (van der Waals) contact.[28] Due to the occurrence of such close contacts, one might have expected a correlation between ϕ_1 and ϕ_2. The data in Table I show clearly that this is not the case. The angle ϕ_2 is close to 0°, irrespective of ϕ_1. Close inspection of the crystal structures shows that with the exception of the cases of internal H bonding noted above, the observed ϕ_1 values are determined primarily by the requirements of intermolecular hydrogen-bond formation, either to adjacent like molecules or to water molecules. It thus appears that, as in the carbohydrates,[29] intermolecular packing is such as to provide more favorable geometry for intermolecular hydrogen-bond formation than can be obtained internally for I or II without considerable bending of valence angles from tetrahedral and trigonal.

Given this phenomenological indication that intermolecular

Table I. Crystallographic Data[a]

Molecule	Conformational angles, deg[b] ϕ_1	ϕ_2	ϕ_3	d, Å[b]	Ref	Key to Figure 2
(A) α-Hydroxycarboxylic Acids						
Glycolic acid[c]						
anhydrous (N)[d]	100	−6	−3	2.95	2	a
	100	2	−3	2.90		b
Tartaric acid[e]						
D-monohydrate (N)	25	−2	−2	3.58	3a	c
	−109	−6	7	2.81		d
meso-monohydrate	−3	−4	−6	3.34	3b	e
(triclinic)	12	−6	−1	3.29		f
meso-monohydrate	−6	9	−6	3.47	3b	g
(monoclinic)	26	170	10	3.45		h
meso-anhydrous	−19	−8	7	3.30	3b	i
(triclinic)	69	7	−39	3.34		j
Acid group in monohydrogen tartrates						
D-anhydrous (NH_4^+ monoanion)	−61	7	−4	3.37	7b	k
meso-anhydrous[f] (K^+ monoanion)	−105	1	−3	2.74	7d	l
Tartronic acid[g]						
anhydrous	147	16	−13	2.23	4	m
	−91	−19	9	2.93		n
Citric acid[h]						
anhydrous	143	12	0	2.29	5a	o
monohydrate	160	2	12	2.29	5b	p
(B) α-Hydroxycarboxylates						
Glycolate						
anhydrous (Li^+ monoanion	−99	7		2.86	6	
Tartrate						
D-dihydrate	173	8		2.04	7a	
($2Na^+$ dianion)	123	15		2.86		
D-anhydrous (NH_4^+ monoanion)	−117	−5		2.71	7b	
meso-dihydrate	−146	−10		2.48	7c	
(K^+ dianion)	130	4		2.78		
meso-anhydrous (K^+ monoanion)[f]	−118	2		2.64	7d	
Gluconate[i]						
D-monohydrate (N) Phase A	146	6		2.12	8	
(K^+ monoanion)[j] Phase B	114	3		2.64		
Citrate						
anhydrous (Na^+ monoanion)	−14	−17		3.44	9a	
monohydrate (Li^+, NH_4^+ dianion)	0	4		3.49	9b	

[a] Structures included are those for which reliable values of the parameters ϕ_1, ϕ_2, ϕ_3, and d are available. In most cases these quantities were not explicitly reported and had to be calculated from the unit-cell dimensions and the atomic coordinates. All the data are from x-ray single-crystal structure determinations except where denoted by (N) for a neutron diffraction analysis; D refers to the absolute configuration. [b] Defined in structure I. [c] CH_2OH-COOH: see structure I. [d] Two independent molecules in unit cell. [e] (CH_2OH-COOH$)_2$. Two sets of values for ϕ_1, ϕ_2. ϕ_3, and d are also available for the dimethyl ester of tartaric acid; 118, −1, −7°, 2.64 Å, and 136. 0, −1°, 2.52 Å (J. Kroon and J. A. Kanters, *Acta Crystallogr., Sect. B,* **29,** 1278 (1973). [f] Although two independent molecules are found in the unit cell, two of the carboxyl groups are coupled across a center of symmetry in a strong ionic intermolecular hydrogen bond of the type $(\text{-O}\cdots\text{H}\cdots\text{O-})^-$. The ϕ values associated with these carboxyl groups have not been included in the table since the intramolecular conformations might be expected to be dominated by the strong intermolecular interaction. Even in this case, however, the ϕ_2 values are close to 0° as usual, although one of the two ϕ_3 values is close to 180° in contrast to the other crystal data, as noted in ref 27. [g] HOOC-CHOH-COOH (α-hydroxymalonic acid). [h] HOOC-COH-(CH_2COOH$)_2$. [i] Anion of HOOC-(CHOH$)_4$-CH_2OH. [j] From two different crystal structures.

forces play an important role in the crystal conformations of I and II, it still remains to determine whether the observed distribution of conformational angles reflects or is consistent with features of the intramolecular conformational energy surface. While calculations are reported below for all three species, I, II, and III, most attention will be given to I and III, since the stronger intermolecular forces associated with the ionic species II presumably make its intramolecular energetics less relevant to its conformations in crystalline environments.

IV. Methods and Results

Standard, closed-shell, self-consistent molecular orbital theory with the 4-31G extended Gaussian basis set was used.[15] The molecular structure of glycolic acid (I; R, R′ = H) was based on the accurate neutron diffraction study of the crystal.[2] A fixed set of bond lengths and angles was adopted for all conformations and is illustrated in Figure 1 for ϕ_1, ϕ_2, and ϕ_3 = 0°. The conformational energy was calculated as a function of the angles ϕ_1 and ϕ_2 at intervals of 60° and is presented in

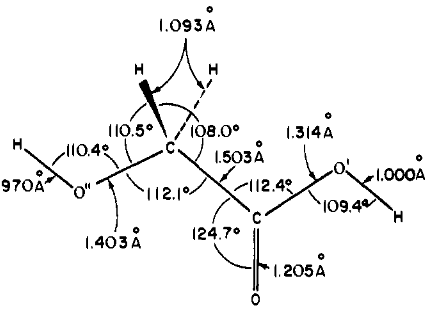


Figure 1. Bond lengths and bond angles employed in the glycolic acid calculations. A local symmetry plane (C_s point group) was assumed for each of the carbon atoms. The figure corresponds to structure Ia (ϕ_1, ϕ_2, $\phi_3 = 0°$).

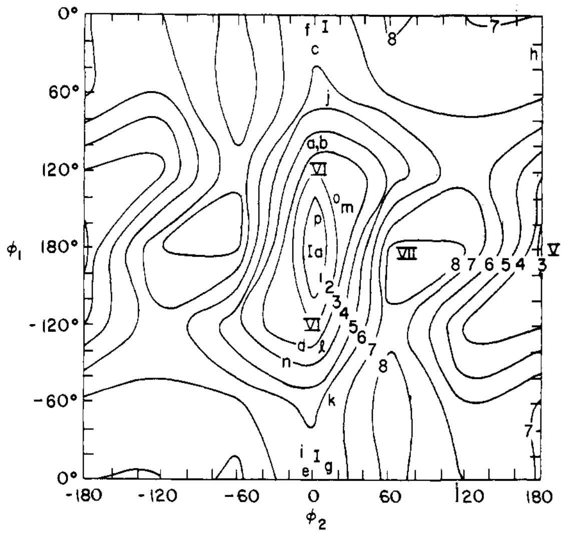


Figure 2. Conformational potential energy map for glycolic acid (based on $\phi_3 = 0°$). Contour labels refer to energy (kcal/mol) relative to $\phi_1 = 180°$, $\phi_2 = 0°$. Roman numerals designate conformational structures referred to in the text. They are not included on the left-hand side of the figure, which is related to the right-hand side by inversion through the center ($\phi_1 = 180$, $\phi_2 = 0°$).[38] The lower case letters identify crystal data points listed in Table IA (see the last column). Note that the letter "a" is near structure VI and should not be confused with structure Ia.

Table II and also as a potential energy contour map in Figure 2, with contours separated by 1 kcal/mol and ranging from 1 to 8 kcal/mol. The energies are all relative to the minimum at $\phi_1 = 180°$, $\phi_2 = 0°$. The letters in Figure 2 refer to the crystal data points for the neutral acids listed in Table I (see last column) and the Roman numerals correspond to the conformations discussed in the text. The third conformational angle (ϕ_3) was kept at 0°, in keeping with the very small values generally observed in the crystal structures.[27] However, conformations with $\phi_3 = 180°$ are considered briefly below. The calculations for the glycolate anion employed the glycolic acid framework geometry, except for the carboxylate group, which was given local C_{2v} symmetry with $r_{CO} = 1.26$ Å and ∢OCO = 125°, based on crystal structure data.[6] Calculated results are given in Table III.

The geometry for III was the same as that for I (Figure 1), except for the replacement of OH by H at the carbonyl group, with $r_{CH} = 1.10$ Å and ∢HCC = 118°, similar to the analogous values in acetaldehyde.[18] This choice for III was thought to be somewhat preferable to alternatives, such as the standard molecular geometry[30] which was used in the previous molecular orbital studies.[14] The main difference is the significant departures from 120° bond angles at the carbonyl carbon atom. At any rate, comparisons show that the relative conformational energies based on the geometry used here and on the standard geometry differ by ≲1 kcal/mol. The conformational energy of III with respect to ϕ_1 and ϕ_2 is given in Table II and also in Figure 3 as contour levels relative to the minimum at $\phi_1 = 180°$ and $\phi_2 = 0°$. Figures 4 and 5 contain various one-dimensional profiles comparing the conformational energetics of I and III, with related curves for ethanol and acetaldehyde presented for comparison. Some data pertinent to hydrogen bonding in I and III are given In Table IV.

After the calculations for III had been completed we became aware of the recent microwave structure[10b] (a refinement of earlier work[10a] which had tentatively postulated structure III), which is quite similar to the one employed here except for the geometry of the hydroxyl group. In spite of the anticipated weakness of the intramolecular H bond due to the strained geometry (∢O''H···O = 121°, ∢H···O=C = 84°); the microwave structure nevertheless suggests a rather strong interaction: i.e., a sharply reduced HO''C bond angle relative to methanol (101 vs. 107°) and a large elongation of the OH bond length (1.05 vs. 0.96 Å).[31,32] The latter effect is surprising, since even in very strong ionic hydrogen-bonding situations the OH elongation is only ~0.25 Å (e.g., the aquated hydronium

Table II. Relative Conformational Energies of Glycolic Acid and Glycolaldehyde

Conformational angles, deg[a]		Energy, kcal/mol[b]	
ϕ_1	ϕ_2	Glycolic acid[c]	Glycolaldehyde[d]
0	0	6.0	6.4
60		5.7	6.4
120		2.0	2.4
180		0.0	0.0
0	60	8.2	8.1
60		7.2	7.3
120		4.3	4.2
180		8.2	7.6
−120		7.7	8.0
−60		8.6	9.3
0	120	7.0	4.7
60		7.3	4.7
120		6.5	3.7
180		7.9	7.3
−120		3.8	5.3
−60		6.1	5.4
0	180	7.0	2.3
60		7.2	2.8
120		4.0	2.7
180		2.7	5.4

[a] Angles are defined in Section II (see structure I). All data are based on $\phi_3 = 0°$. [b] Relative to the minimum energy conformation ($\phi_1 = 180°$, $\phi_2 = 0°$). [c] Total energy for $\phi_1 = 180$, $\phi_2 = 0°$ is −302.20134 au. [d] Total energy of $\phi_1 = 180°$, $\phi_2 = 0°$ is −227.42259 au.

Table III. Relative Conformational Energies of the Glycolate Anion

Conformational angles, deg[a]		
ϕ_1	ϕ_2	Energy, kcal/mol[b]
0	0	18.2
120		9.3
180		0.0
0	90	19.5
120		13.6
180		13.6

[a] See footnote a, Table II. The angle ϕ_3 is not defined for the anion. [b] See footnote b, Table II. The total energy for $\phi_1 = 180°$, $\phi_2 = 0°$ is −301.64808 au.

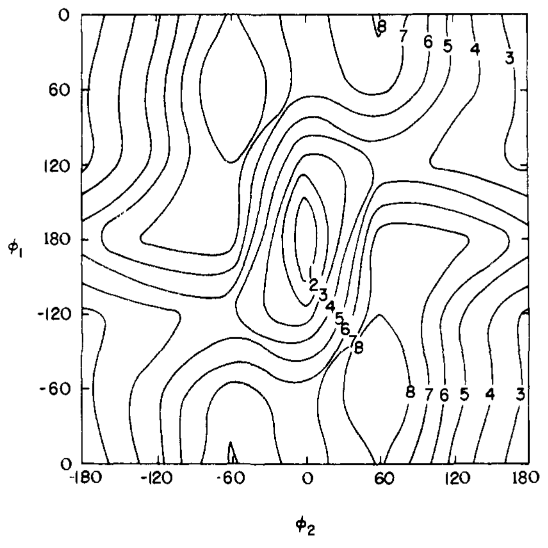


Figure 3. Conformational potential energy map for glycolaldehyde. Contours are labeled as in Figure 2.

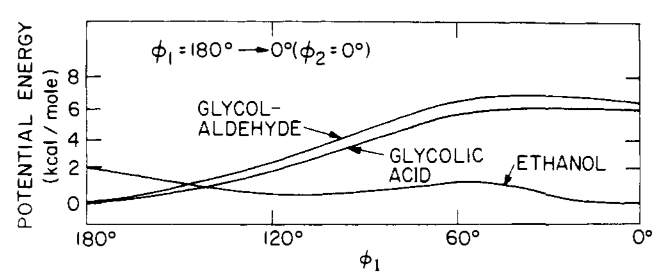


Figure 4. One-dimensional conformational energy profiles for glycolic acid, glycolaldehyde, and ethanol: variation with respect to ϕ_1 with ϕ_2 fixed at 0°.

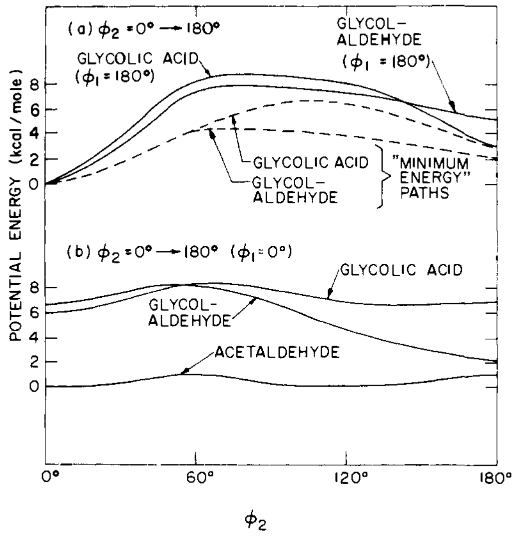


Figure 5. One-dimensional conformational energy profiles for glycolic acid, glycolaldehyde, and acetaldehyde: (a) variation with respect to ϕ_2, with ϕ_1 set equal to 180° or defined by the minimum energy path; (b) variation with respect to ϕ_2, with ϕ_1 fixed at 0°.

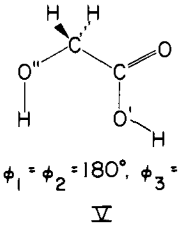
ion),[33,34] and neutral H-bonded systems such as the water dimer exhibit very little lengthening (~0.01 Å).[35] Microwave structures for 2-amino- and 2-haloethanols have also given indications of unusual OH elongation, presumably due to H bonding.[36] Accordingly, we simultaneously varied the total energy of structure III ($\phi_1 = 180°$, $\phi_2 = 0°$) with respect to ∢HO″C and r_{OH}. The calculations indicated no significant stretching of OH or reduction of the bond angle relative to the methanol values.[37] These details of the OH-bond geometry clearly warrant further attention in the future, both theoretical and experimental. In previous studies, the 4-31G basis has been shown to give good quantitative account of OH-bond lengthening due to hydrogen bonding.[34b]

V. Discussion

In the following discussion we first point out the close correspondence between the crystal structure data and the ab initio conformational energy surfaces of glycolic acid and the glycolate anion.[38] The surface of glycolic acid is then examined further, with particular emphasis on the characterization of internal hydrogen bonding. Finally, comparisons are made between glycolic acid and related systems such as glycolaldehyde (III) and the nonhydroxylic species mentioned in Section II.

A. Analysis of the Crystal Structure Data. The energy calculations show (Figure 2) that the isolated glycolic acid molecule prefers a conformation with $\phi_1 = 180°$ and $\phi_2 = 0°$, which is the optimum geometry for intramolecular hydrogen-bond formation. In the crystalline state, and probably in aqueous solutions also, intermolecular hydrogen bonding is energetically more favorable. This, however, requires a conformational change, depending on the molecular packing, to permit the hydroxyl hydrogen to be directed toward the hydrogen-bond acceptor atom on the adjacent molecule. The energy contour map, Figure 2, shows that in general such a conformational change can be achieved more easily by changing ϕ_1 than ϕ_2. A 90° change in ϕ_1, for example, can be made at the cost of somewhat less than 4 kcal/mol, whereas for ϕ_2 this would require more than 8 kcal/mol. The distribution of the experimental points along the ϕ_1 axis is therefore consistent with the theoretical result in that this is the direction in which we observe the greatest range of conformational change, while ϕ_2 remains relatively constant and close to 0°. The clustering of ϕ_2 values near 0° reflects the fact that for any value of ϕ_1, the minimum internal energy always occurs for $\phi_2 = 0°$. The greatest intramolecular energy cost is seen to be associated with those experimental points whose $|\phi_1|$ values are near 0°, but this energy (~ 6 kcal/mol) can clearly be recovered by intermolecular H bonds. Consistent with this picture is the fact that the molecule whose crystal structure conformation lies the closest to the intramolecular energy minimum—i.e., tartronic acid (vide supra)—is one whose α-hydroxy group is not involved in any intermolecular hydrogen bonding.

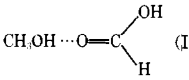
A comparison of the one-dimensional profiles for glycolic acid in Figures 4 and 5a gives further illustration of the relative sensitivities of the conformational energy with respect to ϕ_1 and ϕ_2. The energy in the vicinity of structure Ia rises much more sharply with ϕ_2 even on the minimum energy path (i.e., based on the minimum energy ϕ_1 value for each ϕ_2). Analogous calculations[26] for the isoelectronic species, glycine, reveal a much flatter energy as a function of ϕ_2 because the two protons on the donor NH_2 group allow considerably greater flexibility in H-bond formation, including the possibility of multiple H bonding (i.e., two bent NH···O bonds to the carbonyl oxygen). It is apparent that while the ϕ_1 profile for glycolic acid is monotonic (Figure 4), the ϕ_2 profile finally descends as ϕ_2 approaches 180° (Figure 5a), corresponding to the presence of a second local minimum (see Figure 2 and structure V). This



$\phi_1 = \phi_2 = 180°$, $\phi_3 = 0°$

V

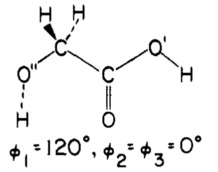
Table IV. Population Analysis of the $-O''H\cdots O-$ Linkage[a,b]

Species	Atomic population shifts (Δq)[c] $\Delta q_{O''}$	Δq_H	Δq_O	Overlap populations $OP_{O\cdots H}$	$OP_{O\cdots O''}$	$\Delta OP_{O''H}$[d]	H-bond energy, kcal/mol[e]
(A) Intramolecular H Bond							
Glycolic acid (Ia)	0.034	−0.025	0.036	0.032	−0.012	0.005	(6.1)
Glycolaldehyde (III)	0.034	−0,024	0.041	0.042	−0.008	0.002	(6.4)
Propane-1,3-diol[b]							
(gauche reference structure)	0.061	−0.061	0.052	0.040	−0.052	0.006	(9.5)
(all-trans reference structure)	0.020	−0.049	0.011	0.040	−0.052	−0.005	(0.04)
(B) Intermolecular H Bond							
 $CH_3OH\cdots O{=}C(OH)H$ (IX)[f]	0.069	−0.068	0.043	0.046	−0.030	−0.017	5.7
$(H_2O)_2$	0.065	−0.056	0.011	0.050	−0.018	−0.015	8.1

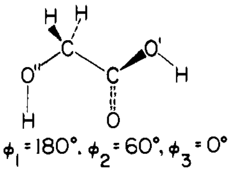
[a] All population changes (Δq, ΔOP) and H-bond energies are defined relative to nonhydrogen-bonded reference species: the reference for structures Ia and III is the $\phi_1 = 0$, $\phi_2 = 0°$ conformation (structure I, for glycolic acid); the reference for each dimer is the associated pair of isolated monomers. [b] Two different nonhydrogen-bonded reference structures have been considered for propane-1,3-diol, as defined in ref 42a. [c] Positive Δq corresponds to an increase in atomic electron population. [d] Positive ΔOP corresponds to an increase in the population of the O″H bond. [e] The intramolecular hydrogen-bond energies are placed in parentheses to emphasize their dependence on the selection of a reference conformation. [f] Based on the same $O\cdots O$ distance (2.73 Å) as in structure Ia, but with a linear hydrogen bond ($H\cdots O$ = 1.76 Å). For comparison, a similar calculation based on the $H\cdots O$ distance of structure Ia (2.22 Å), and hence with $r_{O\cdots O}$ = 3.19 Å, yields essentially the same bond energy (5.8 kcal/mol), but with somewhat smaller populations and population shifts: 0.038, −0.030, 0.020, 0.039, −0.006, and −0.012, respectively.

minimum, like that represented by structure Ia, involves internal hydrogen bonding, which will be discussed in the following paragraphs. In the crystal structures, neither of these intramolecular hydrogen-bonded conformations is populated, due primarily to the fact that more favorable intermolecular H bonds can generally be formed.

Some insight into the skewing of the central basin in the ϕ_1 direction (Figure 2) is offered by considering, for example, the structures obtained from Ia by varying either ϕ_1 or ϕ_2 by 60°, VI and VII, respectively. Structure VII is calculated to be 6.2 kcal/mol less stable than VI. The O″···O and distances are very similar for the two structures (2.73 Å for VI and 2.96 Å for VII), and the O″···H distances (>2.6 Å) indicate that these 60° distortions from Ia have eliminated any hydrogen bonding. Perhaps the most important factor contributing to the 6 kcal/mol difference is that the process Ia → VI leads to relief of eclipsing between the O″H and CC bonds, while the process Ia → VII creates additional eclipsing of single bonds (CO′ and CH). The relative energies of structures Ia, VI, and VII could not be correlated in terms of appreciable differences in the overlap population of the CC bond. Such differences might be expected if differential hyperconjugation were playing an important role.



VI



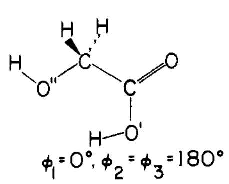
VII

The remarks made above with regard to the distribution of the ϕ_1 and ϕ_2 values for the undissociated α-hydroxy acids can also be applied to the α-hydroxycarboxylate anions (see Table IB and Table III). The fact that the ϕ_1 values for the anion are appreciably closer to 180° than in the case of the neutral (8 of the 11 ϕ_1 values are within ~60° of 180°) probably reflects the much sharper rise in energy with respect to ϕ_1 in the vicinity of $\phi_2 = 0$, as revealed by the calculated results for the glycolate anion.

B. Intramolecular Hydrogen Bonding. In spite of the general absence of internal hydrogen bonding in the crystal structure data already discussed, it seems clear that such bonding has an important bearing on the conformational behavior of molecules like glycolic acid when isolated or in a nonhydrogen-bonding environment, and we consider the matter in some detail.

Geometrical Characterization. The geometry of the minimum energy conformation (structure Ia) suggests a rather distorted internal hydrogen bond: $r_{O''\cdots O}$ = 2.73; $r_{O''\cdots H}$ = 2.22 Å; ∢O″H···O = 112; and ∢H···OC = 81°. In an unstrained situation, the latter two angles would be expected to approach ~180 and ~120°, respectively.[39] The second local minimum at ϕ_1 = 180°, ϕ_2 = 180° noted in Section VA (structure V) also possesses a bent hydrogen-bond geometry ($r_{O\cdots H}$ = 1.96; $r_{O\cdots O}$ = 2.53 Å) and lies 2.7 kcal/mol above Ia (an analogous separation of 2.5 kcal/mol is found for glycine[26]). The latter fact may appear surprising, since $r_{O''\cdots H}$ is shorter than in Ia (1.96 Å). However, within a carboxyl group the carbonyl oxygen is expected to be a better acceptor than the hydroxyl oxygen.[40] In addition, the CO single bonds are eclipsed in structure V, and with the rigid rotor geometry adopted here the O″···O contact is quite close (2.53 Å).

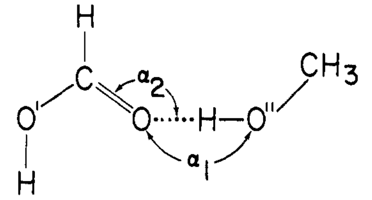
Rotation of both ϕ_1 and ϕ_3 by 180° in structure V leads to another hydrogen-bonded interaction of the two hydroxyl groups (structure VIII), with the donor and acceptor roles of O′ and O″ interchanged. Structure VIII lies ~2.7 kcal/mol above structure V (or 5.4 kcal/mol above Ia). Although O″ is expected to be a better proton acceptor than O′ (see ref 40), the fact that V is *more* stable than VIII can be rationalized as follows. The eclipsing of the O″H and CC bonds destabilizes V relative to VIII by ~2.1 kcal/mol (from comparable studies of ethanol[14]), but the cis conformation of the carboxyl group (H—O—C=O) stabilizes V by ~6.3 kcal/mol (from comparable studies of formic acid[14]), since VIII contains the less favorable trans conformation. If it were not for internal hydrogen bonding, V should therefore be more stable than VIII by 4.2 kcal/mol. The net calculated value of 2.7 kcal/mol implies that the hydrogen bond in VIII is *more* stable than that in V by ~1.5 kcal/mol.[41]



VIII

Charge Distribution and Energetics. Charge distribution and energetics provide additional criteria for assessing the extent of hydrogen bonding. The reliability of the 4-31G basis for analyzing differences in hydrogen-bond strength has recently been documented in a study which systematically considered a variety of atomic orbital basis sets.[17c] Typical weak intermolecular hydrogen bonds are characterized by a stabilization energy of a few kilocalories per mole relative to isolated monomers, a gain in the electronic population on the electronegative donor and acceptor atoms (oxygen, in the present case), and a decrease in the population of the donated proton.[17] These criteria can also be applied to intramolecular H bonding, although relatively few detailed studies of such systems exist.[42] The intramolecular H-bond energy cannot, of course, be based on isolated monomers, but may be defined in terms of an appropriate non H-bonded conformation of the molecule, thereby introducing a certain degree of arbitrariness. The process of converting the nonhydrogen-bonded conformation into the hydrogen-bonded one not only leads to short-range interactions between the donor atom proton and the acceptor atom lone pair, an important component in any hydrogen bond, but can also cause appreciable energy changes due to variation in dipole–dipole orientations and local barriers to internal rotation.

The analysis of the internal hydrogen bonding in structures Ia and III is summarized in Table IV, which includes a comparison with an analogous intermolecular interaction between formic acid (acceptor) and methanol (donor), all geometrical parameters of the monomers having been taken from the corresponding glycolic acid values (Figure 1). This dimer is depicted in structure IX. Values of 180 and 120° were assigned to α_1 and α_2, respectively (the system is planar except for two of the methyl protons), and the O···O″ distance was taken as 2.73 Å, the same as in structure Ia. Further comparisons are provided in Table IV by the water dimer and propane-1,3-diol, two systems which have in the past stimulated great interest as examples of inter- and intramolecular hydrogen bonding, respectively.[13,17,42a]



IX

The population analysis data for structures Ia and III exhibit the characteristics of hydrogen bonding noted above, but suggests a substantially weaker interaction than that observed in the intermolecular cases. In this connection, the nature of the donor OH bond merits some attention.

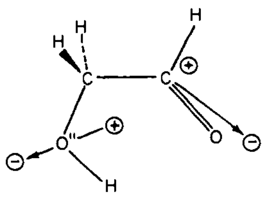
A traditional probe of hydrogen bonding, both inter- and intramolecular, has been the red shift of the OH stretching frequency,[13] attributed to weakening of the donor OH bond, although in intramolecular cases the relationship between H-bond strength and real shift appears to be quite complicated[36d] (see also the theoretical discussion in ref 42b). It is therefore of interest to examine the donor OH overlap populations in Table IV. As opposed to the intermolecular cases, the populations for the hydrogen-bonded forms of glycolic acid and glycolaldehyde are slightly *larger* than those for the reference molecules. A similar absence of OH weakening is found for propane-1,3-diol when the non-H-bonded reference structure has the same carbon–oxygen framework conformation,[42a] analogous to the situation for structures I and Ia. However, with respect to the lower energy reference structure corresponding to the completely trans-staggered conformation of propane-1,3-diol,[42a] a small O″H bond weakening is implied. Irrespective of the sign, the magnitude of the change in OH-bond population is seen to be relatively small for all of the intramolecular cases.

The *intra*molecular "hydrogen bond" energies listed in Table IV, based on the reference structures defined above, clearly do not make possible a direct comparison of the intrinsic strengths of inter- and intramolecular hydrogen bonding. The dependence of the intramolecular "hydrogen-bond" energy on the reference structure is particularly emphasized by the case of propane-1,3-diol. These energy differences are, of course, composites of various short- and long-range factors, as noted above. Rotating ϕ_1 from 0 to 180° in glycolic acid (I → Ia) in addition to facilitating the O″H···O interaction might be expected to reduce the nonbonded interactions between O″ and O (the lone pairs of O″ are directed away from O when $\phi_1 = 0°$) and lead to a more favorable dipole–dipole interaction with the carbonyl bond (see discussion of III below); however, this process is also seen to entail eclipsing of the O″H and CC bonds. The net result is an energy lowering of 6.1 kcal/mol. With regard to the O″···O interaction, the overlap population gives no indication of significant repulsion in spite of the short separation (2.73 Å). In fact, the population is slightly positive (0.010) for $\phi_1 = 0$ (cf., −0.012 for $\phi_1 = 180°$). Overlap populations are, of course, not definitive indications of interaction energies. The only suggestion of O″···O repulsion is the slight increase in the O″CC bond angle exhibited by many of the molecules under discussion.[1-10] Typical values are ~112° (vs. a standard value of ~110°).[43] However, this increase does not appear to be correlated with the ϕ_1 angle, and a few examples of unusually small O″CC angles (~107–108°) are also found in the tartaric acids[3] and the citrates.[9]

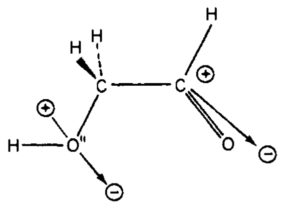
C. Further Comparisons of Conformational Energetics. Glycolaldehyde (III) offers interesting similarities and contrasts in conformational behavior, relative to that of glycolic acid. It is somewhat simpler to analyze from a theoretical point of view, primarily since it involves the interaction of only a single pair of CO bonds. It also has the advantage of having been studied experimentally in the gas phase,[12,13] thus providing data for direct comparison with calculations on the isolated species. Not surprisingly, the relative conformational energies of glycolic acid and glycolaldehyde are quite similar for small values of ϕ_2 (Figures 3 and 4),[44] with glycolaldehyde exhibiting the same (but somewhat less extended) elongated basin (cf. Figures 2 and 3), centered about the minimum-energy structure III, whose weak hydrogen bonding has already been discussed in Section VB (see Table IV).

Glycolaldehyde possesses a second local minimum at $\phi_2 = 180°$ (2.3 kcal/mol above the $\phi_2 = 0°$ isomer), but here it differs sharply from glycolic acid, since for $\phi_2 = 180°$ it prefers a trans-staggered O″H conformation ($\phi_1 = 0°$) in the absence of the possibility of H bonding. This divergence of behavior at large ϕ_2 is illustrated in terms of the crossing of the two one-dimensional profiles (with ϕ_1 fixed at 180°) as ϕ_2 increases in Figure 5a (the "minimum energy" paths by definition lead to the proper local minima at $\phi_2 = 180°$). The second isomer of glycolaldehyde has not been observed so far in the gas phase despite a careful search in the microwave experiments.[10] The corresponding pair of isomers for the isoelectronic α-aminoacetaldehyde is calculated (using standard bond lengths and angles)[30] to have a separation of ~1.4 kcal/mol,[26] a remarkable result in light of the fact that all three bonds at the nitrogen are eclipsed with other single bonds (CC and CH) in the higher energy $\phi_1 = 0$, $\phi_2 = 180°$ isomer.[45]

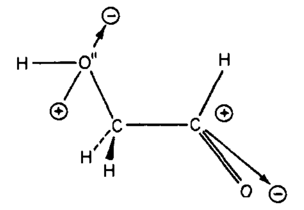
The most direct comparison between the α-halo carbonyl systems and glycolic acid and glycolaldehyde is revealed by the nonhydrogen-bonded (i.e., $\phi_1 = 0°$) portions of the potential energy surfaces displayed in Figure 5b. (The sensitivity of the conformational energy with respect to ϕ_2 is emphasized by comparison with the analogous profile for unsubstituted ac-



(a) $|\mu|_{tot}$ = 3.0D



(b) $|\mu|_{tot}$ = 5.3D



(c) $|\mu|_{tot}$ = 3.4D

Figure 6. Schematic representation of dipole–dipole interactions for selected conformations of glycolaldehyde: (a) ϕ_1 = 180, ϕ_2 = 0°; (b) ϕ_1 = 0, ϕ_2 = 0°; (c) ϕ_1 = 0, ϕ_2 = 180°. The $|\mu|_{tot}$ values refer to the magnitude of the calculated (4-31G) dipole moments. The local aldehyde and alcohol dipole moments are 3.3 and 2.1 D, respectively, as discussed in the text.

etaldehyde.) Relative to ϕ_2 = 0°, glycolic acid is seen to have a second minimum at slightly higher energy (0.7 kcal/mol) located at 150°, the same angle observed for the second isomer of the nonfluoro α-haloacetyl halides.[23] The small barrier (~0.3 kcal/mol) associated with the ϕ_2 = 180° conformation is also qualitatively consistent with the microwave analysis of the fluoro derivative.[46] In the case of glycolaldehyde, however, the constraint of ϕ_1 = 0° causes the trans isomer (ϕ_2 = 180°) to be ~4.6 kcal/mol *lower* than the cis isomer (ϕ_2 = 0°), in quantitative agreement with corresponding calculations for fluoroacetaldehyde (~4.1 kcal/mol)[16] and in qualitative agreement with the known energetics of rotational isomers in α-halo ketones (see Section II).[47] Thus in the case of glycolic acid, the possibility of hydrogen bonding (ϕ_1 = 180°) *reinforces* the preference for ϕ_2 = 0° over ϕ_2 = 150–180° exhibited by the ϕ_1 = 0° conformations and by the α-haloacetyl halides and related systems. On the other hand, H bonding in glycolaldehyde (for ϕ_2 = 0°) *reverses* the energy ordering for ϕ_2 = 0° and ϕ_2 = 180° displayed by the ϕ_1 = 0° isomers and by the α-halo aldehydes and ketones. An important factor in the preference for ϕ_2 = 180° over ϕ_2 = 0° in glycolaldehyde (with ϕ_1 fixed at 0°) is the interaction between the dipole moments of the aldehyde (μ = 3.3 D) and alcohol (μ = 2.1 D) moieties (see Figure 6);[48] they are nearly parallel in the completely trans-staggered conformation (ϕ_1 = ϕ_2 = 0°), with a total dipole moment of 5.3 D, and roughly perpendicular for the ϕ_1 = 0, ϕ_2 = 180° (total dipole = 3.4 D).[49] The local bond moments are also nearly perpendicular in the minimum energy, H-bonded structure III, whose calculated dipole moment is 3.0 D, compared with the macrowave value of 2.34 D. The calculated dipole moments for acetaldehyde and ethanol are exaggerated by a similar amount (~25%) as is typical for the 4-31G or other split valence basis sets.[17d,e,50]

VI. Summary

Ab initio calculation of the conformational potential energy surfaces for various α-hydroxycarbonyl systems has led to the following conclusions: (1) The minimum-energy conformation of the isolated species corresponds to an internally hydrogen-bonded geometry (ϕ_1 = 180° and ϕ_2 = 0°). (2) Departures from this conformation in the ϕ_1 direction generally cost less energy than do similar variations of ϕ_2, a result consistent with the experimental crystal data for the neutral acids and carboxylate anions, where the formation of intermolecular hydrogen bonding is seen to entail conformational changes in the ϕ_1 coordinate, with the ϕ_2 values remaining clustered about zero. (3) Although the relative stabilities associated with structures Ia and III may be described partly in terms of internal hydrogen bonding, analysis of the charge distribution indicates that the short-range (O''H···O) effects are smaller than those generally found in intermolecular H bonding. In particular, no weakening of the O''H bond is found when Ia and III are compared with non-H-bonded reference conformers. (4) The isolated glycolic acid and glycolaldehyde molecules have local conformational minima for ϕ_2 close to 180° within ~2–3 kcal/mol of the lowest energy ϕ_2 = 0° conformations, and hence they should be amenable to experimental detection. (5) It is emphasized that all low-lying local minima in both molecules correspond to a planar framework (ϕ_2 ≅ 0 or 180°) even in the absence of hydrogen bonding, a situation which most likely indicates the importance of dipolar interactions in the conformational energetics. (6) Selected sections of the potential energy surfaces for I and III are consistent with known energetics of rotational isomers in related systems where H bonding is not possible.

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(32) There is also some indication of a small red shift in the OH stretching frequency (a standard characteristic of hydrogen bonding),[13] as inferred by comparison with ethanol,[10] but no intramolecular red shift data based on other conformations is available.

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(37) Since the 4-31G basis is expected to exaggerate the equilibrium HOC bond angle (the 4-31G methanol value is $\sim 113°$, compared to an accurate microwave value of 106°[31]), we note that even when the glycolaldehyde HO''C angle was held at the reported microwave value of 102°,[10a] the calculations still gave no indication of appreciable O''H stretching (a value of 0.96 Å was obtained). Furthermore, the calculated O''H and ∢HO''C values were virtually insensitive to the small differences between the experimental values[10a] and the values adopted here for the other structural parameters of the molecule.

(38) Note that the potential energy surfaces displayed in Figures 2 and 3 are invariant with respect to inversion through the center ($\phi_1 = 180°$, $\phi_2 = 0°$). This invariance is not a property of the experimental data due to the presence of the crystalline environment.

(39) For a discussion of angles associated with hydrogen-bonded carboxyl oxygens see ref 17b, 17d, K. Morokuma, *J. Chem. Phys.*, **55**, 1236 (1971), and J. E. Del Bene, *ibid.*, **62**, 1314 (1975). The strained angles quoted for structure Ia are quite similar to those found experimentally[10a] for glycolaldehyde (structure III).

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(41) We wish to acknowledge the referee for noting this point and for making several other helpful suggestions.

(42) (a) For example, propane-1,3-diol has been studied by A. Johansson, P. A. Kollman, and S. Rothenberg, *Chem. Phys. Lett.*, **18**, 276 (1973). We have carried out calculations for this molecule at the 4-31G level using somewhat different values of the conformational angles. The H-bonded structure employed gauche (60°) conformations for the two OCCC moieties and for the HOCC proton donor end of the molecule; the other HOCC group was trans staggered and the other angles are as given by Kollman et al.; the ∢CCC was 109.47°. Two non-H-bonded reference structures were considered: (i) the same carbon-oxygen framework as above, but with both HOCC groups trans staggered; and (ii) the completely trans-staggered conformation; the latter one is more stable, as indicated in Table IV. It must be emphasized that the results for propane-1,3-diol are used here only for illustrative purposes. A detailed examination of the conformational surface would undoubtedly reveal a departure from perfect gauche conformations due to the oxygen-oxygen conformations. Kollman et al. have also pointed out that bond angles might be expected to open up for similar reasons. (b) A study of substituted phenols has recently been completed by S. W. Dietrich, E. C. Jorgensen, P. A. Kollman, and S. Rothenberg, submitted for publication. (c) The possibility of stronger, symmetrical internal hydrogen bonding in β-dicarbonyls has led to recent studies by G. Karlström, H. Wennerström, B. Jönsson, S. Forsen, J. Almlöf, and B. Roos, *J. Am. Chem. Soc.*, **97**, 4188 (1975), and A. D. Isaacson and K. Morokuma, *ibid.*, **97**, 4453 (1975).

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(44) The energy variation with respect to ϕ_1 is compared with the corresponding behavior for a simple alcohol (C_2H_5OH) in Figure 4.

(45) $\phi_1 = 0°$ is defined analogously to the case of glycolic acid (I) and glycolaldehyde (III),[12] except that the bisector of the HNH angle of the amino group takes the place of the O''H bond.

(46) The microwave study[24] of fluoroacetal fluoride suggested a local minimum at $\phi_2 = 180°$ but could not rule out a small bump centered at $\phi_2 = 180°$. An increase in ϕ_2 (relative to 150°) in going from OH and the larger halogens to fluorine may well reflect the somewhat smaller van der Waals radius[28] of the latter substitutent.

(47) A smaller energy separation for the ketones relative to the aldehydes may be expected, since the ketone methyl group leads to greater nonbonded repulsion with the α-substituent than does the aldehyde proton in the $\phi_2 = 180°$ isomer.

(48) This effect more than offsets the eclipsing of the CO single bonds in the $\phi_2 = 180°$ conformation.

(49) The magnitude and direction of the local bond moments are based on 4-31G calculations for acetaldehyde and ethanol. The geometrical parameters were the same as those used in the glycolaldehyde calculation, as described in Section IV.

(50) Although inclusion of polarization functions generally improves the 4-31G dipole moments for simple hydrides,[17c] 6-31G* calculations for glycolaldehyde have a rather small effect on the dipole moments (relative to the 4-31G results).[26]