

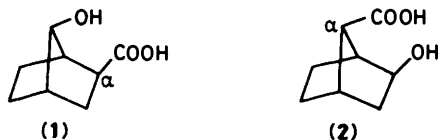
Conformational Energetics, Geometric Disposition, and Intramolecular Reactivity in Six Semi-rigid Hydroxy Acids

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MM2 Methods were applied to six hydroxy acids whose hydroxy groups are attached to rigid or semi-rigid frameworks and whose lactonization rates span a range of 3 730-fold. A comprehensive analysis for each compound provided energy minima and maxima as the hydroxys and carboxys were systematically rotated in small increments. Each hydroxy acid exists in four or five important energy minima. For example, 2-*endo*-hydroxy-6-*endo*-carboxynorbornane has five conformational minima comprising 44, 28, 18, 7, and 2% of the total population. These minima were characterized geometrically in terms of HO...C=O distance r and the angular disposition (θ and ϕ) of the hydroxy with respect to the carbonyl. It was found that r changes by $<0.1 \text{ \AA}$ from minimum to minimum for any given hydroxy acid. There is a definite tendency for an electron pair on the hydroxy to point, in preference to the hydroxy proton, toward the carbonyl carbon. Neither van der Waals repulsion nor hydrogen-bonding between the hydroxy proton and the carbonyl oxygen contributes substantially to the energy terms controlling rotational equilibria. Bending distortions, which ameliorate repulsion between the hydroxy proton and carboxy OH, dominate the energy content of the conformational maxima. Lactonization rates could not be correlated with widely varying 'attack angles' θ and ϕ . Nor could distance r (remaining relatively constant at $2.90 \pm 0.06 \text{ \AA}$ among the lowest-energy conformers of the hydroxy acids) provide an explanation for the rate data. This does not mean, of course, that distance never has a bearing on reactivity as claimed recently by Dorigo and Houk. Rather, the HO...C=O distances are all sufficiently similar to the contact distance invoked in the 'spatiotemporal hypothesis' that the compounds would lactonize at enzyme-like rates were it not for deleterious ring-strain effects. Finally, errors and uncertainties in the Dorigo-Houk paper, and the dangers of computing small rate differences (such as those affecting product ratios) in terms of structure, are discussed.

Storm and Koshland¹ published lactonization rates for a series of semi-rigid hydroxy acids (Table 1). Rate differences among the compounds were attributed primarily to variations in 'attack angle' (defined as HO...C=O-C_α). Since we were concerned that other factors (strain and distance) were contributing to the rate effects, we examined several hydroxy acids [*e.g.* (1) and (2)] in which the angle constituted the only important variable;² strain and distance were substantially controlled in the 'reversomers'.[†] It was found that (1) and (2), although



differing in their attack angles, lactonized at identical rates, thereby casting a shadow on the Storm-Koshland hypothesis. We have recently proposed that *distance* rather than angle often determines reactivity in solution.³ When two species are held at or near the van der Waals contact distance, enzymatic rates are possible. No doubt desolvation that accompanies such a geometric disposition contributes heavily to the speed of the actual bond-forming step. This does not mean that one is obtaining 'something for nothing.' It costs energy to fix two atoms at a reactive distance. In the case of an intramolecular

[†] Geometric parameters of (1) and (2) reported in ref. 2 were recalculated in our laboratory. Although the absolute values are somewhat different, it was reaffirmed that (1) and (2) have nearly identical strain and distance parameters but differing attack angles.

organic system, the energy is incorporated into the compound during its synthesis; in the case of an enzyme, binding energy is sacrificed to achieve proper sustained alignment.³

A laborious synthetic effort is required to secure compounds such as (1) and (2) where only a single geometric parameter is altered. This is, admittedly, a disadvantage of our past approach.^{2,3} Obviously, a great deal of synthetic work could be avoided were it feasible to analyse the rates of compounds whose angle, distance, and strain parameters all varied simultaneously. We attempted to do this using MM2 methods on the hydroxy acids in Table 1. The hope was to understand the source of the 3 730-fold range in lactonization rates.

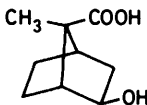
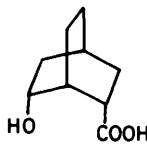
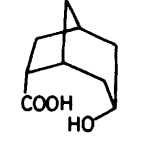
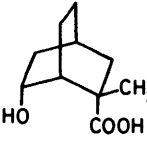
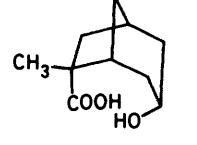
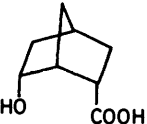
Methodology

MM2 Calculations, performed on a VAX/785 computer, utilized Allinger's 1977 force field.⁴ A series of programs was written to facilitate the analysis of the MM2 output.

Crude internal co-ordinates (bond distances, 1,3-bond angles, and 1,4-torsional angles) for each compound in Table 1, obtained from Dreiding models, were converted by a MNDO program into rough Cartesian co-ordinates. An initial MM2 minimization using these co-ordinates (with the assistance of the 'co-ordinate calculation' option to add on hydrogens and other substituents) served as a starting point for further calculations.

Three-dimensional energy surfaces [*e.g.* Figures 1 and 2 for compound (4)] were generated by 'driving' the carboxy and hydroxy dihedral angles in 20° increments. For example, an energy minimization for (4) was executed while maintaining

Table 1. Relative lactonization rates for six hydroxy acids^a

Compound	Structure	Relative rate
(3)		1.0
(4)		3.2
(5)		33
(6)		357
(7)		1 740
(8)		3 730

^a Measured in aqueous acid. See R. M. Moriarty and T. Adams, *J. Am. Chem. Soc.*, 1973, **95**, 4070.

the hydroxy dihedral angle [C(7)/C(2)/O(1)/H(15)] and the carboxy dihedral angle [C(7)/C(6)/C(10)/O(11)] at 180°. Next, with the hydroxy dihedral angle fixed at 180°, the carboxy dihedral angle was rotated in 20° steps, each time minimizing the energy. The whole process was then repeated using a hydroxy dihedral angle of 160° (and 140, 120° *etc.*). In such a manner, we could detect local minima separated by energy barriers of 0.07–0.10 kcal mol⁻¹. Obviously, several hundred energy minimizations per compound were required to achieve this level of sensitivity. But the effort was justified because it enabled us to locate with certainty all the minima for the compounds including the global minima.

Structures of each minimum detected by the above procedure were minimized with full optimization until the steric energies changed by <0.1%. ORTEP drawings were made of each final conformation as shown for compound (4) in Figure 3.

Tetrahedral intermediates were handled in a similar manner as the hydroxyacids, generating the energy surface by driving simultaneously the dihedral angles of the hydroxy groups. Lactones were found to be rigid with only one conformation for each compound. Figure 3 provides the tetrahedral intermediate and lactone structures for (4).

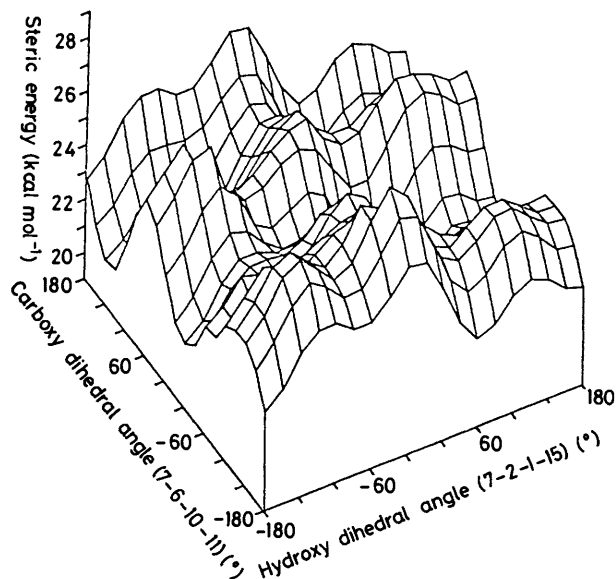
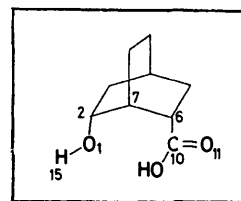


Figure 1. Plot of steric energy *versus* carboxy and hydroxy group rotation in compound (4)

A few additional details should be mentioned. Methyl groups, when present, were allowed to relax freely as were the acid group hydroxys (whose proton maintained throughout their initial *syn* relationships to the carbonyl oxygens). Both the [2.2.2] and [3.2.1] ring systems are somewhat flexible. Thus, the unsubstituted [2.2.2] framework is known to assume a 'spiral' conformation with a barrier to pseudorotation of *ca.* 0.1 kcal mol⁻¹.⁵ In our substituted [2.2.2] compounds [(4) and (6) in Table 1], the interactions between the hydroxy and carboxy groups supersede this small effect; hence, the skeleton 'flip-flops' as the hydroxy and carboxy groups are rotated. In the case of the [3.2.1] systems [(5) and (7) in Table 1], dihedral driver calculations were carried out on both the chair and boat conformations. However, none of the boat structures was found to contribute significantly to the conformer populations. A dielectric constant of 1.5 was used in all calculations.

Results

Our purpose in performing these extensive MM2 calculations was to correlate, if possible, the rate data in Table 1 with molecular structure. Structural relationships were defined with the aid of Figure 4 where the carboxy unit is fixed in the *xy* plane as shown. Three parameters describe the geometric disposition of the nucleophile (the hydroxy oxygen) with respect to the electrophile (the carbonyl carbon): *r*, θ , and ϕ . Parameter *r* represents the C...O distance. Angle θ measures the deviation of the C...O vector from the positive *z*-axis. Finally ϕ is obtained by projecting the C...O vector onto the *xy* plane and determining the angle formed between the positive *x*-axis and the projection. If the projection is on the same side of the *xz*-plane as C₆, then ϕ is assigned a positive value. Both θ and ϕ are zero when the C...O vector coincides with the positive *z*-axis. The optimal 'attack angle' is approximated by a θ 19° (or 161°) and ϕ 180°.

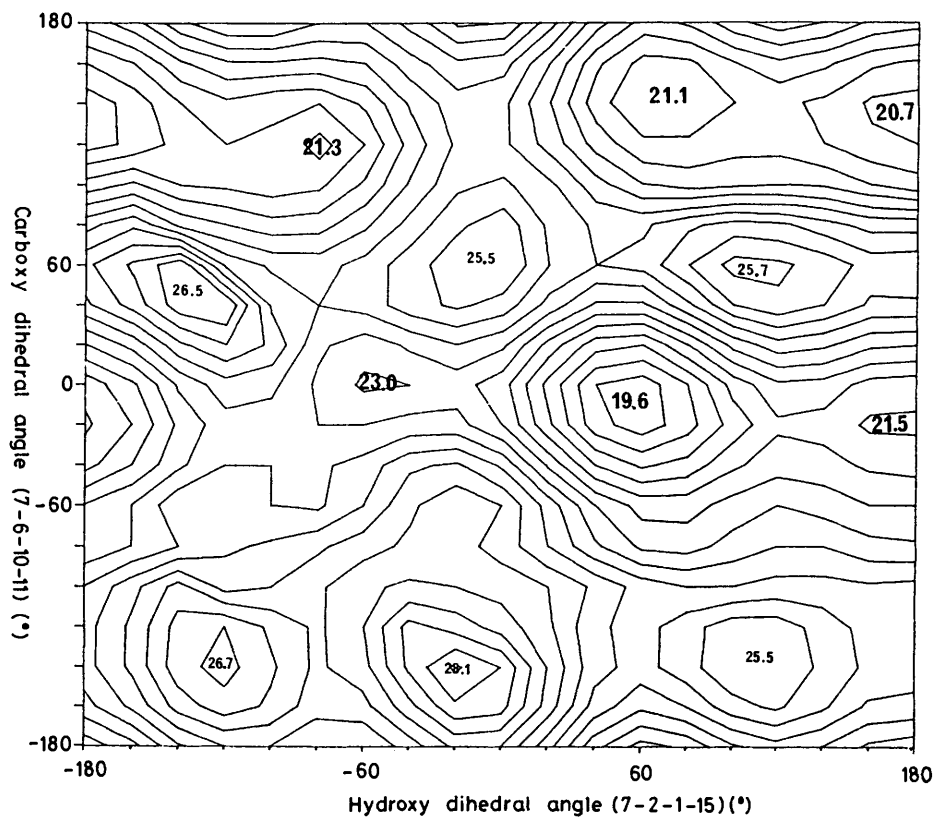


Figure 2. Contour plot of energy surface in Figure 1. Large numbers indicate energy minima and small numbers indicate energy maxima

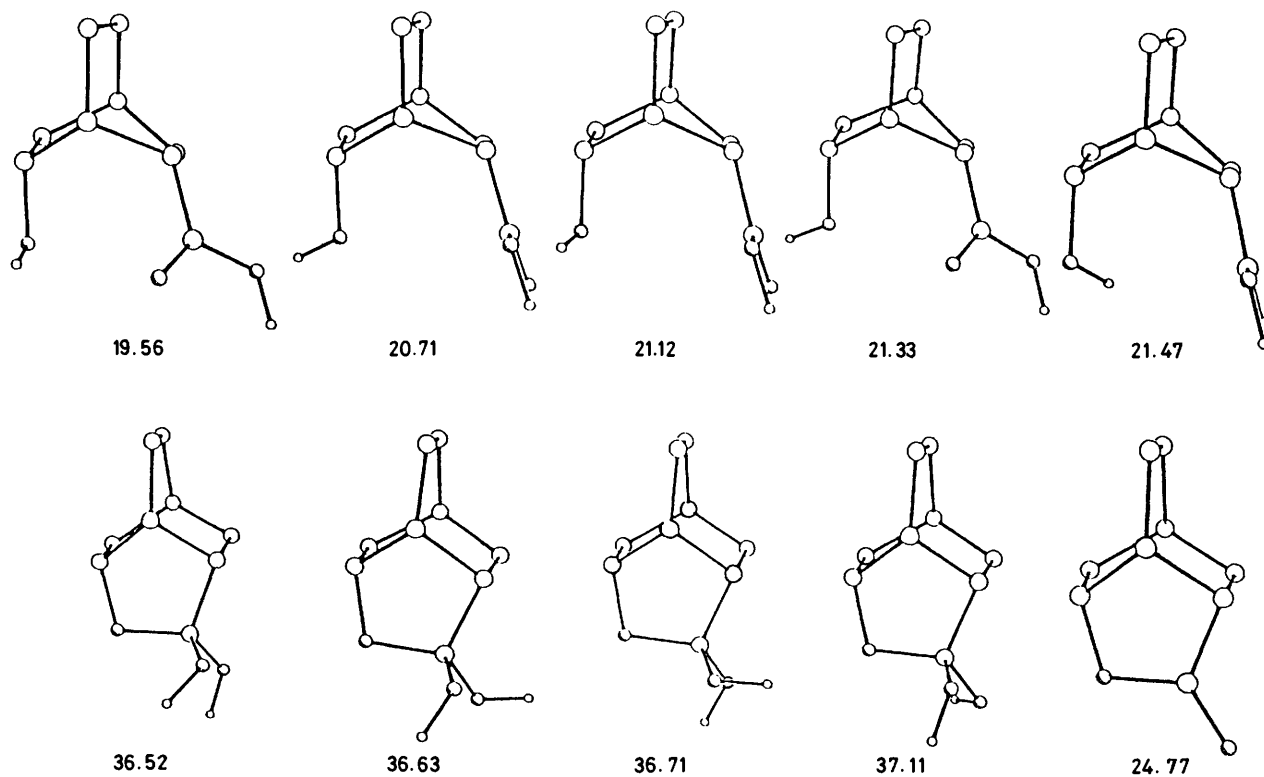


Figure 3. Diagrams of energy minima of compound (4) and its tetrahedral intermediate and lactone. Numbers refer to steric energies

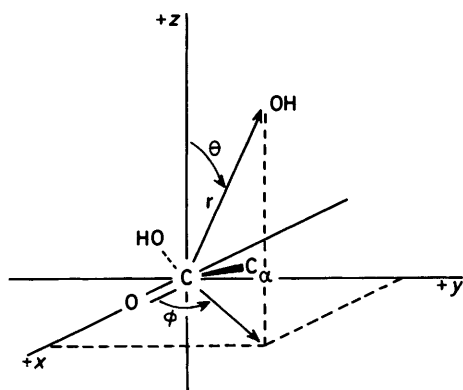


Figure 4. Definition of r , θ , and ϕ

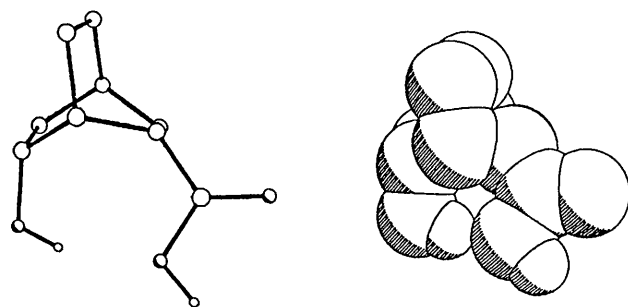


Figure 5. Structure of energy surface maximum for compound (4)

An important point must be inserted here. Past attempts to relate lactonization rates with geometry^{1,2} utilized only a *single* 'attack' angle (*i.e.* the so-called Koshland $HO \cdots C=O-C_\alpha$ angle). Recent calculations of Dorigo and Houk⁶ do likewise. Yet a single angle cannot, obviously, properly define geometry in three-dimensional space. To appreciate this fact fully, one merely has to consider a hydroxyacid with an 'ideal' Koshland angle of 109° but with the hydroxy in the plane of the carbonyl. Absolutely no reaction would occur despite the optimal Koshland angle. For this reason we considered it essential to use modified polar co-ordinates to describe spatial relationships.

Table 2 lists geometric and energy data for all major conformers (>1%) of compounds (3)–(8). Let us define the column headings going from left to right in Table 2 as follows.

(a) Steric energy. Steric energy for a given system encompasses the energy required to stretch and twist the bonds, bend the angles, and compress the non-bonded atoms relative to an 'idealized' molecule with the same constitution.

(b) %. Percentages of total population for each conformer in Table 2 were calculated with the aid of steric energies and the Boltzmann equation.

(c) ΔH_f . Heats of formation in Table 2 are probably reliable to within 2 kcal mol⁻¹.

(d) Strain energy. This energy parameter represents the strain relative to arbitrarily selected 'strainless' reference standards. MM2 utilizes, for example 'strainless' n-alkanes, isobutane, and neobutane to assign strain increments to C–C and C–H bonds.⁴

(e) $HO \cdots C=O-C_\alpha$ and $HO \cdots C=O \cdots C=O$ angles. These angles are included for the sake of completeness because Koshland¹ and Dunitz⁷ used them to define their 'attack' geometries.

(f) van der Waals interactions. Each carbonyl carbon is engaged in non-bonded interactions with its neighbouring hydroxy oxygen and its two unshared pairs of electrons. The three energy terms are summed to give the data in this column

which reflect 'compression' effects between the nucleophilic and electrophilic atoms.

(g) r , θ , and ϕ . The last six columns provide information concerning the position of the carbonyl carbon relative to (i) the hydroxy oxygen and (ii) the closest lone-pair electrons on the hydroxy (see Figure 3). Tables 3 and 4 summarize the MM2 output for the tetrahedral intermediate and lactones corresponding to compounds (3)–(8).

Discussion

We begin by examining the conformational states of the various hydroxy acids (Table 2). It is seen that each hydroxy acid exists in four or five energy minima; these minima differ in the rotational disposition of the hydroxy and carboxy groups (*e.g.* Figures 1 and 2). The intriguing question arises as to how the $HO \cdots C=O$ distance and non-bonded 'compression' vary as the hydroxy and carboxy are rotated relative to one another. Several generalizations are evident from our calculations. (a) The distance r between the hydroxy oxygen and the carbonyl carbon changes by ≤ 0.1 Å from minimum to minimum for any given hydroxyacid. Thus, the two reactive groups, fixed as they are upon the carbon frameworks, do not substantially alter their interatomic distances when equilibrating among the stable conformers. (b) The distance separating the carbonyl carbon from the closest electron pair on the hydroxy (r_e in Table 2) varies within a conformer population by an amount ranging from 0.11 Å for (3) to 0.33 Å for (4). These relatively small changes reflect a tendency for an electron pair to point, in preference to the hydroxy proton, toward the carbonyl carbon (an effect seen in Figure 3). This is primarily a steric phenomenon since MM2 considers a lone-pair to be smaller than a hydroxy proton (0.6 Å versus 0.94 Å). Attractive dipole–dipole interactions between the lone-pair and the carbonyl group also contribute to the orientation. (c) van der Waals repulsions between the carbonyl carbon and the hydroxy oxygen differ only slightly within a particular set of conformers [the largest variation being 0.33 kcal mol⁻¹ for (7)]. Since the van der Waals values in Table 2 are small, and since no correlation exists between '%' and 'van der Waals interactions', carbon–oxygen compression contributes little to the energy terms controlling the rotational equilibria. (d) Hydrogen-bonding between the hydroxy proton and the carbonyl oxygen is weak if present at all. Thus, $C=O \cdots HO$ distances exceed by 0.7–2.6 Å that associated with a well formed hydrogen bond (Table 5). No correlation between '%' and 'C=O \cdots HO distance' is apparent in Table 5. Indeed, the least prevalent conformer of (4), (6)–(8) each possess the *shortest* $C=O \cdots HO$ distance. In a sense, the two functional groups are 'too close' to hydrogen-bond effectively.

It was mentioned in the preceding paragraph that the $HO \cdots C=O$ van der Waals forces and the $C=O \cdots HO$ hydrogen-bonding do not substantially affect the distribution of conformers. What, then, are the important energy terms? A detailed breakdown of the steric energies for the 76 and 4% conformers of (4) (Table 2) shows that dipole–dipole interactions between the hydroxy and carboxy 'as a whole' contribute most heavily to the 1.7 kcal mol⁻¹ energy difference. Since the energy changes within the various rotamer sets are rather small, we will not pursue this line of analysis further.

The highest and lowest points on the energy surface for the [2.2.2] system (4) (Figure 1) differ by 8.4 kcal mol⁻¹. This energy barrier is comprised mainly of three energy terms: bending (3.4 kcal mol⁻¹), torsional (2.6 kcal mol⁻¹), and dipole–dipole (3.4 kcal mol⁻¹). (The whole need not equal exactly the sum of the parts since potential energy functions are never at their minima simultaneously.) Pictorial representations of the highest-energy conformer (Figure 5) show twisting of the ring system and outward flaring of the C–COOH, in order to ameliorate

Table 2. Geometric and energy parameters for the major conformers of six hydroxy acids^a

Compound	Steric energy	%	$-\Delta H_f$	Strain energy	O-C-C _α angle (°)	O-C-O angle (°)	van der Waals interactions	O...C Geometry			O...C Geometry		
								<i>r</i>	θ	φ	<i>r_e</i>	θ _e	φ
(3)	29.0	55	146	22.5	82	107	0.48	2.88	163	-170	2.43	168	-143
(3)	29.3	31	146	22.9	82	107	0.45	2.92	163	-172	2.41	161	-150
(3)	29.9	11	146	23.5	83	80	0.56	2.87	19	57	2.38	15	35
(3)	30.7	3	145	24.2	82	81	0.39	2.90	19	61	2.49	12	37
(4)	19.6	76	154	14.0	73	79	0.34	2.94	33	69	2.48	25	75
(4)	20.7	11	153	15.1	75	98	0.33	2.89	165	123	2.60	162	86
(4)	21.1	5	152	15.6	74	100	0.41	2.95	164	130	2.40	167	112
(4)	21.3	4	152	15.8	72	82	0.18	2.96	31	75	2.73	22	91
(4)	21.5	3	152	15.9	75	96	0.28	2.94	164	112	2.57	169	150
(5)	20.7	67	158	15.1	81	93	0.47	2.95	170	109	2.38	170	131
(5)	21.7	12	152	16.1	82	83	0.27	2.95	17	66	2.55	27	63
(5)	21.7	11	152	16.2	81	94	0.24	2.96	170	113	2.58	166	154
(5)	21.9	8	152	16.3	80	83	0.30	3.03	20	68	2.43	21	64
(6)	24.5	52	158	17.4	79	75	0.62	2.84	31	59	2.39	23	61
(6)	24.8	30	157	17.7	87	100	0.72	2.80	170	-161	2.37	174	-98
(6)	25.2	16	157	18.1	86	100	0.77	2.84	170	-164	2.31	169	-129
(6)	26.5	2	156	19.3	80	88	0.69	2.76	14	82	2.51	9	138
(7)	24.7	73	158	17.5	86	87	0.68	2.87	172	70	2.32	174	113
(7)	25.8	10	156	18.7	86	83	0.41	2.89	12	55	2.49	22	55
(7)	25.9	9	156	18.8	85	89	0.36	2.90	173	81	2.53	170	153
(7)	26.2	6	156	19.0	85	83	0.47	2.96	14	59	2.37	15	54
(8)	24.1	44	143	19.2	77	74	0.53	2.87	34	60	2.41	25	62
(8)	24.4	28	143	19.5	81	97	0.74	2.77	171	137	2.42	169	70
(8)	24.6	18	142	19.7	79	110	0.74	2.85	159	-175	2.31	165	-171
(8)	25.2	7	142	20.3	81	93	0.66	2.80	170	106	2.42	173	179
(8)	25.9	2	141	21.0	78	87	0.60	2.79	17	80	2.52	10	123

^a Steric energies, strain energies, ΔH_f , and van der Waals interactions are in kcal mol⁻¹. Column headings are explained in the Results section.

Table 3. Energy parameters for the major conformers of the neutral tetrahedral intermediates corresponding to the six hydroxy acids^a

Compound	Steric energy	%	ΔH_f	Strain energy
(3)	42.0	38	-117	30.8
(3)	42.0	35	-117	30.8
(3)	42.4	19	-116	31.2
(3)	42.9	8	-116	31.7
(4)	36.5	34	-120	25.0
(4)	36.6	29	-120	25.1
(4)	36.7	25	-120	25.2
(4)	37.1	12	-119	25.6
(5)	37.3	27	-119	25.7
(5)	37.3	27	-119	25.7
(5)	37.3	24	-119	25.8
(5)	37.4	22	-119	25.8
(6)	38.0	36	-127	26.1
(6)	38.1	32	-127	26.2
(6)	38.4	18	-127	26.5
(6)	38.5	14	-126	26.7
(7)	38.7	28	-126	26.9
(7)	38.8	26	-126	26.9
(7)	38.8	26	-126	26.9
(7)	38.9	20	-126	27.0
(8)	37.6	32	-112	26.7
(8)	37.6	31	-112	26.7
(8)	37.8	21	-112	26.9
(8)	38.0	16	-112	27.1

^a All energies are in kcal mol⁻¹.

repulsion between the hydroxy H and carboxy OH. With the more rigid [2.2.1] system (8), bending dominates the valley-to-peak energy differential: bending (6.6 kcal mol⁻¹), torsional (2.0 kcal mol⁻¹), and dipole-dipole (3.5 kcal mol⁻¹).

We now turn to one of the main questions that motivated our

Table 4. Energy parameters for the lactones corresponding to the six hydroxy acids^a

Compound	Steric energy	ΔH_f	Strain energy
(3)	32.8	-94	21.3
(4)	24.8	-99	14.2
(5)	27.1	-97	16.6
(6)	25.0	-108	12.8
(7)	28.2	-105	16.0
(8)	26.0	-92	16.1

^a All energies are in kcal mol⁻¹.

calculations. Do lactonization rates in Table 1 correlate with geometric parameters? Consider first the 'attack' angles θ and φ. Inspection of Table 2 reveals that angular relationships do not, despite past assertions to the contrary,¹ provide an explanation for the rate data in Table 1. Angle θ, the deviation from the z-axis in Figure 4 for the minimum-energy conformers of (3)–(8), equals 163, 33, 170, 31, 172, and 34°, respectively. These values, when converted to the same side of the xy-plane, become 17, 33, 30, 31, 8, and 34° for (3)–(8), respectively, compared to an 'optimal' 20°. No orderly relationship between rate and θ (or rate and φ) is apparent. Moreover, published claims that a 10° angle variation leads to a 10⁴ rates effect¹ cannot be supported by our calculations.

Distance *r* between the hydroxy oxygen and the carbonyl carbon also fails to provide a rationalization for the lactonization rates. Thus, the rates span a range of 3 730 despite a relatively constant *r* (2.90 ± 0.06 Å for the lowest-energy conformations). Values of *r_e*, the distance between an electron pair on the hydroxy and the carbonyl carbon, are likewise similar to each other: 2.40 ± 0.08 Å for compounds (3)–(8). Rate variations in the face of constant distance merit further comment lest it be concluded *incorrectly* that rate and distance

Table 5. Distances between the hydroxy proton to the carbonyl oxygen for the major conformer of the six hydroxy acids

Compound	Steric energy (kcal mol ⁻¹)	Distance (Å)
(3)	29.0	3.91
(3)	29.3	4.17
(3)	29.9	2.82
(3)	30.7	3.76
(4)	19.6	4.20
(4)	20.7	3.99
(4)	21.1	3.69
(4)	21.3	3.88
(4)	21.5	2.72
(5)	20.7	3.04
(5)	21.7	3.57
(5)	21.7	4.11
(5)	21.9	3.37
(6)	24.5	2.34
(6)	24.8	3.76
(6)	25.2	3.86
(6)	26.1	3.81
(7)	24.7	2.77
(7)	25.8	3.51
(7)	25.9	3.96
(7)	26.2	3.33
(8)	24.1	2.34
(8)	24.4	3.79
(8)	24.6	3.76
(8)	25.2	2.54
(8)	25.9	3.81

Table 6. Differences in strain energies between tetrahedral intermediate and hydroxy acid and between tetrahedral intermediate and lactone^a

Compound	TI - HA (kcal mol ⁻¹)	TI - L (kcal mol ⁻¹)
(3)	8.14	9.64
(4)	10.9	10.9
(5)	10.4	9.2
(6)	8.66	13.4
(7)	9.42	10.9
(8)	7.50	10.7

^a Individual strain energies were calculated from the data in Tables 1-3 via a weighted average of all conformers.

are unrelated. As argued below (and in agreement with incontrovertible *ab initio* calculations⁸), rates respond sensitively to fluctuations in distance.

In a recent analysis of intramolecular and enzymatic reactivity,³ the following hypothesis was set forth. The rate of reaction between functionalities A and B is proportional to the time that A and B reside at a critical distance. When A and B are held within a critical distance (<3.0 Å for carbonyl addition), enzymatic rates are possible. Note that no mention is made here of 'ground state' or 'transition state'. This is because two species residing at contact distances are *neither* of these but somewhere in between. Obviously, an input of energy is required to elevate two atoms to a contact geometry, the bulk of it stemming from the need to desolvate prior to bond formation. This is hardly a new idea. In 1952 Glew and Moelwyn-Hughes⁹ suggested that the energy necessary to reorganize solvent molecules around reacting species comprises almost all the activation energy for many reactions. In the case of an intramolecular system, energy is imparted to the compound during its synthesis; in the case of an enzyme, binding energy is sacrificed to achieve the proper sustained alignment. Perhaps the main value of the hypothesis lies in its relevance to enzymes. The hypothesis downplays

chemical mechanisms (e.g. general acid-base catalysis) in favour of binding geometry as the main source of the >10⁸ accelerations. Innumerable examples from organic chemistry³ testify to the huge rates possible when two groups are held at distances that force the extrusion of solvent between them.

How does our construction square with the fact that a 3 730 rate differential in Table 1 is observed despite relatively constant *r* values? Consider (8) which has an *r* 2.87 Å and which lactonizes the fastest among the compounds in Table 1. This hydroxy acid is known to have a 1.8 × 10⁵M 'effective molarity' (defined as *k*_{intra}/*k*_{inter} for corresponding intramolecular and intermolecular reactions operating under identical conditions). Thus, (8) cyclizes extremely rapidly (only 10³-fold less than the accelerations associated with enzymatic catalysis). If one were to adjust for the ring strain generated when the hydroxy acid forms the tetrahedral intermediate, then the reactivity of (8) easily falls into the 'enzyme-like' category. This is exactly what would be expected from the 'spatiotemporal' hypothesis; the hydroxy and carboxy are, after all, held at approximately a van der Waals contact distance and at a separation less than the diameter of a water molecule. Since compounds (3)-(7) also possess *r* 2.8-3.0 Å but react more slowly than (8), additional factors (including strain) must be adversely affecting the lactonization rates. In no way, however, does the role of strain invalidate our hypothesis or prove the irrelevance of distance to reactivity as suggested by Dorigo and Houk in their recent article.⁶ To deny the dependence of rate on distance is to deny a large body of experimental and theoretical evidence.^{7,10}

Although our primary goal was to establish the conformational properties of the hydroxy acids and to relate reactivity with geometry, we also considered the matter of strain. Table 6 lists the changes in strain (ΔSE) as the hydroxy acid cyclizes to tetrahedral intermediate and as tetrahedral intermediate collapses to lactone. Note that the energy values are large in an absolute sense (ranging from 7.50 to 13.4 kcal mol⁻¹). More importantly, differences in ΔSE among the compounds are the same order of magnitude as the kinetic effects in Table 1 (the 3 730 rate range being worth 4.9 kcal mol⁻¹). But as with the angle parameters, there again appears to be no trend. Hydroxy acid (3) generates 8.1 kcal mol⁻¹ strain when cyclizing to intermediate as compared to 9.3 kcal mol⁻¹ for (7), yet the latter lactonizes 1 740 times faster. Compounds (5) and (6) are associated with the lowest and highest ΔSE for intermediate collapse, respectively, but they differ in rate by a factor of only 11. The 'excess stretching energy' of the O-CO bond in the lactones (a measure of 'localized' strain available from the M22 calculations) equals 0.13, 0.083, 0.18, 0.14, 0.20, and 0.13 kcal mol⁻¹ for (3)-(8), respectively. No smooth correlation is evident here either.

Several explanations may be advanced for the lack of a simple correspondence between rate and strain. (a) Lactonizations are carried out in aqueous acid where protons catalyse the process. Thus, it is the protonated carboxy, rather than the carboxy itself, that serves as the actual electrophile. We have of necessity ignored this aspect of lactonization chemistry because MM2 is not suitably parameterized for protonated carboxys. Clearly, our analysis assumes that the pre-equilibrium protonation step affects the six hydroxy acids more or less equally. (b) We have implicitly assumed that formation of the tetrahedral intermediate is rate-determining. This is consistent with the lactonization kinetics of Hershfield and Schmir¹¹ who wrote, 'At low pH, the formation of the intermediates *via* acid-catalyzed and uncatalyzed pathways is rate determining.' If, however, collapse of the intermediate contributes to the observed rate in one or more of the hydroxy acids, the correlations could be perturbed. (c) Finally, our 'modelling' of the transition states by the tetrahedral intermediate, and our ignoring of possible solvation differences among the reactive functionalities, could induce non-

linearity. It would, of course, have been a simple matter to introduce an adjustable parameter into our treatment and thus present a linear plot. Recognizing, however, that *tortured data confess to anything*, we prefer at this point to accept a rather poor rate-strain correlation at face value.*

As already mentioned, Dorigo and Houk⁶ recently published a modified MM2 model for the rates of acid-catalysed lactonizations of hydroxy acids including those in Table 1. They concluded, in accord with us, that strain effects dominate the rate ratios. Yet several aspects of their work appeared disquieting. Thus, Dorigo and Houk wrote, 'In particular, our calculations show that there is no relationship . . . between the distance between reacting atoms in the starting material and the rate of reaction.' This statement is correct for the lactonizations (where, as we have shown, the distances are all similar and the rates are dominated by huge strain differences). Unfortunately, however, Dorigo and Houk *generalize* and thereby dismiss *any* relationship between rate and distance (the basis for our spatiotemporal hypothesis). So bizarre is this conclusion that we must delve here further into its source.

MM2 'transition state modelling' was used to secure a linear plot (unachievable by us) relating lactonization rates to calculated energies.⁶ We have been candid in admitting the assumptions in our approach, and we feel it necessary to mention the uncertainties in the Dorigo-Houk approach as well. (a) Geometries were calculated by them for only *one* energy minimum whereas, as shown in our Table 2, as many as *five* conformations contribute to the ground state. A complete conformational analysis (as performed by us) is particularly important with several hydroxy acids for which Dorigo and Houk report only a single 'blind-alley', and kinetically insignificant, conformation with huge *r* values (e.g. 4.6 Å). (b) A 'two-dimensional' angle, employed in the previous work, cannot be used to characterize a three-dimensional structure. To put it bluntly, as a result of unnecessary shortcuts, Dorigo and Houk did not have on hand the geometric information they needed for a rigorous analysis. (c) 'Transition state modelling' assumes that *all* hydroxy acids possess the *same* degree of bond formation in the transition state, a clear violation of the Hammond principle (and a particularly bothersome assumption in a calculation where *distance* is a main focus). The method further assumes that the transition structure in water corresponds exactly to the energy *minimum* found for related gas-phase reactions (where no energy barrier exists at all). (d) Stretching and bending constants in the transition state are assumed to equal half the ground-state MM2 values. van der Waals and dipole-dipole terms are apparently ignored in spite of the involvement of charged species. (e) Rate-determining collapse of the tetrahedral intermediate is invoked despite experimental evidence of Hershfield and Schmir¹¹ suggesting the contrary. (f) Three different sets of torsional and bending parameters were used. In particular, a separate set of parameters was assigned to their

* Steric effects on lactonizations using hydrocarbon models have been calculated.¹²

most reactive hydroxy acid (a key compound that provided the bulk of their kinetic 'range').

A recent attempt by us to duplicate the Dorigo-Houk values using their published procedure was unsuccessful. A manuscript describing our difficulties with their calculations was ultimately rejected in favour of an 'Additions and Corrections' submitted by the UCLA group. Dorigo and Houk point out therein that 'dipole moments were read in with the right magnitude but the wrong sign'. Although corrected calculations do not ostensibly change the main thrust of their paper, one must be concerned over a methodology in which reversing dipole moments at a reactive centre has no impact on conclusions. Our experience with MM2 instills special misgivings over 'transition state modelling' when applied to small rate changes such as are involved in product ratio calculations. The point is well illustrated by a recent example dealing with the stereochemistry of nitrile oxide cycloadditions to chiral alkenes.¹³ Two products were obtained whose ratios varied, depending upon the alkene structure, from 1:1 to 4:1, a difference corresponding to only 0.8 kcal mol⁻¹. In the face of the uncertainties mentioned above and (perhaps even more importantly) in the face of intractable solvation effects, the quantitative 'prediction' of such small rate changes requires courage if not exaggeration. It is nevertheless easy to visualize great strides in the understanding of solution dynamics as solvent structure¹⁴ and diffusion processes in liquids¹⁵ receive greater and greater attention.

Acknowledgements

This work was supported by the National Science Foundation. We thank Mr. J. Haugaard, Emory University Computing Center, for assistance in preparing the energy contour maps.

References

- 1 D. R. Storm and D. E. Koshland, *J. Am. Chem. Soc.*, 1972, **94**, 5805.
- 2 F. M. Menger and L. E. Glass, *J. Am. Chem. Soc.*, 1980, **102**, 5404.
- 3 F. M. Menger, *Acc. Chem. Res.*, 1985, **18**, 128.
- 4 U. Burkert and N. L. Allinger, 'Molecular Mechanics,' Am. Chem. Soc., Washington, D.C., 1982.
- 5 E. M. Engler, L. Chang, and P. v. R. Schleyer, *Tetrahedron Lett.*, 1972, 2525.
- 6 A. E. Dorigo and K. N. Houk, *J. Am. Chem. Soc.*, 1987, **109**, 3698.
- 7 J. D. Dunitz, 'X-Ray Analysis and the Structure of Organic Molecules,' Cornell University Press, Ithaca, 1979.
- 8 S. Scheiner, *Acc. Chem. Res.*, 1985, **18**, 174.
- 9 D. N. Glew and E. A. Moelwyn-Hughes, *Proc. Roy. Soc.*, 1952, **A211**, 254.
- 10 F. M. Menger, to be published.
- 11 R. Hershfield and G. L. Schmir, *J. Am. Chem. Soc.*, 1973, **95**, 7359.
- 12 D. F. DeTar, *J. Am. Chem. Soc.*, 1974, **96**, 1255.
- 13 K. N. Houk, H.-Y. Duh, Y.-D. Wu, and S. R. Moses, *J. Am. Chem. Soc.*, 1968, **108**, 2754.
- 14 E. Grunwald, *J. Am. Chem. Soc.*, 1986, **108**, 5719.
- 15 A. J. Benesi, *J. Phys. Chem.*, 1984, **88**, 4729.

Received 22nd June 1987; Paper 7/1122