layers were dried and concentrated under a stream of nitrogen. The residues from the two samples were taken up in dichloromethane-*d* for ^{1}H NMR spectroscopy. The sample derived from **11** yielded sufficient material to produce an NMR spectrum identical with that of fluoro-diHETE **5**.

Preparation of 7-Fluoro-5-hydroxyeicosa-6,8,11,14-tetraenoic Acid, 7, Its Lactone 8, and 7-Fluoro-9-hydroxyeicosa-5,7,11,14-tetraenoic Acid, 9, from Methyl 7,7-Difluoroarachidonate, 6a. Methyl 7,7-difluoroarachidonate (**6a**, 10 mg) was hydrolyzed with *Rhizopus arrhizus* lipase (800 μL, 40 000 units) in potassium phosphate buffer (9.9 mL, 0.1 M, 7.02) containing 17.3 mg of NaCl and 107.7 mg of gum arabic (1% solution). The mixture was stirred at 25 °C for 18 h. The reaction was terminated by acidification with 1 N HCl to pH 3.0 and extraction of the product with CH_2Cl_2. Separation of products was achieved by RP-HPLC on a Rainin Instruments Dynamax macro-HPLC column (C-18, 10 mm × 25 cm, 8 μm). Elution occurred with 65% CH_3CN/35% H_2O (pH 3.5) at 3 mL/min, and absorbance was monitored at 205 nm. Three fractions were collected and worked up as follows: The acetonitrile was removed under a stream of nitrogen. The residual aqueous solutions were then extracted 5 times with equal volumes of dichloromethane, and the extracts were dried by passing through a small column of anhydrous sodium sulfate in a disposable pasteur pipette and concentrated under a stream of nitrogen. The products are listed in the order of their elution from the column.

7-Fluoro-9-hydroxyeicosa-5(*Z*),7(*Z*),11(*Z*),14(*Z*)-tetraenoic Acid, 9 (24.0 min): ^{1}H NMR δ 5.68 (dd, 1 H, *J* = 30.4, *J* = 11.4, H-6), 5.55 (m, 1 H, H-5), 5.41 (m, 2 H, vinyl), 5.32 (m, 2 H, vinyl), 4.89 (dd, 1 H, *J* = 35.9, *J* = 8.1, H-8), 4.67 (m, 1 H, H-9), 2.81 (t, 2 H, *J* = 7.1, H-13), 2.46-2.31 (m, 6 H, H-2, H-4, H-10), 2.06 (q, 2 H, *J* = 6.9, H-16), 1.77 (m, 2 H, H-3), 1.39-1.27 (m, 6 H, H-17, H-18, H-19), 0.90 (t, 3 H, *J* = 6.9, H-20); ^{19}F NMR φ 112.6 (dd, *J* = 29.9, *J* = 33.7); UV (ethanol) 231.2 nm; high resolution MS (70 eV, *m/z*), calcd for $C_{20}H_{29}O_2F$ (M - H_2O) 320.2152, found 320.2157 (6.0%); FAB$^-$ 337 (M - 1).

7-Fluoro-5-hydroxyeicosa-6(*Z*),8(*Z*),11(*Z*),14(*Z*)-tetraenoic Acid, 7 (26.8 min): ^{1}H NMR δ 5.65 (dd, 1 H, *J* = 29.4, *J* = 11.2, H-8), 5.53 (m, 1 H, H-9), 5.40 (m, 3 H, vinyl), 5.36 (m, 1 H, vinyl), 4.86 (dd, 1 H, *J* = 35.6, *J* = 9.6, H-6), 4.66 (m, 1 H, H-5), 3.14 (t, 2 H, *J* = 6.0, H-10), 2.81 (t, 2 H, *J* = 6.2, H-13), 2.43 (t, 2 H, *J* = 7.5, H-2), 2.05 (q, 2 H, *J* = 7.2, H-16), 1.70 (m, 4 H, H-3, H-4), 1.40-1.27 (m, 6 H, H-17, H-18, H-19), 0.90 (t, 3 H, *J* = 6.6, H-20); ^{19}F NMR φ 112.8 (dd, *J* = 29.9, *J* = 33.8); UV (ethanol) 231.3 nm; high resolution MS (70 eV, *m/z*), calcd for $C_{20}H_{29}O_2F$ (M - H_2O) 320.2152, found 320.2161 (2.2%); FAB$^-$ 337 (M - 1).

7-Fluoro-5-hydroxyeicosa-6(*Z*),8(*Z*),11(*Z*),14(*Z*)-tetraenoic Acid 1,5-Lactone, 8 (104 min): ^{1}H NMR δ 5.67 (dd, 1 H, *J* = 28.7, *J* = 12.2, H-8), 5.63 (m, 1 H, H-9), 5.46-5.28 (m, 5 H, H-5, H-11, H-12, H-14, H-15), 4.94 (dd, 1 H, *J* = 34.5, *J* = 8.2, H-6), 3.15 (t, 2 H, *J* = 6.1, H-10), 2.81 (t, 2 H, *J* = 6.7, H-13), 2.63 (dt, 1 H, *J* = 17.7, *J* = 7.3, H-2), 2.49 (dt, 1 H, *J* = 17.7, *J* = 7.9, H-2), 2.06 (q, 2 H, *J* = 7.1, H-16), 1.69 (m, 4 H, H-3, H-4), 1.41-1.26 (m, 6 H, H-17, H-18, H-19), 0.91 (t, 3 H, *J* = 7.3, H-20); ^{19}F NMR φ 110.34 (dd, *J* = 28.1, *J* = 34.7); UV (ethanol) 232.8; high resolution MS (70 eV, *m/z*) calcd for $C_{20}H_{29}O_2F$ (M^+) 320.2152, found 320.2151 (4.5%).

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On the Origin of Proximity Effects on Reactivity: A Modified MM2 Model for the Rates of Acid-Catalyzed Lactonizations of Hydroxy Acids

Andrea E. Dorigo and K. N. Houk*

Contribution from the Department of Chemistry and Biochemistry, University of California, Los Angeles, California 90024. *Received July 25, 1986*

Abstract: In order to determine the role of functional group proximity and orientation upon reactivity, we have carried out a computational study of the acid-catalyzed lactonizations of hydroxy acids. Ab initio calculations on the attack of water on protonated formic acid gave information about the preferred geometry of nucleophilic attack. On the basis of the results of these calculations, new parameters have been added to Allinger's MM2 force field, so that the steric energies of the transition states of lactonizations of hydroxy acids can be calculated. Relative activation energies found experimentally are reproduced by this force field. Some of the various models which have been proposed to explain the very high rates of certain intramolecular and enzymatic reactions are evaluated. In particular, our calculations show that there is no relationship between (i) the angle of nucleophilic attack and the reactivity of a hydroxy acid or (ii) the distance between reacting atoms in the starting material and the rate of reaction. Both (i) and (ii) are true even for rigid systems where the spatial relationships between reacting atoms are fixed. Most importantly, our results show that very diverse reactivities (with rate constants varying over ten orders of magnitude) can be accounted for quantitatively by our force field. This constitutes a dramatic improvement over previous qualitative models. Our force field also allows us to make quantitative reactivity predictions for conformationally rigid hydroxy acids.

During the last 20 years, the rates of acid-catalyzed lactonizations of hydroxy acids have been used to assess the importance of proximity and mutual orientation of functional groups upon rates of intramolecular reactions and as models to evaluate the importance of these effects upon the catalytic power of enzymes. We have devised a force field for the transition states of these reactions and describe here the computational model and the general implications of this study for the understanding of proximity and orientation effects on reaction rates.

In a series of recent reports[1-4] it has been suggested that the rates of intramolecular organic reactions are dependent primarily upon the distance between the reacting atoms in the starting

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materials. In particular, Menger has proposed that the distance between reacting centers and the time spent at the "critical distance" at which reaction occurs are the two parameters upon which reactivity depends.[1] Other factors—in particular the relative orientation of the reacting bonds[3]—are said to be unimportant. The latter argument ("orbital steering") was invoked in the early 70s by Koshland[5,6] in order to explain the differences in reactivity measured for several apparently similar bicyclic hydroxy acids[7] and more generally to account for the very high rate enhancements which enzymes can induce in this and other bimolecular reactions.

The concept of orbital steering was subsequently the object of both support and criticism from a number of different sources.[8-15] Bruice[8] suggested that large rate enhancements in such systems could originate from an increase in the entropy of activation, relative to the intermolecular case, and also from the "freezing" of one or more bond rotations in the intramolecular case.[9] Bruice pointed out that the Koshland model implied values for the force constants involving partly formed bonds which were larger than those for fully formed covalent bonds; such force constants are entirely unrealistic. Calculations by Hoare[10] indicated that solvent effects might raise considerably the energy required to align bonds optimally for reaction to take place, even if this required a deviation from the starting geometry of only a few degrees. However, the Hoare model is undoubtedly unrealistically rigid, so that the Bruice criticism is still valid. Delisi and Crothers[11] used Monte Carlo simulations to compare the rates of inter- and intramolecular reactions. They concluded that proximity of the reacting functional groups could enhance the reaction rate by a factor as high as 10^7, depending on the size of the volume to which the reactive units were constrained. These authors concluded that orbital steering was not necessary to explain the observed rate enhancements in intramolecular reactions. Cohen[12] studied the acid- and base-catalyzed lactonization of a series of phenols and interpreted the rate-accelerating effects observed in the series as a result of the increase in the population of a highly reactive conformer ("stereopopulation control") and perhaps an enhancement of reactivity due to induced strain. Some of the acceleration was believed to arise from the improvement in the angular relationship of the reacting centers, in support of the orbital steering model. PRDDO[13] calculations by Scheiner, Lipscomb, and Kleier[14] led to the conclusion that nucleophilic attack of methanol on formic acid has very loose angular requirements and thus a wide "reaction funnel". For example, rocking the methanol molecule away from its preferred approach by 20° caused an energy increase of less than 1 kcal/mol. More recent experimental studies on nucleophilic substitutions[15] and proton transfers[16] have demonstrated that such reactions are favored by "compression" of the reactant units and, in one case,[16] that there are no stringent orientational requirements.

Page and Jencks[17,18] proposed that the origin of the rate enhancement of intramolecular reactions is due to an entropic effect; that is, the loss of translational and rotational entropy slows intermolecular reactions but not intramolecular reactions. These effects alone, according to the authors, may cause the activation entropy of an intramolecular reaction to be as much as 50 eu less negative than that of the intermolecular reaction, corresponding to acceleration by a factor of ca. 10^{10} at 25 °C.

A later review by Page[19] shows how the rates of acid-catalyzed lactonizations can be estimated from the calculated enthalpy and entropy changes which occur in the cyclizations of related hydrocarbons. Obviously this is a crude model, but the agreement with the experimental evidence is astonishingly good. Page's conclusion is that the reactivity of these compounds can be rationalized on the basis of simple thermodynamic arguments, without resorting to other concepts such as orbital steering or proximity effects. Most of the compounds included in the Page study are among the ones investigated by Koshland.[7] However, there are cases where freezing of a single rotation leads to very large (ca. 10^4) rate enhancements.[1,12] In the absence of relevant structural changes, freezing of a single rotation should bring about only a fivefold increase in the rate due to a more favorable entropy of activation.[17,20] Such anomalous cases indicate that conventional thermodynamic arguments might not always suffice to rationalize the reaction rate. This appears evident also from a more recent review by Kirby,[21] in which effective molarities (EM) for a large number of intramolecular reactions are reported. Some of these are much smaller than expectation based upon the Page–Jencks model. In general, nucleophilic catalysis is responsible for large rate enhancements in certain reactions, while the EM in reactions where general base catalysis operates is usually small. In the latter case the "looseness" of the transition state is responsible for the increase in the entropy of activation in the intermolecular case.

Even though conventional concepts can adequately explain most of the experimental findings described above, some results appear to warrant the existence of a special "proximity" factor. In particular, Menger[1] suggested that it was impossible to predict EM values from current theory and proposed that "the rate of reaction between functionalities A and B is proportional to the time that A and B reside at a critical distance".[1] This "spatiotemporal" hypothesis suggests that conventional orientation and strain arguments, even proximity arguments, cannot in themselves explain experimental results. In order to evaluate this and earlier hypotheses, we have devised a force field model to investigate in greater detail the behavior of several hydroxy acids. As noted earlier, Page used a "hydrocarbon analogy" to model these reactions[19] and obtained reasonably good agreement with experiment. We have studied the actual compounds involved in the lactonizations, modeled the transition states of these reactions, and calculated the reactant and product steric energies.

As will be shown in detail, we have found that there is no support for the Koshland or Menger hypothesis. Indeed, the rates of these reactions are nicely rationalized by the relative energies of reactants and the transition state for breakdown of the tetrahedral intermediate to form the protonated lactone. The relative activation energies are influenced in a qualitative way by the distance between, and relative orientation of, the functional groups in reactants. The real determinant of reactivity is the energy required to distort the reacting functional groups into the geometry of the rate-determining transition state. For these reactions, rates are predictable quantitatively by the "conventional" concepts incorporated into the modified MM2 force field. For this series of reactions, a quantitative theory of relative reactivity is now available.

Results and Discussion

Analysis of Reactant Geometries. We have studied most of the hydroxy acids that were studied by Koshland[7,22] and Cohen.[12] The

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Table I. Comparison of Steric Energies (E_s), C--O Distances in the Starting Materials (R_{CO}), Angles of Attack (∠O--C-C and ∠O--C=O), and Rate Constants (k) for Acids **1–15**

hydroxy acid	E_s, kcal/mol	E_s', kcal/mol	R_{CO}, Å	∠O--C-C, deg	∠O--C=O, deg	k, M^{-1} min^{-1}
1	23.6	23.4	3.02	69	78	0.01
2	23.9	23.1	2.95	79	102	0.01
3	27.9	28.0	2.89	74	79	0.3
4	29.0	28.1	2.87	82	103	0.18
5	24.1	23.3	2.86	77	75	1200
6	19.5	19.6	2.98	72	74	0.95
7	26.8	26.5	4.23	(57)[a]	(61)[a]	7.2
8	20.5	20.4	2.98	80	84	10
9	29.3	29.2	2.93	75	69	71
10	24.5	24.1	2.84	78	76	107
11	23.4	22.2	4.27	(63)[a]	(117)[a]	152
12	0.9	-0.1	4.38	(18)[a]	(116)[a]	0.09
13	1.8	0.8	4.37	(18)[a]	(116)[a]	0.13
14	3.2	1.4	4.60	(36)[a]	(110)[a]	45
15	10.6	9.4	2.93	69	75	6.0×10^5

[a] Angles are given in parenthesis when R_{CO} is large and the conformation does not allow direct nucleophilic attack on the carbonyl.

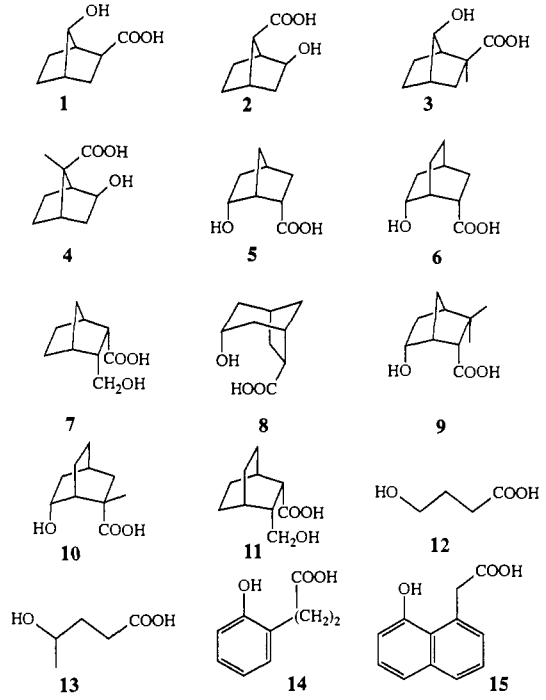

Figure 1.

steric energies of compounds **1–15**, shown in Figure 1, were calculated by using Allinger's MM2[23] program. For the aromatic compounds, **14** and **15**, the parameters developed by Beckhaus were used for the aromatic ring.[24] In all cases, rotations about the carbon–alcoholic oxygen bond and the carbon–carboxylic acid carbon bond were investigated in order to locate the lowest energy conformation. This was done by rotating about one bond at 60° intervals and performing the same set of rotations for the other bond independently, generating a total of 36 conformations. The same procedure was adopted for single bonds in those compounds in which rotation can occur. The validity of this procedure was checked for compounds **1**, **2**, and **3**, for which dihedral driver calculations were performed in which both the C—C—C=O and the C—C—O—H dihedral angles were changed by 10° intervals from 0–360°. Table I shows the results obtained from these calculations. Two sets of energies have been calculated and are indicated by E_s and E_s' in the table. The E_s values are derived by assuming a dielectric constant ϵ of 1.5, which mimicks the gas phase, while in the calculation of E_s' ϵ was set equal to 80, the value for water. The C--O distances obtained for ϵ = 1.5 and the angles of attack of the alcoholic oxygen onto the C—C and C=O bonds of the carboxyl group (O--C-C and O--C=O, respectively) are also listed, together with the measured rate constant. This attack angle is the quantity which Koshland proposed is crucial in determining reactivity.

Table II. Steric Energies of Major Conformers (in Decreasing Order) and Mean Steric Energy of Acids **1–6**

	E_v	E_{iv}	E_{iii}	E_{ii}	E_i	E_m
1			25.2	25.0	23.6	23.8
2	25.6	25.5	24.8	24.2	23.9	24.2
3	30.0	29.5	29.3	29.1	27.9	28.2
4	31.0	30.7	29.9	29.3	29.0	29.3
5	25.9	25.1	24.6	24.3	24.1	24.4
6		21.3	20.9	20.7	19.5	19.8

The energies given in Table I refer to the most stable conformer for compounds **1–15**. However, each acid has several possible conformations due to rotation about the alcoholic C-O bond and the carboxylic C-C bond. The steric energies ($E_i - E_v$) of the major conformers have been calculated for acids **1–6**, for ϵ = 1.5, and are shown in Table II. In each case, all conformers within 2.0 kcal/mol are listed. A mean value of the steric energy (E_m) of each acid can then be calculated from the energies of individual conformers by assuming a Boltzmann distribution. A comparison of this value (E_m) with the steric energy of the most stable conformer (E_i) (last two columns of Table II) shows that the difference between the two values is small and essentially constant (0.2–0.3 kcal/mol) in all cases. It is therefore a reasonable approximation, when comparing the *relative* activation energies of the lactonizations, to use the energy of the global minimum as the energy of the acid, without including higher energy conformers. This approximate procedure was adopted here.

As Table I shows, there is no straightforward relationship between the calculated distances and the experimental reactivities. For example, the calculated C--O distance for compounds **4** and **5** is virtually the same, yet **5** is more than 10^4 times more reactive than **4**. Similarly, in **2** and **9** the interatomic distances differ by only 0.02 Å, but **9** reacts about 7000 times faster. On the other hand, compounds with rather different C--O distances like **1** and **2**, or like **9** and **10**, exhibit similar reactivities. These considerations invalidate the Menger model as quoted earlier; there is no simple relationship between distance between functional groups in reactants and reactivity. Obviously, as intimated by Menger in qualifying statements, the structural features and the strain energies in the series vary; the rate of reaction must be determined by the change in strain energy upon proceeding from reactants to products. There should be an obvious qualitative relationship with functionality distance, but not the quantitative relationship that Menger implies. The Menger model seems to be applicable only to severely limited cases in which both the C--O distance and the difference in strain energy between reactants and products are essentially identical, as for his compounds **3** and **4**.

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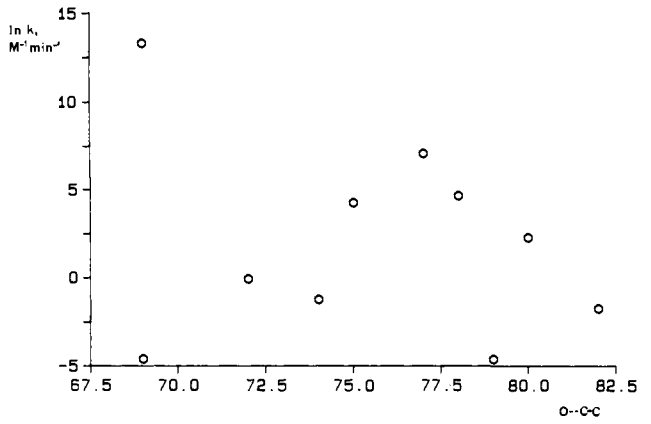

Figure 2.

The Koshland orbital steering model is also irrelevant to the observed experimental results. Figure 2 shows a plot of ln k, the experimental rate constant (M^{-1} min^{-1}) for acid-catalyzed lactonization, vs. the O--C-C attack angle in those acids where the minimum energy conformation allows for direct attack of the alcoholic hydroxyl on the carbonyl. The acids are labeled in the figure. It is evident that there is again no simple relationship (except the rollercoaster pattern) between the O--C-C angle and the measured rate constant. For example, **4**, **8**, and **10** have very similar attack angles (82°, 80°, and 78°, respectively), but **10** is over ten times more reactive than **8** and over 500 times more reactive than **4**. Similarly, **9** is two orders of magnitude more reactive than **3**, but both have the same attack angle. On the other hand, **3** and **4** have different angles of attack (74° and 82°, respectively) but similar reactivities, and the same holds for **1** and **2**. In this respect, our results are in full accord with Menger's previous reports.[3]

A MM2 Model for Acid-Catalyzed Lactonizations.[25] We have developed a more general model which accounts for the relative activation energies for the reactions of these compounds. The model provides energies for both reactant and transition state in order to predict the activation barrier and thus the rate constant in each case. No model can reliably predict this energy gap without accounting for the solvation of both ground and transition state. The difference in the energy of solvation of the two species is the critical factor in determining the activation energy of the reaction in solution—indeed the reaction proceeds with no barrier in the gas phase. The magnitude of this factor is unknown; however, it should not vary appreciably in a series of structurally similar compounds. Thus, the effect of solvation is expected to cancel out when comparing reactivities within a series of structurally similar species. Calculations on isolated molecules and their transition states can therefore be used to predict the relative reactivities within a class of compounds even though the absolute rate constants cannot be evaluated. For this reason, and because of the prohibitive computational cost of including solvent effects in these systems, we have chosen to evaluate the energies of the *isolated* hydroxy acids and reaction transition states.

Ab initio methods have been used to study a simple model system, and subsequently we have derived a force field model for the transition state based on the ab initio calculation. The model system is the attack of a water molecule on protonated formic acid—a process that mimics the nucleophilic attack of the alcoholic oxygen on the carboxyl group in acid-catalyzed lactonizations as well as the breakdown of a protonated tetrahedral intermediate. All calculations have been performed by using the GAUSSIAN 82 series of programs developed by Pople and co-workers.[26] An RHF/3-21G[27] geometry optimization was performed on a number

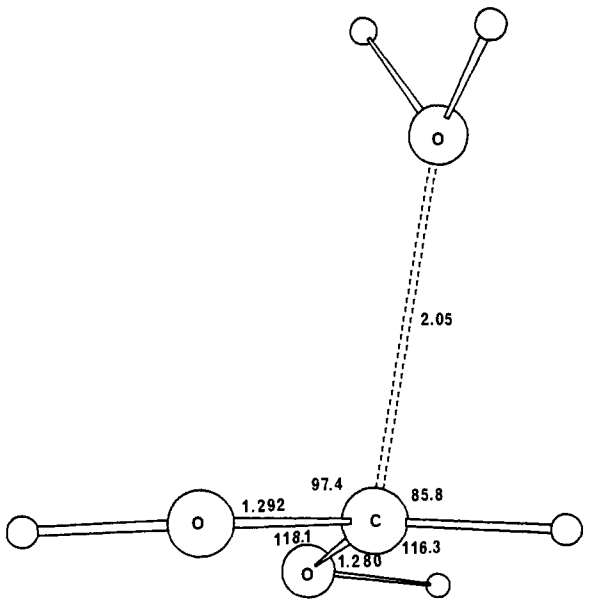

Figure 3.

of structures in which the C--O distance was constrained at different values. The reaction was found to proceed with no activation barrier, as is expected in the gas phase. This result is in agreement with reports of ab initio calculations on related nucleophilic additions to carbonyls.[28,29] An energy minimum was found for C--O equal to 2.05 Å. The minimum energy structure according to our calculations is shown in Figure 3. In this structure, the carbon–oxygen bonds in the formic acid molecule are intermediate in length between single and double bonds. The angles formed by the water oxygen with the two carbon–oxygen bonds are 97.4° and 102.2°. These results agree with Koshland's[7] prediction that the angle of attack should be between 90° and 109°. The protonated formic acid moiety has a "sickle" conformation as is also calculated to be preferred for isolated protonated formic acid.[30]

In solution, the reaction proceeds with a barrier, since the reactants are solvated more effectively than any intermediate geometries, in which the charge is delocalized extensively. A computational analysis of the alkaline hydrolysis of formamide including solvation effects using molecular mechanics has recently been performed by Weiner et al.[31] They first performed ab initio HF/4-31G[26] geometry optimizations followed by energy calculations of the optimized geometries at the MP2[32]/6-31G*[26] and 4-31+G[26] level. These calculations indicated that in the gas phase there is no barrier to the formation of the tetrahedral complex. On the other hand, when energy refinement was carried out with explicit inclusion of water molecules, a maximum was obtained for C--O = 2.08 Å. Similar results have been found by Madura and Jorgensen[33] in the study of the addition of hydroxide anion to formaldehyde. The importance of including solvation in order to obtain the correct energetic relationship between reactants and transition states in these systems has been shown also by Maggiora

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Table III. Calculated Differences in Steric Energy and Experimental Free Energy Differences between Reactants and Products

compd	ΔE_{rp}	$\Delta\Delta E_{rp}'$	$\Delta G°$	$\Delta\Delta G°'$
5	1.9	0.0	−5.7	0.0
7	2.8	0.9	−4.2	0.9
12	5.0	3.1	−1.1	4.6
13	4.2	2.3	−1.4	4.3
14	10.3	8.4	2.0	7.7

and Schowen in their ab initio study of the hydration of formaldehyde.[34] The forming C--O distance of 2.1 Å seems to be reasonable for a transition state, and so we expect the structure corresponding to a minimum in our calculation to be similar to that of the transition state in solution. However, the effect of solvation on a delocalized charged species, as is the case here, is expected to be smaller. This has been noted in the study of the reaction of the hydroxide anion with formamide,[31] where solvation affects dramatically the transition from OH^- to the delocalized tetrahedral intermediate but not the subsequent step from the intermediate to the formate anion.

We have developed an MM2 model for the transition state of the lactonization based upon this assumption. We first verified that MM2 calculations could reproduce the relative stabilities of reactants and products. That is, the calculated difference in steric energy between each pair of hydroxy acid and lactone should be proportional to the equilibrium constant for that pair. Table III shows that this is in fact the case to a very satisfactory degree for the limited number of compounds for which equilibrium constants are available.[7,12] Table III compares the calculated steric energy difference in each case (ΔE_{rp}) with the difference in free energy, $\Delta G°$, derived from the experimental equilibrium constant. The calculated and experimental energy differences relative to **5**, which has the highest value of the equilibrium constant, are denoted $\Delta\Delta E_{rp}'$ and $\Delta\Delta G°'$, respectively. These results show that MM2 gives a realistic picture of the position of the equilibrium between starting hydroxy acid and lactone in each case.[35]

We next devised an MM2 model for the transition state of the lactonization reaction, based on the geometry found from the ab initio calculation. In this model, all normal bond lengths and angles involving the breaking or forming bonds are set equal to the corresponding values calculated in the ab initio study. All other geometrical parameters in the system are standard MM2 values. This procedure defines the geometry of the transition state but does not determine the force constants for those vibrational modes which involve partially formed bonds. Standard MM2 parameters are inadequate for the purpose. We have thus introduced new parameters defining the stretching, bending, and torsional constants which involve the breaking and forming bonds. A complete list of the parameters inputed in the model is provided in the Appendix.

In the model, the central carbon atom is treated like an sp^3 atom. The two short (ca. 1.30 Å) C–O bonds are treated like C_{sp^3}–O_{sp^3} *single* bonds. The third oxygen atom is also treated like an sp^3 atom; however, the C--O bond in this case is much longer (2.05 Å) and is therefore treated differently from the other two. Thus the force constants for the stretching and bending modes involving this bond are set equal to one-half of the standard MM2 values for the corresponding distortions in ground-state molecules. All other force constants and natural bond lengths and angles are normal ground-state values.

All model species are neutral in our calculations, even though the transition state for the acid-catalyzed reaction obviously has a positive charge. This choice was made since MM2 does not allow charges to delocalize over a system of atoms (as is the case here), nor does it optimize charge distribution during energy minimization. All bonds are treated as dipoles; thus, for example, the bond moment employed by MM2 for a C_{sp^3}–O_{sp^3} bond is used for all such C–O bonds in the molecule, including those which are involved in the transition state. The dielectric constant was varied in two sets of calculations (vide infra), one mimicking gas-phase conditions and the other modeling the aqueous phase.

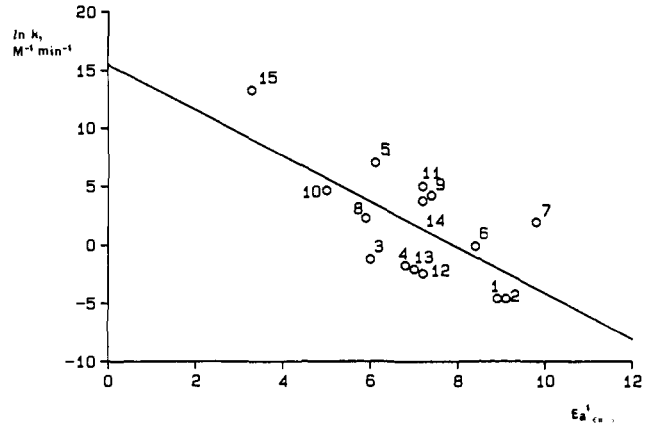


Figure 4. Plot of ln k (see text) vs. the calculated activation energy for the first transition state of the lactonization of hydroxy acids **1–15**.

In order to test the performance of the model as the new empirical parameters are changed, these were varied in three other sets of calculations, which we shall refer to as II, III, and IV. In II, the bending constants for all angles involving the forming C--O bond and the stretching constant for this bond were set equal to one-half the values used in the first calculation (i.e., one-half of standard MM2 values for a C–O bond type). In III, the bending constants and the C--O stretching constant were set equal to twice this value, that is, equal to the standard MM2 values for this bond type. In IV, the carboxylic acid carbon and the four atoms bonded to it were frozen in the transition-state orientation, so that the critical angles and bond lengths were rigidly fixed. These modifications correspond to weakening (model II) and strengthening (models III and IV) the C--O bond strength over a wide range. In all cases, torsional potential terms about the forming bond were neglected. The results of these sets of calculations showed that, although the absolute values of the calculated transition-state energies obviously vary in each case, the predicted relative reactivities do not change significantly in the first three models. The last, "rigid" model is in line with the others for most compounds but in a few cases gives results in considerable disagreement with them and with the experimental rates. All the results reported here are the ones obtained by using model I. Thus, there will be a whole family of models which will give similar results to those described here. In order to devise parameters on a more rational basis than done here, it would be necessary to have experimental or good computational information on geometries and energies of transition states of reactions of many more molecules of widely different structural types.

Figure 4 shows a plot of the calculated activation energy $E_a^1{}_{(\epsilon=1.5)}$ (kcal/mol) for the attack of the hydroxyl group on the protonated acid vs. ln k, where k is the experimental reaction rate constant. The activation energy $E_a^1{}_{(\epsilon=1.5)}$ is defined as the difference between the steric energies of the transition state and the starting hydroxy acid, calculated at $\epsilon = 1.5$, the default value of ϵ in MM2. Figure 5 shows the structures of the calculated transition states for all hydroxy acids. The geometrical parameters of interest are given in Table IV. Here, together with $E_a^1{}_{(\epsilon=1.5)}$, we also show the activation energies $E_a^1{}_{(\epsilon=80)}$ obtained from model I but with a dielectric constant of 80, the value of ϵ for water. In the table, R_{C--O} is the length of the forming carbon–oxygen bond, and ∠O--C–C, ∠O--C–O′, and ∠O--C–O″ are the angles which the alcoholic oxygen forms with the carbon–carbon and the two carbon–oxygen bonds of the carboxylic group. In all cases the H–O–C–O–H moiety of the acid assumes a U-shaped, rather than sickle-shaped, conformation. Additional torsional parameters would have to be introduced in order to achieve the correct geometrical preference.[36] The relative transition-state energies,

(34) Williams, I. H.; Spangler, D.; Femec, D. A.; Maggiora, G. M.; Schowen, R. L. *J. Am. Chem. Soc.* **1983**, *105*, 31.

(35) MM2 has not been parameterized for aromatic or vinyl esters. Thus some of the parameters used in the calculation of the product of **14** are the ones defined for alkyl esters. See the Appendix for more details.

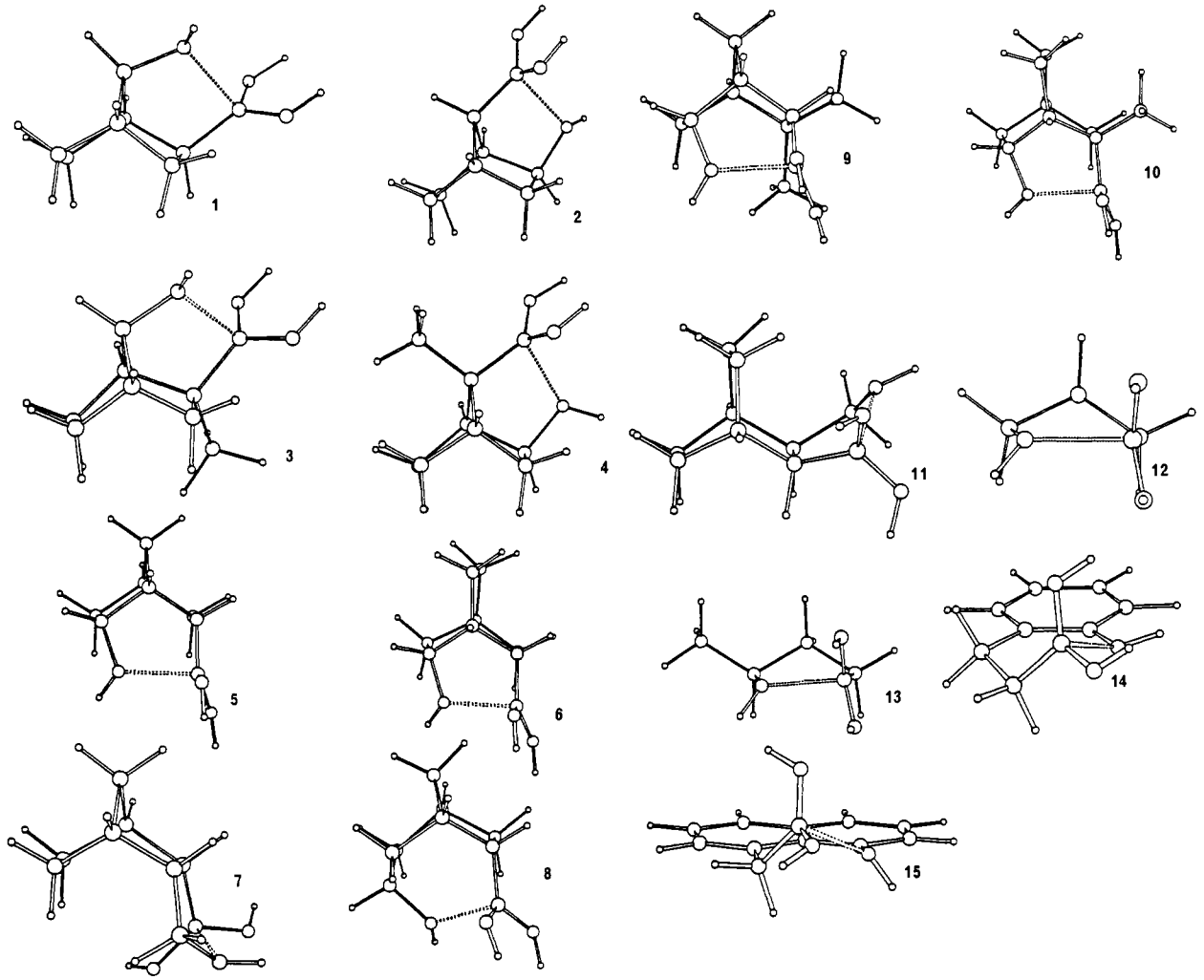


Figure 5. Structures of the first transition state of the lactonization of hydroxy acids **1–15**.

Table IV

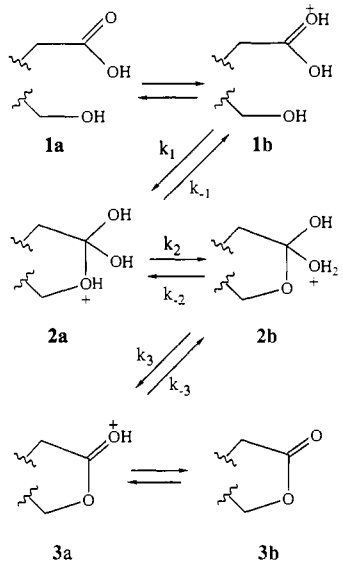
hydroxy acid	$E_a^{\ddagger}{}_{(\epsilon=1.5)}$	$E_a^{\ddagger}{}_{(\epsilon=80)}$	$R_{C\cdots O}$, Å	∠O--C-C	∠O--C-O′	∠O--C-O″	ln k
1	9.1	11.7	2.05	82	106	104	-4.6
2	8.9	12.1	2.05	86	104	102	-4.6
3	6.0	8.3	2.05	83	105	104	-1.2
4	6.8	7.7	2.05	87	109	97	-1.7
5	6.1	9.4	2.05	86	103	102	7.1
6	8.4	11.0	2.06	84	105	102	-0.1
7	9.8	12.1	2.06	86	105	96	2.0
8	5.9	8.5	2.05	91	107	100	2.3
9	7.4	9.7	2.05	85	103	105	4.3
10	5.0	8.1	2.05	85	103	103	4.7
11	7.2	10.7	2.05	86	102	102	5.0
12	7.2	11.3	2.06	86	106	95	-2.4
13	7.0	11.4	2.06	86	105	99	-2.0
14	7.2	9.8	2.05	91	103	101	3.8
15	3.3	4.7	2.04	90	104	102	13.3

however, are not expected to change.

It is noteworthy that the C--O distance in all cases is equal or very close to 2.05 Å. Even the C-O bonds of the carboxylic moiety are always equal or very close (within 0.01 Å) to the ones calculated in the ab initio study. On the contrary, the values of the ∠O--C-C angle vary considerably in the series and are often different from the "ideal" angle of attack. The latter, according to our ab initio HF/3-21G calculations, should be equal to 85.8°. The same is found for the ∠O--C-O′ and ∠O--C-O″ angles, which ideally should be equal to 97.4° and 102.2°. These results were obtained when the bending constants involving the C--O bond and the C--O stretching constant were set equal to half the corresponding standard MM2 values. If a larger bending constant were chosen for these two angles, the deviation from the "ideal" angle would be smaller and within the experimental error of MM2. However, even when standard MM2 values were assigned for angular distortions (model III), the deviations from the ideal values for the angle of attack were still significant in many cases. We agree with Bruice's conclusion[8] that it would be unrealistic to consider the bending motion involving partly formed bonds to be more difficult than that involving full bonds. Our earlier ab initio studies on the abstraction of a methane

(36) For a recent treatment of torsional parameters in the O-C-O-C and O-C-O-1p groups of acetals, see: Norskov-Lauritsen, L.; Allinger, N. L. *J. Comput. Chem.* **1984**, *5*, 326.

Scheme I



hydrogen by hydroxy radical[37] showed that bending the O--H--C angle by 20° is energetically less costly than stretching either of the partially formed bonds by only 0.1 Å.

A comparison of the calculated value of $E_a^1{}_{(\epsilon=1.5)}$ and the logarithm of the rate constant k (Figure 4) shows that the agreement between theory and experiment is unsatisfactory. The estimated error on the experimental rate constants is about 50%,[3] so that we are only concerned with the order of magnitude of the calculated and experimental data. Nonetheless, some compounds are evidently not in line with the others; for example, hydroxy acids **3** and **4** are predicted to be among the most reactive ($E_a^1{}_{(\epsilon=1.5)}$ = 6.0 and 6.8 kcal/mol, respectively), but experimentally the rate constants for these two acids are considerably lower than those of most others. Similarly, **1** and **2** have much lower rate constants than predicted. On the other hand, compounds **5** and **11** would be predicted to have rate constants in the range 1–10 M^{-1} min^{-1}, comparable to the ones predicted for most other compounds. The experimental evidence is quite the opposite, since **5** is much more reactive than all the other bicyclic acids, and **11** has a rate constant larger than 100 M^{-1} min^{-1}. In general, there is a poor correlation between the predicted and the experimental reactivities. The least-squares line shown has an r value of only −0.62. As shown in the table, the difference between $E_a^1{}_{(\epsilon=1.5)}$ and $E_a^1{}_{(\epsilon=80)}$ varies from a minimum of 0.9 kcal/mol (compound **4**) to a maximum of 4.4 kcal/mol (compound **13**), the mean difference being 2.7 ± 0.9 kcal/mol. For most compounds, the change in the calculated energy of activation is fairly constant and close to the mean value of 2.7 kcal/mol, so that the correlation between $E_a^1{}_{(\epsilon=80)}$ and ln k is found to be just as poor (r = −0.64) as in the case of $E_a^1{}_{(\epsilon=1.5)}$.

Solvation effects could in principle be responsible for these anomalies in the model, or the first step of the reaction may not be the rate-determining step of the reaction. Since the reaction proceeds through the formation of several labile intermediates, the global rate constant can be derived from a steady-state analysis. Referring to the reaction pathway shown in Scheme I, we can express the global rate constant, k, in terms of the rate constants for each reversible step. If we assume that the basicities of starting material and product do not vary significantly in this series, then the magnitude of the reaction rate R for each substrate will depend on k_1, k_{-1}, k_2, k_{-2}, k_3, and k_{-3}. A steady-state kinetic treatment shows that the reaction rate depends on k_1 alone only if the breakdown of the tetrahedral intermediate to give the product is much faster than the return to the starting material. This cannot be assumed to hold true, especially since the ring opening to give the hydroxy acid molecule is accompanied by a release in bending strain. Indeed, according to Kirby,[21] the rate-determining step is in general the breakdown of the tetrahedral intermediate. In other words, k_3 in Scheme I is small, and the reaction rate is then proportional to the product of k_3 and the equilibrium constants of the preceding steps. Milstein and Cohen[12] also found the loss of water from the intermediate to be the rate-determining step. In their study of the lactonizations of coumarinic acids, Hershfield and Schmir[38] found that the reaction kinetics was pH dependent, with the attack of the phenolic hydroxyl onto the carboxyl becoming rate-determining at low pH. However, the authors also suggest that the coumarinic acids are the exception, due to the unsaturation in the side chain. More evidence in favor of the breakdown of the tetrahedral intermediate is provided by the good correlation found by Gandour between the rates and the equilibrium constants for lactonization of four hydroxy acids and for the esterification of acetic acid.[39]

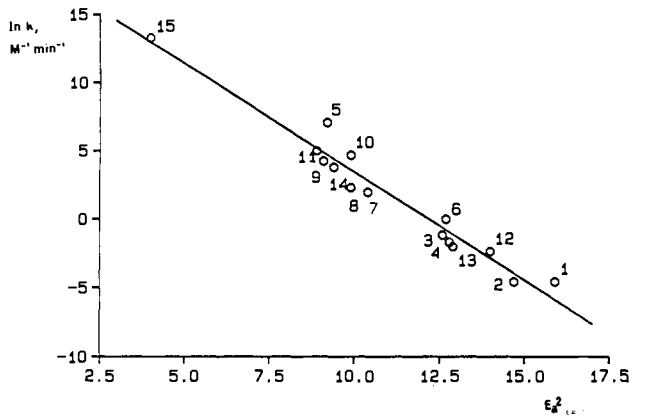


Figure 6. Plot of ln k (see text) vs. the calculated activation energy for the second transition state of the lactonization of hydroxy acids **1–15**.

In order to determine whether calculations support this idea, we calculated the energy of the second transition state—corresponding to the loss of water from the protonated tetrahedral intermediate—for all compounds in our study. The second transition state has been modeled in a fashion completely analogous to that used for the first. The force constants for these transition states, which are provided in the Appendix, are the same as those for the first one, although they now refer to different bonds involved in bond making and bond breaking. We have once again performed four sets of calculations in which the parameters involving the breaking bonds have been varied over the range of values described for the first transition state. We have thus ascertained that the results of our calculations are not highly dependent on one particular choice of parameters. Once again, the model in which the central atoms of the transition state are fixed in space is somewhat less satisfactory than the other three. In the ensuing discussion we shall refer to energies and geometries calculated by setting stretching and bending parameters involving the partially formed bonds equal to half of the standard MM2 values for those bonds, as we have described above for the first transition state (model I).

The energy differences, $E_a^2{}_{(\epsilon=1.5)}$ between the second transition states and the starting materials are plotted vs. the experimental ln k in Figure 6. There is a good correlation (r = −0.97) between the calculated and experimental reactivities, considering the crudeness of the model, the neglect of specific solvation effects, and the inaccuracies of some of the experimental data. The structures of the transition states in each case are given in Figure 7. In accordance with our findings for the first energy maximum, we note that the C--O distance varies little, if at all, from 2.05 Å. Details of the geometry of the transition state are given in Table V, together with $E_a^2{}_{(\epsilon=1.5)}$ and ln k. The angles of attack relevant to the Koshland model are also shown for comparison. We have also calculated the effect of setting the dielectric constant to 80 on the activation energies, denoted by $E_a^2{}_{(\epsilon=80)}$. Here we

(37) Dorigo, A. E.; Houk, K. N., unpublished results.

(38) Hershfield, R.; Schmir, G. L. *J. Am. Chem. Soc.* **1973**, *95*, 7359; **1973**, *95*, 8032.

(39) Gandour, R. D. In *Transition States of Biochemical Processes*; Gandour, R. D., Schowen, R. L., Eds.; Plenum Press: New York, 1978; p 537.

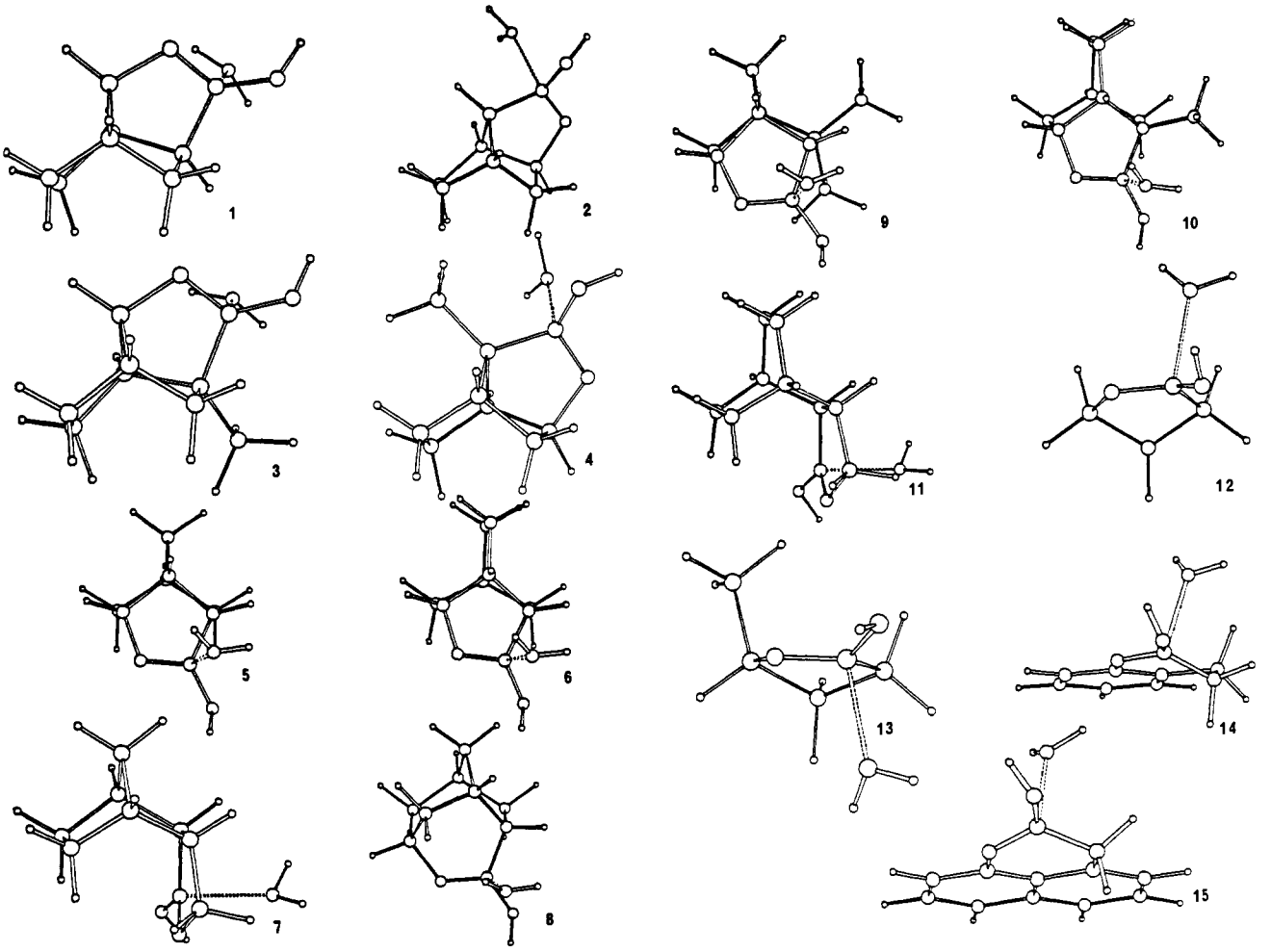


Figure 7. Structures of the second transition state of the lactonization of hydroxy acids **1–15**.

Table V

hydroxy acid	$E_a^2{}_{(\epsilon=1.5)}$	$E_a^2{}_{(\epsilon=80)}$	$R_{C\cdots O}$, Å	∠O···C–C	ln k
1	15.9	16.5	2.05	69	−4.6
2	14.7	15.7	2.05	79	−4.6
3	12.6	12.9	2.05	74	−1.2
4	12.8	13.7	2.04	82	−1.7
5	9.2	10.4	2.05	77	7.1
6	12.7	13.0	2.05	52	−0.1
7	10.4	11.4	2.06	(57)	2.0
8	9.9	10.5	2.05	80	2.3
9	9.1	9.9	2.06	75	4.3
10	9.9	10.7	2.05	78	4.7
11	8.9	10.8	2.06	(63)	5.0
12	14.0	15.5	2.06	(17)	−2.4
13	12.9	14.4	2.05	(18)	−2.0
14	9.4	11.0	2.05	(36)	3.8
15	4.0	3.9	2.06	93	13.3

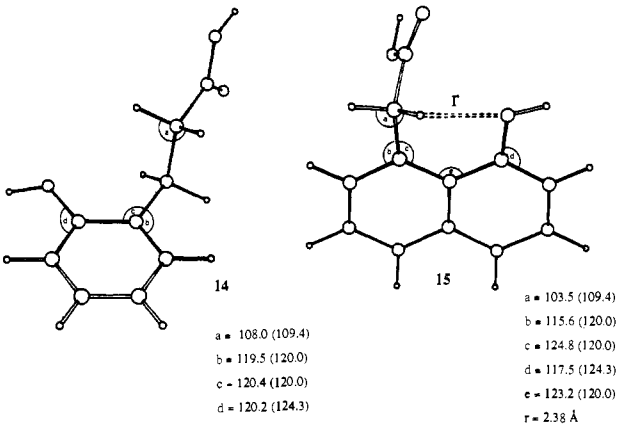


Figure 8.

find that the difference between $E_a^2{}_{(\epsilon=1.5)}$ and $E_a^2{}_{(\epsilon=80)}$ values is small (1.0 ± 0.5 kcal/mol) and approximately constant in the series, so that a good correlation (r = −0.97) is obtained even between $E_a^2{}_{(\epsilon=80)}$ and ln k values.

A direct comparison of the reactivity of the two phenols with all the other aliphatic alcohols is not expected to be realistic, due to differences in solvation, in the experimental conditions employed in the studies[7,12] of the two systems and intrinsic differences in the reactivity of the two types of compounds. Nevertheless, the relative reactivity of the two phenols is reproduced very well by our calculations. In these calculations the C(sp^2)–O–C(sp^3)–O torsion, which is not defined in MM2, was treated as a C(sp^2)–O–C(sp^3)–C(sp^3) torsional mode. According to our calculations, a large part of the difference in the activation energies for the two compounds arises from angular distortions and unfavorable nonbonded interactions which are present in the hydroxy acid **15** and which involve the phenolic hydroxyl group and the CH_2COOH group. These distortions are evident when a comparison of the geometries of the two starting materials is made, as shown in Figure 8. The numbers in brackets are the minimum energy bond angles (according to the MM2 force field); it is seen that in **15** significant angular distortion is necessary in order to alleviate the strong nonbonding interactions between the OH and CH_2COOH groups. These destabilizing factors are not present in the transition state where bonding occurs between the two groups. Thus the difference in reactivity can be explained in terms of conventional steric arguments.

Menger[1] refers to this pair of compounds to argue that the combination of "proximity" and a prolonged "time of residence" at a suitable distance—both factors being present in **15**—brings

Table VI. Calculated Steric Energies (E_s) and C--O Distances (R_{CO}) in Starting Materials, Steric Energies in Second Transition States (E_{ts}), Activation Energies ($E_a^2{}_{(\epsilon=1.5)}$ and $E_a^2{}_{(\epsilon=80)}$), and Predicted Experimental Rate Constants (k) for Acids **16–23**

hydroxy acid	E_s	E_s'	R_{CO}	E_{ts}	E_{ts}'	$E_a^2{}_{(\epsilon=1.5)}$	$E_a^2{}_{(\epsilon=80)}$	k, M^{-1} min^{-1}
16	88.2	87.1	2.66	97.5	97.6	9.3	10.5	95
17	47.5	46.5	2.73	61.6	61.6	14.1	15.1	0.05
18	46.2	45.4	2.88	59.1	59.3	12.9	13.9	0.3
19	45.7	45.8	2.92	60.5	60.9	13.8	15.1	0.07
20	51.8	51.0	2.83	62.6	62.4	10.8	11.8	8.7
21	49.5	49.5	2.79	61.3	61.6	11.8	12.1	1.8
22	57.7	57.0	2.57	51.1	51.3	−6.6	−5.7	9.1×10^{17}
23	64.5	64.1	2.56	59.0	58.8	−5.5	−5.3	1.6×10^{12}

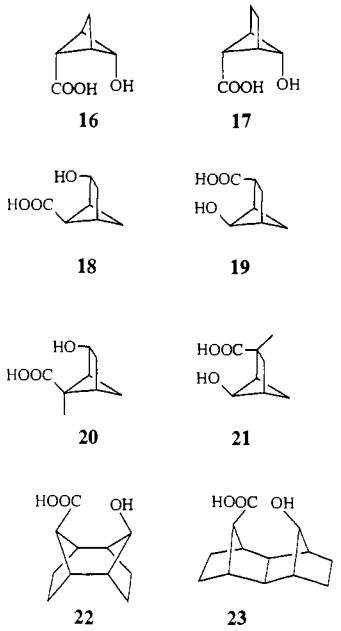


Figure 9.

about huge reactivity enhancements. He also points out that according to Page and Jencks[17,19] the extra bond rotation which **14** possesses should make it only five times less reactive than **15** and that therefore the much larger reactivity of **15** cannot be explained by conventional theories. This argument ignores the basis of the Page–Jencks postulate, which is derived from a comparison of the entropies accompanying the cyclization of acyclic hydrocarbons of varying chain length.[17] In these cases the loss of a bond rotation does not bring the reacting termini in close contact, as is the case in **15**. Thus the Page–Jencks postulate does not apply to the case of the two phenolic hydroxy acids. The reactivity enhancement is not a consequence of simply "freezing" a bond rotation but rather follows from the introduction of severe repulsive interactions between nonbonded groups.

Reactivity Predictions. As an extension of our modeling study, we have performed MM2 calculations on a number of strained hydroxy acids which are either unknown or which have not been studied kinetically under lactonization conditions. Our results for these compounds thus constitute genuine reactivity predictions. The eight acids studied are shown in Figure 9. Calculations of the steric energies of starting material, E_0, and second transition state, E_{ts}, together with the C--O distance R_{CO} in the hydroxy acids are summarized in Table VI. The transition-state calculations employed the same parameters (model I) used for all previous cases. The predicted experimental rate constants, k, are derived from the calculated values of the activation energy $E_a^2{}_{(\epsilon=1.5)}$ and interpolation from the plot in Figure 6. For compounds **22** and **23**, the calculated value of $E_a^2{}_{(\epsilon=1.5)}$ is much lower than any other calculated in this study and falls well outside of the range of our plot. For this reason, the predicted values of the rate constants may not be quantitatively correct. We can however conclude that both acids are extremely reactive. Once again, values of E_s', E_{ts}', and $E_a^2{}_{(\epsilon=80)}$ have been calculated for $\epsilon = 80$,

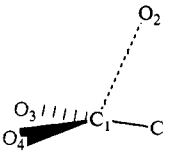


Figure 10.

and the energies $E_a^2{}_{(\epsilon=80)}$ differ from the $E_a^2{}_{(\epsilon=1.5)}$ values by essentially the same amount (0.9 ± 0.4 kcal/mol) calculated for acids **1–15**. From these calculations, a second set of predicted rate constants, k' can be derived. As Table VI shows, the rate constants k and k' predicted by the two sets of calculations are very similar.

The geometric constraints in most of these compounds are such that the O--C distance is smaller than in any of the previous ones calculated. However, acids **16–21** are so rigid that further compression of the reacting units results in the introduction of considerable strain in the rest of the molecule. Thus in spite of the favorable "spatiotemporal" requirements, these compounds are not predicted to be particularly reactive. On the contrary, the rate constants for five of these six compounds fall at the lower end of our reactivity scale. Thus our reactivity predictions are actually opposite to those which might be based on the distances between the reactive functionalities in the starting material. For **22** and **23**, the initial C--O distances are very small (less than 2.6 Å), and little skeletal deformation is necessary in order to form a new cycle. In fact, bond formation relieves the strong repulsive nonbonding interactions present. These compounds are predicted to be exceedingly reactive in lactonizations.

Summary and Conclusion

One purpose of this study was to evaluate some of the most prominent theories regarding the prediction of reactivity in intramolecular reactions, a topic of importance since it is related to the very high rate enhancements of which enzymes are capable. In particular, we have investigated the proposed dependence of the reaction rate on (i) the "angularity" of the reaction (the Koshland model) and on (ii) the distance between the reacting moieties (the Menger postulate). Our results do not lend support to either. The calculated angle formed by the alcoholic oxygen and the carbon–carbon bond of the C–COOH group in the starting materials is in most cases quite different from the best attack angle according to our ab initio calculations (86°), and it is also outside of the range estimated empirically by Koshland (90° to 109°).[7] Yet the for most reactive alcoholic hydroxy acid **5** the calculated angle in the starting material is equal to 77°, very far from the ideal. Since the breakdown of the tetrahedral intermediate is believed to be the rate-determining step,[21] the "angularity" of attack is unlikely to be a factor in any case.

Our results do not corroborate Menger's model either. In our model transition states, the forming bond lengths are practically identical with the ones we predict on the basis of ab initio calculations. That is, the transition-state bond lengths, like normal bond lengths, are not as easily deformable as angles, etc. It is, however, incorrect to conclude that the reaction rate can be rationalized on the basis of the distance between the reacting units in the ground state, even in cases like the ones in our study where the "time of residence" at a given distance should be more than

sufficient for interaction to occur. According to our calculations, the differences in reactivities arise from the changes in strain which occur upon deforming reactants to highest transition-state geometries. The fact that the forming C--O bond is a nearly constant 2.05 Å in the transition states shows that the bond stretching factor is the most important single factor influencing activation energies. In order to achieve an optimum C--O bond distance in the transition state, strain must be introduced in the system; the higher the total strain energy the lower the reactivity will be. There may be some qualitative correspondence between the ground-state distance between functional groups and the rate of reaction, since molecules in which the groups are held tightly together are often more easily transformed into the transition state. However, this is just an example of part of the activation energy of a reaction being overcome by precompression of the reactants. In other words, partial motion occurs along the repulsive part of the potential energy barrier of the reaction. This is where the analogy to enzymatic processes can be drawn: enzymes might accelerate reactions by orienting functional groups of two molecules in a way favorable to reaction (i.e., forcing them part way toward the transition state). The energy to do this could be compensated for by the binding of the reactants to the enzyme active stie. There are, of course, a variety of other ways in which an enzyme can accelerate a reaction, such as favorable electrostatic interactions with the transition state or desolvation of the reactants in cases like the ones shown here, where the unsolvated species react with no barrier.

While this work was in progress, we learned of an analysis of the same reaction, by using MM2 (with no modifications), by Menger and Sherrod.[40] The authors investigate six hydroxy acids, five of which are **4**, **5**, **6**, **8**, and **10** in our article. They compare the energies of tetrahedral intermediates (TI) and hydroxy acids (HA) and the energies of tetrahedral intermediates and lactones (L). No correlation is found between the difference in energy TI–HA and the logarithm of the experimental rate constant, and the authors conclude that differences in solvation alone are responsible for the variations in the reaction rates. Menger and Sherrod do not attempt to correlate ln k and the difference in energy between hydroxy acids and products, HA–L. This correlation is the most likely to succeed, since the rate-determining step is in general the breakdown of the tetrahedral intermediate to the products, and this rate-determining transition state is relatively close to the products in structure and energy.[12,21,38,39] The tetrahedral intermediate is a poorer model for the rate-determining transition state, so that the lack of correlation between TI–HA and ln k is not surprising. Moreover, MM2 has been parameterized for alcohols but not for compounds bearing three oxygen atoms on the same carbon as in the intermediates. Yet standard MM2 parameters are used throughout by Menger and Sherrod. In contrast to the conclusion that these authors make, Bruice and Turner[41] have shown that solvation effects are not responsible for the acceleration of intramolecular reactions over intermolecular ones.

In this paper we have described a rapid and economical method for the prediction of reactivity. We believe that our procedure, consisting of an ab initio analysis of an elementary model reaction and subsequent modified force-field energy calculation on the actual related system of interest, enables us to reproduce with reasonable accuracy the trend in reactivity for the relative lactonization rates in a series of bicyclic hydroxy acids. The same general procedure has been used previously in the modeling of stereoselectivity in organic reactions.[42] The reproducibility of the experimental activation energies shows that, while there is no simple rule which can provide quantitative reactivity predictions based on starting material geometries, the factors controlling rates are indeed well understood and can be easily incorporated into a classical force field.

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Table VII

	Torsional		
	$V1$	$V2$	$V3$
C-C1-O2-C	0.00	0.00	0.00
O3-C1-O_2-C	0.00	0.00	0.00
O4-C1-O2-C	0.00	0.00	0.00
C-C1-O2-H	0.00	0.00	0.00
O3-C1-O2-H	0.00	0.00	0.00
O4-C1-O2-H	0.00	0.00	0.00
C-C1-O2-lp	0.00	0.00	0.00
O3-C1-O2-lp	0.00	0.00	0.00
O4-C1-O2-lp	0.00	0.00	0.00

	Bond Stretching and Compression	
	k_s	l_0
C1-O2	2.68	2.050
C1-O3	5.36	1.280
C1-O4	5.36	1.292

	Dipole Interaction
C1-O2	0.440
C1-O3	0.440
C1-O4	0.440

	Angle Bending	
	k_θ	θ_0
O2-C1-O4	0.230	102.170
C-C1-O4	0.700	116.340
O3-C1-O4	0.460	118.130
O3-C1-O2	0.230	97.360
C-C1-O3	0.700	123.220
C-C1-O2	0.350	85.800
C-O2-C1	0.385	123.090
C-O2-H	0.350	110.210
C1-O2-H	0.175	123.090
H-O4-C1	0.350	118.370
H-O3-C1	0.350	119.750
C-O4-C1	0.770	118.370
H-O2-H	0.350	110.210

Table VIII

	Torsional		
	$V1$	$V2$	$V2$
O3-C1-O2-C(sp^2)	0.0	0.0	0.0
O4-C1-O2-C(sp^2)	0.0	0.0	0.0
C(sp^2)-O4-C1-O3	0.0	0.0	0.400
C(sp^2)-O4-C1-O2	0.0	0.0	0.400

	Angle Bending	
	k_θ	θ_0
C(sp^2)-O2-H	0.350	108.000
C(sp^2)-O4-H	0.350	108.000

Table IX

	Torsional		
	$V1$	$V2$	$V3$
O=C*-O-C(sp^2)	-1.660	8.980	0.0
C*-O-C(sp^2)-C(sp^2)	0.0	0.0	0.0
C(sp^2)-O-C*-C(sp^3)	0.0	0.0	0.0

	Angle Bending	
	k_θ	θ_0
C*-O-C(sp^2)	0.600	109.900

Appendix

Table VII is a list of the parameters used in the force field model of the transition states of the reaction. These parameters redefine the torsional, stretching, and bending modes involving those bonds which are being broken or formed in the reaction. For all force constants not included in the list, an "equivalence statement" has been used, whereby the carbon atom of the carboxylic group (C1

in Figure X) is treated as an sp^3 carbon atom in the transition state, the nucleophilic oxygen atom (O2) is treated as an sp^3 atom, and the two remaining oxygen atoms are also treated as sp^3.

For acids **14** and **15**, the parameters defined by Beckaus[24] were employed for the aromatic rings. In addition, the parameters in Table VIII were defined in the transition state calculations.

For the calculation of the product derived from **14**, the parameters in Table IX were defined (C* = carbonyl CO).

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Electrophilic Nitration, Halogenation, Acylation, and Alkylation of α,α,α-Trifluoromethoxybenzene[1a]

George A. Olah,* Takehiko Yamato, Toshihiko Hashimoto,[1b] Joseph G. Shih, Nirupam Trivedi, Brij P. Singh, Marc Piteau,[1c] and Judith A. Olah

Contribution from the Donald P. and Katherine B. Loker Hydrocarbon Research Institute and Department of Chemistry, University of Southern California, Los Angeles, California 90089-1661. *Received September 2, 1986*

Abstract: Electrophilic nitration of α,α,α-trifluoromethoxybenzene gave 88–93% para and 12–7% ortho isomer with no meta isomer detected. The relative reactivity of α,α,α-trifluoromethoxybenzene compared to benzene (determined in competition experiments) was found to be comparable to that of fluorobenzene. A Hammett–Brown plot of log k_X/k_H vs. σ^+ for nitration with nitronium tetrafluoroborate in nitromethane solution gave excellent linear correlation (correlation factor $r = 0.999$). A σ^+ value of 0.067 was obtained for the OCF_3 group from this plot. $FeCl_3$- and I_2-catalyzed bromination also showed exclusive para/ortho orientation, whereas in the $FeCl_3$-catalyzed chlorination 6% meta isomer was also obtained. $FeCl_3$-catalyzed acetylation and benzoylation in nitromethane solution gave predominant (or exclusive) para substitution. The $AlCl_3$-catalyzed Friedel–Crafts alklation of α,α,α-trifluoromethoxybenzene with *tert*-butyl and benzyl chlorides gave nearly exclusive para or para/ortho substitution (99.4% para, 0.6% meta, and 85% para, 1% meta, 14% ortho, respectively). Isopropylation with isopropyl chloride (bromide) gave 29.5–28.5% ortho, 9.5–8.5% meta, and 61–63% para isomer. In attempted $AlCl_3$-catalyzed alkylation with methyl and ethyl chlorides chlorine exchange of the trifluoromethoxy group became predominant. BF_3-catalyzed alkylation with alkyl fluorides avoids such exchange. The amount of meta isomer in BF_3-catalyzed ethylation with ethyl fluoride increased to ~31% in contrast to related isopropylation, *tert*-butylation, and benzylation which showed no or very limited meta substitution. This is considered to be due to concurrent intramolecular ethyl and hydrogen shifts in the arenium ion type alkylation intermediates in the case of ethylation ($C_2H_5^+$ is a very poor leaving group), in contrast to *tert*-butylation and benzylation, where carbocationic alkyl shifts are intermolecular. Isopropylation is of intermediate nature, with both inter- and intramolecular alkyl shifts taking place. Attempts of methylation with CH_3F and BF_3 gave only marginal reaction. Alkylations (and to some degree chlorination) showing significantly increased meta substitution are considered to be affected by thermodynamically controlled intramolecular rearrangement processes taking place in the arenium ion intermediates of the substitution reactions but do not necessarily involve isomerization of the products themselves. Under predominantly kinetic conditions such as in nitration, bromination, and acylations or when alkyl (halogen) transfer is intermolecular, α,α,α-trifluoromethoxybenzene is predominantly para–ortho substituted. The $-I > +K$ effect of the CF_3O group, with the inductive effect diminishing with distance while the conjugative effect remains unaffected, results in predominant para substitution.

The study of the directing effect of substituent groups in benzene has provided over the years fundamental mechanistic understanding of electrophilic aromatic substitution reactions. In our continuing study of aromatic substitution, we extended our investigations to the directing effect of the trifluoromethoxy group in electrophilic nitration, halogenation, acylation, and alkylation of α,α,α-trifluoromethoxybenzene. Sheppard and co-workers[2a,b] have reported the preparation of α,α,α-trifluoromethoxybenzene by reacting phenol with carbonyl fluoride to form phenyl fluoroformate and its subsequent reaction with sulfur tetrafluoride. Feiring[2c] subsequently developed a much simplified synthesis by reacting phenols with carbon tetrachloride in HF. The reaction gave satisfactory yield with some substjtuted phenols but only low yield (ca. 10%) with phenol itself. As the reaction of 3-bromophenol with CCl_4 and HF gives *p*-bromo-α,α,α-trifluoromethoxybenzene in good yield (ca. 70%), its reduction with H_2 over Pd/C offers a convenient synthesis of α,α,α-trifluoromethoxybenzene. Early work on the electrophilic substitution of α,α,α-trifluoromethoxybenzene has been carried out by Yagupolsky et al.[3] as well as by Sheppard.[2] No systematic study has, however, been reported.

We undertook a detailed study of the directing effect of the trifluoromethoxy group in electrophilic nitration, halogenation, acylation, and alkylation of α,α,α-trifluoromethoxybenzene and report our findings herein.

Results and Discussion

Nitration. α,α,α-Trifluoromethoxybenzene was nitrated under usual nitration conditions with a mixture of nitric and sulfuric acids in homogeneous glacial acetic acid solution, as well as under

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