Effect of Small Changes in Orientation on Reaction Rate

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Abstract: To evaluate the effect of orientation on reaction rate, perturbations of the structure of compounds involved in five-membered ring lactonization have been introduced in order to affect the orientation of the reacting atoms. The types of perturbations used were (a) alteration of the attacking nucleophile from a hydroxyl group to a sulfhydryl group, (b) changes in the supporting structure to which the five-membered lactone is attached from a bicyclo[2.2.1] system to a bicyclo[2.2.2] system, and (c) the introduction of a neighboring methyl group which interacts with the reacting carboxyl. In each case large differences in rate were observed. The perturbations in some cases increased the rate and in other cases decreased it. Controls showed that the perturbations had minimal effects on the ir stretching frequencies, the pK's, the alkaline hydrolysis rates, and the ^{13}C nmr frequencies. The only systematic explanation which appeared to apply to all of the changes was that the orientation of the reacting atoms was perturbed. Furthermore, a rough empirical correlation could be obtained between the velocity of the reaction and the alteration of the angle of approach between the reacting atoms.

In the previous papers[1-4] in the series it had been suggested that large rate enhancements may result from the optimization of the orientation requirements in chemical reactions. In essence this hypothesis suggests that a major factor in the intramolecular enhancements in lactonization rates results from the fact that the approach of the attacking atoms is confined to certain pathways as compared to the random orientations occurring with bimolecular collisions. This conclusion was reached by measuring the rates of intramolecular reactions and comparing them with their bimolecular counterparts after correcting for contributions from proximity, strain, compression, etc. The remaining large rate factors were identified with orientation effects.

Another approach to this same problem would be to design certain compounds in which it was expected that proximity, strain, solvation, etc., would be essentially constant and then perturb these compounds so that the angle of approach between the attacking atoms was changed slightly. If orientation effects are important in the reaction, then appreciable change in the rate should occur. If not, the reaction should be insensitive to such perturbations. In this article we shall discuss three such perturbations. The first involves a change in the supporting ring structure from the bicyclo[2.2.1] to the bicyclo[2.2.2] ring system which causes small orientation changes between the hydroxyl and carboxyl groups appended to these structures. The second is the addition of methyl groups to the ring systems in such a way that they will favor certain orientations over others. This should, therefore, affect the velocity of the reaction if the carboxyl group is either deflected away from an optimal orientation or deflected into an optimal orientation. The third approach was to change the size of the attacking nucleophilic atom by converting it from oxygen to sulfur. By normalizing the reaction to the sulfur derivative, *i.e.*, comparison of thiolactonizations with thioesterification, the effects on rate caused by change in the bond length and/or orbital orientation could be assessed. The results are seen to be consistent with the conclusion that the reactions are sensitive to small changes in orientation of the reacting atoms.

Experimental Section

Instrumentation. Infrared spectra were taken with a Perkin-Elmer Model 257 grating infrared spectrophotometer using chloroform solutions in NaCl cavity cells or KBr pellets. A Varian Associates A-60 spectrometer was used to obtain nmr spectra. All nmr spectra were taken in deuteriochloroform with tetramethylsilane as an internal standard. A Thomas-Hoover capillary melting point apparatus was used for the determination of melting points. A Gilford recording spectrophotometer Model 2000 equipped with an insulated cell compartment which was thermostated ±0.1 by means of a K-2/R Lauda/Brinkmann circulator was used for spectrophotometric monitoring reaction kinetics. Analyses were done by the microchemical analytical laboratory, University of California, Berkeley.

Syntheses. 6-*endo*-Hydroxy-2-*exo*-methylbicyclo[2.2.1]heptane-2-*endo*-carboxylic Acid Lactone. This lactone was synthesized by the method of Meek and Trapp:[5] mp 125–126° (lit. mp 125–126°); ir ($CHCl_3$) 1774 (γ-lactone C=O); nmr ($CDCl_3$) δ 4.50 (t, 1, J_{6-1} = 3.0 Hz, J_{6-5exo} = 3.0 Hz, C-6 hydrogen) and 1.21 ppm (s, 3, methyl hydrogens).

Anal. Calcd for $C_9H_{12}O_2$: C, 71.03; H, 7.95. Found: C, 70.52; H, 8.29.

6-*endo*-Hydroxy-3,3-dimethylbicyclo[2.2.1]heptane-2-*endo*-carboxylic Acid Lactone. β,β-Dimethylacrylic acid (75 g) and 60 ml of freshly distilled cyclopentadiene were heated in a 500-ml, round-bottom flask equipped with a reflux condensor to 170°. This mixture was refluxed for 8 hr and another 60 ml of fresh cyclopentadiene was added. Refluxing was then continued for another 16 hr. The reaction mixture was dissolved in chloroform and the acidic components were extracted into saturated bicarbonate. The bicarbonate solution was acidified and extracted with ether. The ether solution was dried over anhydrous calcium sulfate and the ether was removed on a rotoevaporator. The mixture of β,β-dimethylacrylic acid and the bicyclic acids was distilled at 3-mm pressure. Most of the β,β-dimethylacrylic acid distilled over at 78–82°. The fraction boiling at 90–95° was approximately a 50:50 mixture of β,β-dimethylacrylic and the bicyclic acids. A portion of this mixture (2.5 g) was stirred with 30 ml of 75% H_2SO_4 for 24 hr, diluted to 250 ml with ice water, and extracted with chloroform. The chloroform solution was extracted with saturated bicarbonate and dried over anhydrous calcium sulfate, and the chloroform was removed. The product was then vacuum sublimed to give 1.3 g of product: mp 140–141° (lit.[6] mp 143–144°); ir ($CHCl_3$) 1775 (γ-

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(2) D. R. Storm and D. E. Koshland, Jr., *J. Amer. Chem. Soc.*, **94**, 5805 (1972).
(3) G. A. Dafforn and D. E. Koshland, Jr., *Bioorg. Chem.*, **1**, 129 (1971).
(4) G. A. Dafforn and D. E. Koshland, Jr., *Proc. Nat. Acad. Sci. U. S.*, **68**, 2463 (1971).
(5) J. S. Meek and W. B. Trapp, *J. Amer. Chem. Soc.*, **79**, 3909 (1957).
(6) S. Beckmann and H. Geiger, *Chem. Ber.*, **94**, 48 (1961).

lactone C=O); nmr ($CDCl_3$) δ 4.78 (t, 1, J_{6-1} = 6.0 Hz, J_{6-5exo} = 6.0 Hz, C-6 hydrogen), 3.19 (t, 1 J_{1-2} = 5.2 Hz, J_{1-6} = 6.0 Hz, C-1 hydrogen), and 1.13 ppm (s, 6 methyl hydrogens).

Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.48. Found: C, 72.1; H, 8.52.

***cis*-2-Hydroxymethylbicyclo[2.2.2]octane-3-carboxylic Acid Lactone.** This lactone was synthesized by the method which was used for the synthesis of the analogous bicyclo[2.2.1] lactone:[7] mp 136–138°; ir ($CHCl_3$) 1760 (γ-lactone C=O); nmr ($CDCl_3$) δ 4.33 ppm (ABX, 2, J_{AX} = 3.0 Hz, J_{BX} = 7.4 Hz, γ hydrogens).

Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 71.71; H, 8.44.

6-Hydroxybicyclo[2.2.2]octane-2-carboxylic Acid Lactone and 5-Hydroxybicyclo[2.2.2]octane-2-carboxylic Acid Lactone. A mixture of *exo*- and *endo*-bicyclo[2.2.2]oct-5-ene-2-carboxylic acids was prepared by the method of Boehme.[8] The exo,endo mixture (5.5 g) was treated with 50 ml of 75% sulfuric acid for 24 hr. The reaction mixture was diluted with 200 ml of ice water and extracted with ether. The ether solution was washed with saturated sodium bicarbonate to remove unreacted acid. The ether solution was then dried and evaporated to yield 3.4 g of product which was approximately a 50/50 mixture of the two lactones. The infrared spectrum of this product showed two carbonyl absorptions, 1745 and 1760 cm^{-1}, consistent with the δ- and γ-lactones, respectively.[9] The corresponding 5-*exo*-iodolactones have been obtained from this same mixture of acids.[8] The two lactones were separated by silica gel chromatography using a 3:1 petroleum ether–methylene chloride solvent mixture and both lactones were recrystallized from petroleum ether. The 2,6-lactone melted at 204.5–205° (lit.[8] mp 207–208°); ir ($CHCl_3$) 1760 (γ-lactone C=O).

Anal. Calcd for $C_9H_{12}O_2$: C, 71.02; H, 7.70. Found: C, 70.84; H, 7.85. The 2,5-lactone melted at 229–230°; ir ($CHCl_3$) 1735 (δ-lactone C=O).

Anal. Calcd for $C_9H_{12}O_2$: C, 71.02; H, 7.70. Found: C, 70.82; H, 7.66.

6-Hydroxy-2-methylbicyclo[2.2.2]octane-2-carboxylic Acid Lactone and 5-Hydroxy-2-methylbicyclo[2.2.2]octane-2-carboxylic Acid Lactone. Isomeric 2-methylbicyclo[2.2.2]oct-5-ene-2-carboxylic acid was prepared by the Diels–Alder condensation of methacrylic acid and 1,3-cyclohexadiene.[8] The fraction distilling at 140–160° (20 mm) was recrystallized from petroleum ether. This isomeric acid (10 g) was stirred with 100 ml of 75% (v/v) H_2SO_4 for 24 hr at room temperature. This solution was then diluted fivefold with ice water and the products were extracted into ether. The ether solution was washed with saturated bicarbonate, dried, and the solvent was removed. The infrared spectrum of this crude product showed two lactone carbonyl peaks at 1760 and 1735 cm^{-1} which are due to the γ- and δ-lactones, respectively.[9] The mixture of lactones was vacuum sublimed yielding 5 g of product. The two lactones were separated by silica gel chromatography using a 4:1 benzene–methylene chloride solvent system. Each lactone was then vacuum sublimed once more. The 2,6-lactone melted at 131–132°; ir ($CHCl_3$) 1770 (γ-lactone C=O).

Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.35; H, 8.52. The 2,5 lactone melted at 123–124°; ir ($CHCl_3$) 1735 cm^{-1} (δ-lactone C=O).

Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 71.84; H, 8.50.

γ-Thiobutyrolactone. This compound was synthesized from thiourea and β-chlorobutyronitrile according to the method of Truce and Abraham.[10] The yellow liquid obtained was distilled under reduced pressure: bp 52–55° (3 mm) (lit. bp 53–54° (3 mm)); $n^{25}D$ 1.5224 (lit. $n^{25}D$ 1.5220); ir ($CHCl_3$) 1695 (γ-thiolactone C=O); nmr ($CDCl_3$) δ 3.43 ppm (t, 2, J = 6.4 Hz, γ hydrogens); uv_{max} (95% ethanol) 240 mμ (ϵ 4000).

Anal. Calcd for C_4H_6OS: C, 47.19; H, 6.17; S, 31.48. Found: C, 47.12; H, 6.11; S, 31.49.

2-Thiophthalide. This thiolactone was synthesized by the method of Protiva[11] and recrystallized from ethanol: mp 56–57° (lit. mp 58°); ir ($CHCl_3$) 1684 (γ-thiolactone C=O); nmr ($CDCl_3$) δ 3.71 ppm (s, 2, γ hydrogens).

Anal. Calcd for C_8H_6OS: C, 63.97; H, 4.03; S, 21.35. Found: C, 63.94; H, 4.02; S, 21.58.

2-*endo*-Mercaptomethylbicyclo[2.2.1]heptane-3-*endo*-carboxylic Acid Thiolactone. 2-*endo*-Hydroxymethylbicyclo[2.2.1]heptane-3-*endo*-carboxylic acid lactone (11.7 g, 0.077 mol) and benzyl mercaptan (9.55 g, 0.077 mol) were refluxed 5 hr in sodium ethoxide (1.5 g of Na and 33 ml of anhydrous ethanol). The solvent was removed under vacuum and the residue was dissolved in 60 ml of hot water and filtered. This solution was acidified to pH 2 with concentrated HCl and the precipitate was recrystallized from aqueous ethanol. This product was then treated with 30 ml of polyphosphoric acid for 30 min at 120°, diluted tenfold with distilled water, and extracted with ether. The ether solution was washed with 10% NaOH, distilled water, and dried over anhydrous $CaCO_3$, and the solvent was removed under vacuum. The product was purified by silica gel chromatography (cyclohexane) and vacuum sublimed to give 2.2 g of thiolactone: mp 132–133°; ir ($CHCl_3$) 1686 (γ-thiolactone C=O); nmr ($CDCl_3$) δ 3.42 ppm (ABX, 2, J_{AX} = 1.5 Hz, J_{BX} = 2.0 Hz, γ hydrogens); uv_{max} (95% ethanol) 240 mμ (ϵ 3780).

Anal. Calcd for $C_9H_{12}OS$: C, 64.25; H, 7.19; S, 19.06. Found: C, 64.42; H, 7.26; S, 18.88.

6-*endo*-Mercaptobicyclo[2.2.1]heptane-2-*endo*-carboxylic Acid Thiolactone. 5-Norbornene-2-*endo*-carboxylic acid was separated from a mixture of the exo and endo isomers by means of the iodolactonization method.[12] The endo acid (28.2 g, 0.20 mol) and thionyl chloride (26.8 g, 0.25 mol) were refluxed together in benzene for 1 hr in the presence of 3 g of Mg turnings. The benzene and excess thionyl chloride were removed by vacuum distillation and the acid chloride was distilled at 135–140° (10 mm). The freshly distilled acid chloride was added dropwise to 29 g (0.40 mol) of KSH in 90 ml of 90% ethanol, stirred for 3 hr, filtered, and brought to dryness under vacuum. The resulting residue was dissolved in 75 ml of distilled water, filtered, and acidified with 6 *N* HCl. The ether solution was dried over anhydrous calcium sulfate and the ether was removed under vacuum. The product was recrystallized from 50% aqueous ethanol and vacuum sublimed giving 1.9 g of product: mp 121–122°; ir ($CHCl_3$) 1695 (γ-thiolactone C=O); nmr ($CDCl_3$) δ 3.70 ppm (m, 1, γ hydrogens); uv_{max} (95% ethanol) 240 mμ (ϵ 2960).

Anal. Calcd for $C_8H_{10}OS$: C, 62.32; H, 6.49; S, 20.76. Found: C, 62.28; H, 6.47; S, 20.69.

***cis*-2-Mercaptomethylbicyclo[2.2.2]octane-3-carboxylic Acid Thiolactone.** This thiolactone was synthesized from *cis*-2-hydroxymethylbicyclo[2.2.2]octane-3-carboxylic acid lactone and benzylmercaptan by the method used for the synthesis of the analogous bicyclo[2.2.1] thiolactone. The crude product was vacuum distilled and the fraction boiling between 90 and 110° (1.5 mm) was purified by silica gel chromatography using acetonitrile as a solvent: mp 58–60°; ir ($CHCl_3$) 1693 (γ-thiolactone C=O).

Anal. Calcd for $C_{10}H_{14}OS$: C, 65.89; H, 7.75; S, 17.59. Found: C, 65.70; H, 8.21; S, 17.70.

Sodium Salts of the γ-Hydroxy and γ-Mercapto Acids. The sodium salts were prepared from the lactones and thiolactones by hydrolysis with stoichiometric amounts of aqueous sodium hydroxide followed by filtration and lyophillization. Because of susceptibility to oxidation, the salts of the γ-mercapto acids were prepared immediately before use and stored under nitrogen. In all cases, ir spectra (KBr pellets) of the hydrolysis products from the lactones and thiolactones showed the characteristic carboxylate anion absorbance at ~1430 and ~1600 cm^{-1}. Further support for the structures assigned to these lactones and thiolactones was given by the observation that treatment of these hydrolysis products with 1 *N* HCl resulted in the formation of the appropriate lactone and thiolactone absorbances in the infrared and ultraviolet.

Kinetic Procedures. The rates of acid-catalyzed lactonizations were followed spectrophotometrically by the change in optical density in the range 225–238 mμ. At substrate concentrations of approximately 1×10^{-2} *M* there are optical density changes from 0.05 to 0.2 optical density units during the course of the reaction. Kinetic runs were initiated by bringing a weighed amount of the sodium salt of the hydroxy acid to volume with the appropriate acid solution or buffer. The acidities ranged from 0.1 *N* HCl to 10^{-4} *N* in 0.5 *M* formate buffers. At pH 2 reactions were studied

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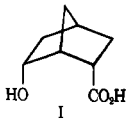
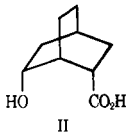
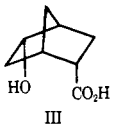
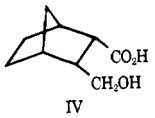
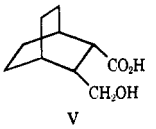
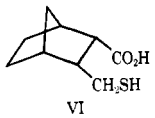
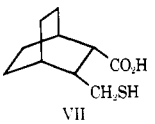
(12) J. A. Berson and D. A. Ben-Efraim, *J. Amer. Chem. Soc.*, **81**, 4083 (1959).

Table I. Effect of Ring Structure on Lactonization Rates

Compd	Obsd rate of lactonization	$k^{OH^-}_{hydrolysis}$	$k^{H^+}_{hydrolysis} \times 10^3$	pK_a	Ir (lactone)
 I	1120	81	88.1	5.44	1776
 II	0.950	78	50.5	6.34	1770
 III	10.00	12	54.0	5.22	1735 (δ lactone)
 IV	7.23	13	2.6	5.09	1761
 V	152	42	4.00	5.18	1760
 VI	2.88×10^{-4}	16.1	0.29	5.42	1686
 VII	1.50×10^{-2}	7.5	0.24		1693

in 0.2 M Na_2SO_4–HCl buffers. All kinetics studied in buffers were measured as a function of buffer concentration at constant pH and ionic strength and the reported rates are those extrapolated to zero buffer concentration. All lactonizations were studied in 20% (v/v) ethanolic solutions with $\mu = 0.400$. All rates were determined at 25° unless otherwise specified.

Thermodynamic activation parameters were determined from the variation of the rates with temperature over a range from 5 to 60°. All Arrhenius plots were linear with a minimum of six points for each curve.

Acid-catalyzed thiolactonizations were monitored spectrophotometrically at 240 mμ with substrate concentrations approximately 1×10^{-4} M. Thiolactonizations were studied in acidities ranging from 0.1 to 0.4 N HCl in 20% ethanol with $\mu = 0.40$ at 25°.

First-order rate constants were determined from semilog plots of $(A_\infty - A_t)$ *vs.* time in the usual manner. The lactonizations and thiolactonizations were strictly first order in that they gave linear semilog plots through three or more half-lives and rate constants were invariant with substrate concentration.

Basic Hydrolyses of Lactones and Thiolactones. Basic hydrolyses of the individual lactones and thiolactones were followed spectrophotometrically at wavelengths the same as those used to study their lactonizations and thiolactonizations. The hydrolyses were carried out in 0.2 M phosphate buffers at pH 11–11.5 at 25°. In order to evaluate the buffer independent rate of hydrolyses, these rates were determined as a function of buffer concentration at constant pH and the reported rates are those extrapolated to zero buffer concentration.

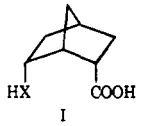
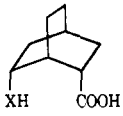
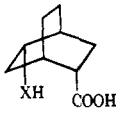
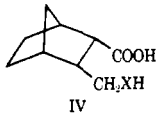
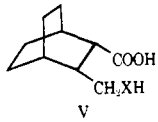
Equilibrium Constants for Lactone and Thiolactone Formation. The equilibrium constants for lactone formation from their hydroxy acids were determined using the hydroxamate assay as previously described.[2] Because the thiolactones have high molar absorptivities at 240 mμ and the γ-mercapto acids have negligible absorbance at this wavelength the equilibrium for thiolactonizations in acidic media can be determined in the following manner. Weighed amounts of thiolactone giving final concentrations of 1×10^{-4} M were brought to volume in 0.1 N HCl (10% v/v ethanol). The equilibrium constant for thiolactonization was then determined from the initial and equilibrium optical densities at 240 mμ.

Ionization Constants for the Carboxylic Acids. The ionization constants for the carboxylic acids were determined by potentiometric titration in 10% (v/v) ethanol, $\mu = 1.00$ at 25° Three determinations were made for each dissociation constant.

Results

Effect of Changing the Supporting Ring System from [2.2.1] to [2.2.2]. The results of some lactonizations and thiolactonizations of five- and six-membered ring systems attached to a [2.2.1]cycloheptane system are shown in Table I. The rates of the same lactonization process is then compared with a similar compound in which the [2.2.1] bicyclo ring system is replaced by a [2.2.2] bicyclooctane system.

Comparison of Dreiding models of the two ring systems shows that the approaches of the reacting atoms are systematically altered by approximately 10° by this change in the support structure (*cf.* Table II). This change is not between one discrete structure and another discrete structure since rotation can occur about the carbon–oxygen bond, carbon–carboxyl bond and,

Compd	Distance between C of carboxyl and X of XH where X = O	X = S	Angle ϕ where[b] X = O	X = S
 I	2.2	2.1	96	97
 II	2.1 and 2.3[a]		86–91	
 III	2.4 and 4.5[a]			
 IV	1.7	1.7	105	116
 V	1.7	1.7	98	108

[a] Distance in two different conformers. [b] ϕ is angle between α carbon, carbonyl carbon, and nucleophile at its distance of closest approach.

in some cases, the carbon–methylene bond. However, the change in the supporting ring system does create a systematic change in orientation of each of the intermediates so that the angle of approach of the attacking atoms are changed statistically. On the other hand, in none of the pairs of compounds is the proximity factor altered. There are no changes in the number of bonds free to rotate, little change in the distances between the reacting atoms, and the general microsolvation medium should be almost identical. Thus, the proximity, angle strain, compression, and the environment of the reacting atoms remain highly similar in the analogous pairs. Nevertheless, dramatic changes in the rates of reaction are observed.

For example, in the case of the 2,6-lactones (compounds I and II of Table I) a difference in rate of 1000-fold occurs by the small perturbation of changing the [2.2.1] to the [2.2.2] bicyclo ring system. Comparison of the infrared stretching frequencies and the basic hydrolysis rates of the two lactones indicate they are very similar. The acid-catalyzed rates of hydrolysis of the lactones are also extremely similar and acid-catalyzed ester hydrolyses are sensitive to steric effects so these data add further argument to the similarity of the final structures. The distance between the oxygen and carbon atoms in the hydroxy acids are essentially identical in the two structures, 2.2 Å *vs.* 2.3 Å (*cf.* Table II). Thus strain, steric factors, and the distance between reacting atoms are very similar for the two structures whereas the angle of approach differs.

If one now compares a different type of ring cyclization, *e.g.*, compounds I and III in Table I, a factor of 100 is seen. In this case, the analogy is not the same as in the case of the previous two compounds since lactonization of compound III involves a six-membered ring. However, because of the supporting structure the oxygen and carboxyls are at essentially the same distance from each other as the hydroxyl and carboxyl in the [2.2.1] system (*cf.* Table II). The main difference appears to be in the angle of approach. In this case again the acid hydrolysis rate is essentially the same for the two compounds. The basic hydrolysis rate, however, differs by a factor of 7. The alkaline hydrolysis rate of lactones may be subject to dipole effect or there might be some difference in the ring strain of the two structures. It is to be noted that compound III is a δ-lactone, not a γ-lactone. The ring strain indicated by the ratio of 5 in the alkaline hydrolysis would seem to be small compared to the 100-fold differences in lactonization. Moreover, correction for ring strain would serve to increase the ratio identified with orientation.

A similar change in rate is observed on comparing compounds IV and V of Table I. In these cases it might be expected that the changes in velocity should be lower than those reported above because an added degree of freedom has been introduced. Although the supporting ring structure changes from [2.2.1] to [2.2.2] as before, the rotation around the C-3 carbon of the norbornane structure and the methylene carbon of the alcohol allows only a comparison of averages rather than of two discrete conformers. Nevertheless, there is approximately a 21-fold difference in rate with an approximately 7° difference in the angle of approach of the reacting atoms.

A comparison of the effect of support on the thiolactonizations is shown in compounds VI and VII of Table I and here the effect is 50-fold. The alkaline hydrolysis rates, ir stretching frequencies, etc., are different from the oxygen compounds but are very similar to each other. The distances are also similar (Table II) but again the angle of approach is changed slightly.

The rates of base-catalyzed hydrolysis, carboxyl stretching frequency, and ΔpK_a are amazingly similar (Table I). The only change in property which seems to be larger than minor deviations is the change in pK of the carboxyl group of compound II relative to compound I. This change of 0.9 pK unit might indicate some microsolvation effects around this carboxyl group which might be a contributor to its rate of reaction. However, from the insensitivity of lactonizations to pKs of the carboxyl groups and the fact that this is the only compound in which a very significant pK difference is observed, such a contribution would not appear to be a common factor explaining the varying rates observed for these different compounds.

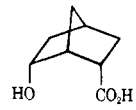
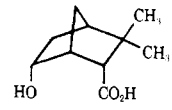
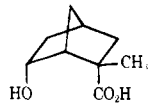
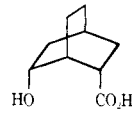
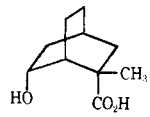
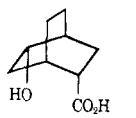
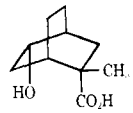
It is worthy of emphasis that the change from a bicyclo[2.2.2] to a bicyclo[2.2.1] supporting ring system sometimes increases the lactonization rate and sometimes decreases it. This would further suggest that these are not the result of a special internal property of the bicyclo[2.2.1] or the bicyclo[2.2.2] system such as internal strain but rather its pertubation of the geometry of the reactants which are appended to it.

A factor which might require further correction in a more sophisticated analysis is the fact that the bicyclo-

[2.2.2] ring system can exist in two conformational isomers which are easily detected on construction of the Dreiding models. In some cases such as compound III one of these isomers does not place the hydroxyl and carboxyl groups near enough for reaction to occur and therefore the amount of material in each isomer should be included in the calculation. For example, if there is an equal distribution of the molecules in the two isomers, the rate constant from the reactive isomer should be multiplied by two.

Effect of Neighboring Methyl Groups. Another way of affecting the orientation of the reacting atoms is to introduce neighboring methyl groups. The *gem*-methyl effect is well known in the organic literature,[13] and it is generally assumed to be a compression effect which accelerates reactions by forcing the reacting atoms within their van der Waal's radii or by increasing the proximity of the reactants by favoring conformations in which the reacting atoms are juxtaposed. Bunnett and Hauser,[14] however, have pointed out that their effect may be orienting in nature by careful controls to eliminate inductive effects in aromatic ring systems. In point of fact, if space filling models of the compounds shown in Table III are compared, there is essentially no interaction between the *gem*-methyl group and the neighboring carboxyl groups in many orientations. In other orientations, however, there is a strong interaction. The methyl groups, therefore, might alter the relative orientation between the carboxyl and hydroxyl groups by making some orientations energetically preferable. Accordingly, neighboring methyl groups were incorporated in a number of the compounds studied previously, such as those in Table I, in order to see their effect on the reaction rates.

Table III. Effect of Methyl Groups on Rates of Lactonization

Compd	k^{H^+}, M^{-1} min^{-1}	Rate rel to unsubstituted compd
	1120	1
	71.0	0.63×10^{-2}
	0.30	2.7×10^{-4}
	0.950	1
	107.0	113
	10.0	1
	522.0	52.2

Typical of the type of reactions which occur are those shown comparing compounds I and III in Table III. Attaching a methyl group in place of hydrogen on the same carbon as the carboxyl decreases the rate of reaction by a factor of 3740. If relief of strain, *i.e.*, compression, were responsible for the high rate of lactonization of the 2,6-norbornane derivative (I), the substitution of a methyl group should, if anything, accelerate the reaction. In fact, it does just the opposite, it decreases the rate by a large amount. Although it is not yet possible to calculate theoretically which are the favored orientations for the lactonization reaction, it is clear that the methyl group can perturb the orientations and thus provide a plausible explanation for the variations in lactonization rates. This conclusion is further supported by the relative rates of alkaline hydrolysis (compound II of Table IV) which are quite similar for the methyl compounds and unsubstituted derivatives.

An interesting feature is the change in the rate of acid-catalyzed hydrolysis which is 56-fold greater in the non-methyl molecule relative to the methyl modified (compound II of Table IV). Since acid-catalyzed esterifications are sensitive to steric effects and since both forward and reverse rates are decreased, this suggests that the methyl group sterically interferes with the tetrahedral intermediate. If this were true, one could separate the effect of the methyl group into two factors (a methyl interaction with the intermediate which decreases both forward and reverse reactions by a factor of 60 and a methyl influence on the ground state which decreases the forward reaction selectively by another factor of 60).

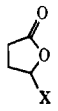
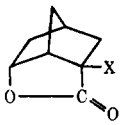
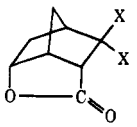
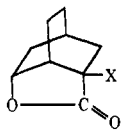
A comparison of compounds IV and V (Table III) shows another effect of a methyl group. In this case, in contrast of the norbornane system, the introduction of the methyl group increases the rate by a factor of 100. By itself such an increase in rate might be explained by compression but since the distance between hydroxyl and carboxyl in the [2.2.2] system is very similar to that in the [2.2.1] system, that argument is questionable. A compression contribution would lead to a calculated deceleration of rate caused by the methyl group of 10^5 since the observed deceleration of 3000 would have to be corrected by an acceleration of 100 due to compression. In fact, a comparison of the models shows that there are large van der Waal's overlap at certain positions but only small interactions at other positions, *i.e.*, similar to the effects in the [2.2.1] system. If the acceleration in the [2.2.2] system was caused by steric compression, the models would suggest that it acts only on selective orientations of the hydroxyl and carboxyl groups.

An equivalent effect of the neighboring methyl can be seen in the last two compounds in Table III which in-

(13) (a) R. M. Beesley, C K Ingold, and J. F. Thorpe, *J. Chem. Soc.*, **107**, 1080 (1915); (b) F. G. Bordwell, C. E. Osborn, and R. D. Chapman, *J. Amer. Chem. Soc.*, **81**, 2698 (1959); (c) T. C. Bruice and U. K. Pandit, *ibid.*, **82**, 5858 (1960); (d) S. Milstein and L. A. Cohen, *Proc. Nat. Acad. Sci. U. S.*, **67**, 1143 (1970).

(14) J. F. Bunnett and C. F. Hauser, *J. Amer. Chem. Soc.*, **87**, 2214 (1965).

Table IV. Effect of Methyl Substitution on Alkaline Hydrolysis, Acid Hydrolysis, and Infrared Stretching Frequency of C=O Various Lactones

Compd	$k^{OH^-}_{hydrolysis}$, M^{-1} min^{-1} X = CH_3	X = H	Ir of C=O X = CH_3	X = H	$k^{H^+}_{hydrolysis}$, M^{-1} min^{-1} X = CH_3	X = H
	36	123	1773	1773	11.4	14
	51	81	1774	1776	1.5	88
	10	81	1775	1776		88
	6.4	78	1770	1770		51

volve formation of δ-lactones rather than γ. In this case there is a six-membered ring closure but the methyl group increases the rate by a factor of 50, very similar to the other [2.2.2] systems with a five-membered ring closure.

Finally, a different kind of methyl effect is shown by comparison of the first two compounds in Table III. In this case, two methyl groups are placed two carbon atoms away from the carboxyl group and the rate of reaction is decreased by a factor of approximately 16. The *exo*-methyl at C-3 does not appear to interact with the carboxyl group but the *endo*-methyl group does. It appears therefore most logical to assume that the methyl group makes the preferred orientation energetically less favorable.

As in the case of the changes from the [2.2.1] to the [2.2.2] system, the introduction of a neighboring methyl group can either increase or decrease the rate of lactonization. If these changes occur all in one direction, it might be possible to say that adding a methyl group alters the solvent environment, increases the van der Waal's strain, increases the ring strain, or any of the usual other suggestions for increase in intramolecular rates. In fact, as seen here, it can either increase or decrease the rate. Moreover, if space filling models are made, it is seen that in certain rotations of the methyl and carboxyl groups there are no interactions. If there were minor orientational requirements, the methyl groups should therefore have only a slight effect on reactivity. The fact that it changes rates greatly suggests that certain orientations are preferred for high reactivity and the methyl group will increase or decrease rates depending on the geometry of the particular compound. These results do not say that compression effects may not occur as a result of introducing methyl groups, but they do support Bunnett and Hauser's hypothesis that orientational effects by methyl are very important.

Substitution of SH for OH. Another way of altering the orientation between the reactive groups is to insert an atom which has very similar reactivity but a different orbital structure and a different bond length. In the case of oxygen, such a substitution is relatively easy since sulfur has properties which are very similar to oxygen, particularly in esterification reactions.

Thioesterifications of primary and secondary mercepto groups generally proceed by the $A_{Ac}2$ mechanism.[15] Carbonium ion mechanisms for the lactonization of a mercapto acid will lead to the production of hydrogen sulfide and the corresponding lactone. No hydrogen sulfide was produced during any of the acid-catalyzed thiolactonizations studied and product analysis demonstrated that the γ-mercapto acids were converted stoichiometrically to their respective thiolactones under the conditions used to study the kinetics of thiolactonizations.

The acid-catalyzed thiolactonizations are in principle reversible and the first-order rate constants for thiolactonizations were determined from the observed first-order rate constants and the extent of thiolactone formation at equilibrium. The extent of thiolactonization at equilibrium was determined by the hydroxamate assay and the optical density at 250 mμ. First-order constants at constant $[H^+]$ were shown to be linear in $[H^+]$ and were normalized to 1 N H^+.

In Table V are shown the results of an analogous series of sulfur compounds in which reactivity measurements are compared using the bimolecular reaction as the normalizing rate. In Table VI the relative reactivities compared with the oxygen compounds, the alkaline hydrolysis rates, and the ir stretching frequencies are summarized. It is seen that the overall picture is very similar to that with the oxygen compounds. In fact, the 2,6-norbornane derivative shows a reactivity which is approximately the same relative to the bimolecular reaction as the 2,6-oxygen derivative. On the other hand, the reactivity of the intermediate compounds is not the same (*cf.* Table V). The most

(15) (a) R. N. Rylander and D. S. Tarbell, *J. Amer. Chem. Soc.*, 72, 3021 (1950); (b) B. K. Morse and D. S. Tarbell, *ibid.*, 74, 416 (1952); (c) J. R. Schaefgren, *ibid.*, 70, 1308 (1948); (d) J. Gerstein and W. P. Jencks, *ibid.*, 86, 4655 (1964).

Table V. Relative Rates of Acid-Catalyzed Thiolactonizations

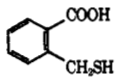
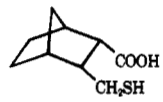
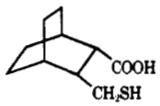
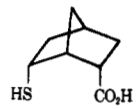
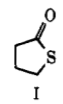
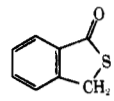
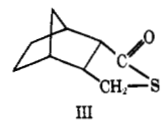
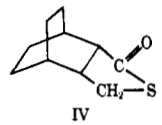
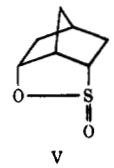
Compd	k^{H^+}, M^{-1} min^{-1}	Rel rate	Correction factors	Rel corrected rate
CH_3CH_2SH + CH_3CO_2H I	3.20×10^{-6}	1	Proximity, 55 ×	1
 II	1.23×10^{-3}	384	Conformational isomers, 4.5 × Torsional strain, 64 ×	2,020
 III	3.00×10^{-3}	936	Conformational isomers, 3 ×	51
 IV	2.88×10^{-4}	90	Conformational isomers, 3 ×	5
 V	1.50×10^{-2}	4,700	Conformational isomers, 3 ×	256
 VI	2.63	821,000		15,000

Table VI. Basic Hydrolysis of Thiolactones and Their Infrared Carbonyl Stretching Frequencies, and Relative Rates

Compd	$k^{OH^-}_{hydrolysis}$, M^{-1} min^{-1}	Ir C=O, cm^{-1}	Ratio of corrected lactonization rates,[a] k_{OH}/k_{SH}
 I	34.9	1695	70
 II	5.3	1684	110
 III	16.1	1686	11,500
 IV	7.5	1693	5,250
 V	11.1	1695	425
CH_3CH_2SH + CH_3COOH VI	5.8[b]		340

[a] Rates corrected for proximity and torsional strain. [b] Reference 15c.

dramatic of the differences is that of the 2,3 derivative (IV) which shows a corrected relative rate constant -10^3 higher for the analogous hydroxy acid. Thus, the relative reactivities of the sulfur compounds, after being normalized to the bimolecular reaction, are not the same as the oxygen compounds, and in two cases they are dramatically different. This suggests, as expected, that optimal orientations for oxygen compounds are not necessarily optimal orientations for sulfur compounds. Sulfur has a van der Waal's diameter of 3.70 Å, a covalent single bond radius of 1.04 Å, and a covalent single bond angle of 92°. Corresponding values for oxygen are 2.80 and 0.7 Å and 105°.

Like the hydroxy acids, because of single bond rotations, we are not comparing one precise orientation with another but rather a distribution of conformations, some of which may be reactive and some of which may not. Also, one is not at all sure precisely how molecules are to be placed on a reactivity *vs.* angle relationship. Nevertheless, the rate changes are large and suggest that both reactions are sensitive to small changes in orientation. Again, as in the case of the oxygen compounds, the pK's of the carboxyl groups are very similar and suggest there are no strong changes in the microenvironment (*cf.* Table VII). The carbonyl infrared stretching frequencies (Table VI) appear to be similar in all of the thiolactones and indicate that the thiolactone rings are all equivalently strained. Since the steric requirements for acid and base hydrolyses are similar, it would be predicted that the rates of basic hydrolyses would also not vary greatly. These data are given in Table V. The basic hydrolysis rates do not vary greatly and there is no apparent relationship between the hydrolysis rates and the thiolactonization rates.

The equilibrium constants for thiolactone formation from the γ-mercapto acids were determined spectrophotometrically in 0.1 N HCl. These values are reported in Table VIII. Apparently the equilibrium constant for the formation of 2,6-norbornane thio-

Table VII. pK_a's of the γ-Mercapto Acids

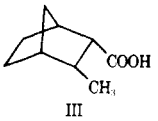
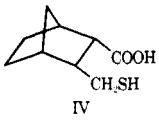
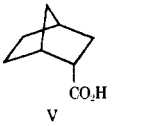
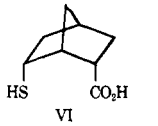
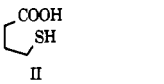
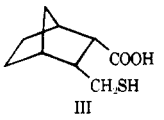
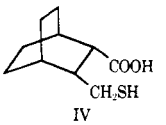
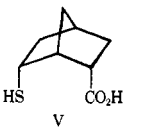
Compd	pK_a	ΔpK_a
$CH_3(CH_2)_2CO_2H$ I	4.82	
$HSCH_2(CH_2)_2CO_2H$ II	4.70	−0.10
 III	5.30	
 IV	5.42	+0.12
 V	5.30	
 VI	5.06	−0.24

Table VIII. Equilibrium Constants for Thiolactone Formation and Their Rates of Acidic Hydrolyses

Compd	K_{eq}	$k^{H^+}_{hydrolysis}$
CH_3CO_2H + CH_3CH_2SH I	6.6×10^{-4} [a]	4.85×10^{-3}
 II	2.44	0.50×10^{-3}
 III	1.10	0.29×10^{-3}
 IV	63	0.24×10^{-3}
 V	>100	

[a] Reference 15d.

lactone from its γ-mercapto acid favors the thiolactone greatly since no optical density decrease at 240 mμ was detectable and no decrease in thiolactone concentration could be measured by the hydroxamate assay. The equilibrium constant for this thiolactonization was therefore at least greater than 100 and probably much greater. The rates of acid-catalyzed hydrolyses are recorded, having been calculated from the ratio of observed equilibrium constants to the rates of acid-catalyzed thiolactonizations (Table V).

The hydrolyses rates varied over a 20-fold range while in contrast the rates of thioesterification varied over 6 orders of magnitude. This is analogous to the acid-catalyzed esterifications and lactonizations, in which case there was a parallel between the rates of lactonization and the equilibrium constants for lactone formation. This can be due either to a selection of ground states or a selection of particularly favorable orientations in the transition state. As a result, the acid-catalyzed hydrolysis rates are rather similar for all the compounds, a situation which would arise if the relative energies for the lactone and the transition state remain the same.

Entropies and Energies of Activation. The comparison of relative rates has been made in the above cases by comparing actual rate constants, rather than activation energies or entropies of activation. This selection for comparisons is based on the general conclusion that rates which are proportional to free energies of activation ($\Delta F^{\pm}$) are more meaningful than the $\Delta H^{\pm}$ or the $\Delta S^{\pm}$ for the overall comparisons. However, it is significant to compare activation energies and entropies since these may be helpful in certain gas-phase reactions. Unfortunately, in solutions, interpretations of activation energies and entropies are very difficult. In many cyclization reactions entropy actually increases rather than decreases, a conclusion which is against the general cliche that a more constrained transition state should lead to a decrease in entropy. The reason for such anomalies is that the organization of solvent is important in solution reactions and a cyclization reaction which leads to a higher orientation of the organic compound and a decreased orientation of water may therefore have a positive $\Delta S^{\pm}$.

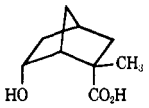
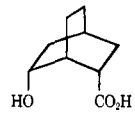
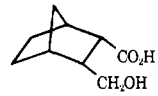
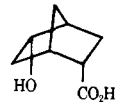
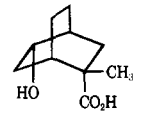
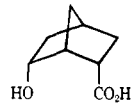
To the extent that they are useful, the values for the $\Delta H^{\pm}$ and $\Delta S^{\pm}$ for a number of compounds are listed in Table IX. A dramatic change is observed in the entropy and in the enthalpy in various reactions which are accompanied by large changes in rates. Interestingly enough, some rather large changes in rate are observed for reactions in which neither the entropy or energy change dramatically but both change somewhat. It is not easy to interpret these results and probably very easy to overinterpret them. Nevertheless, the theoretical calculations published elsewhere on the contribution of orientation factors in reactions would suggest that both entropic and enthalpic terms should contribute to the orientation factor.[3,4] Selection for conformations which are oriented most propitiously should be reflected largely in entropic terms and in the preexponential factor. On the other hand, deviation from preferred angles should lead to increases in energies. Calculations of orientation effects can be justified on either basis and, insofar as the results are Table IV are interpretable, they would suggest that both type of effects would be observed.

Theoretical and Correlation of the Experimental Data. It seemed of interest to attempt to correlate the reactions of the wide range of compounds in some general framework. Although the precise geometric details are not known for the relevant transition states, perhaps preferred orientations could be ascertained by considering some theoretical factors and some empirical data.

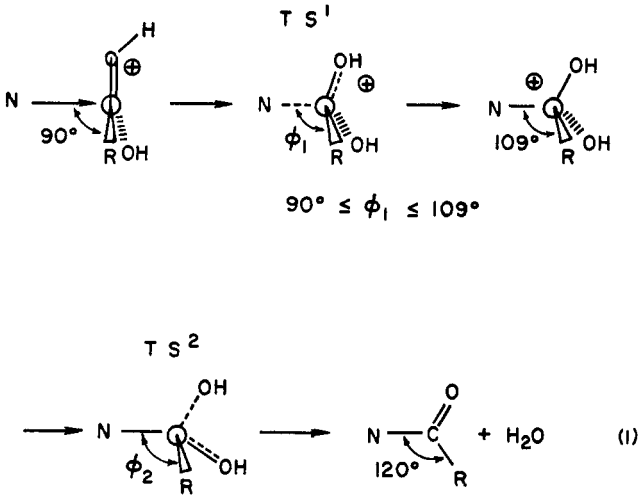
Bender[16] has postulated that a perpendicular approach of the nucleophile to the π-electron system should be preferred over a coplanar approach since it would tend to maximize overlap between the nucleophile

(16) M. L. Bender, *Chem. Rev.*, 60, 53 (1960).

Table IX. Entropies and Enthalpies of Activation for Lactonizations

Compd	Rate rel to ethyl acetate	$\Delta H^{\ddagger}$, cal	$\Delta S^{\ddagger}$, eu
	79.5	12,060	−31.5
	276	11,234	−31.2
	871	11,943	−26.46
	6,620	9,650	−30.1
	9,117	9,556	−26.78
	479,000	8,122	−23.35
	1,030,000	14,900	−2.1

and the π electrons of the carboxyl bond. This is certainly a reasonable possibility. However, consideration of the steps between starting materials and products given in eq 1 indicates that other angles might also be

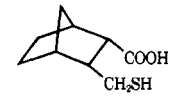
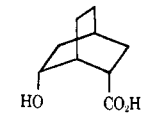
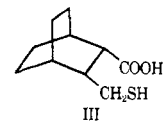
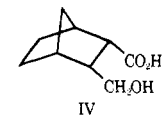
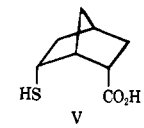
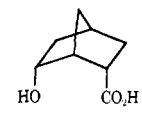
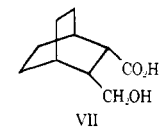


important at various stages in the reaction. The angle, θ_1, between the nucleophile (N), carbonyl carbon atom, and the R group in the first transition state (TS^1) should lie between 90 and 109°. The equivalent angle for the transition state leading to the breakdown of the tetrahedral intermediate (TS^2) probably lies between 109 and 120°.

From a theoretical viewpoint, therefore, an angle between 90 and 120° would seem reasonable depending on the rate-determining step. If the formation of the tetrahedral intermediate is the rate-determining step, an angle between 90 and 109° is logical, the precise angle being determined by whether the transition state is closer to the reactants or to the tetrahedral intermediate.

To correlate the results the rate constants of the compounds reported in the previous article and in this one are summarized in Table X. The compounds with

Table X. Dependence of Lactonizations and Thiolactonizations on the Relative Orientation between the Nucleophile and Carboxyl Group

Compd	$\Delta\theta^a$	Log k_{rel}^b
 I	+18	0.70
 II	−12	1.20
 III	+10	2.41
 IV	+7	3.22
 V	−1	4.18
 VI	−2	4.27
 VII	0	4.58

[a] $\Delta\theta$ is given in terms of the deviation from the angle $\phi = 98°$. For definition of ϕ see Table II. [b] Rates of lactonizations and thiolactonizations relative to the bimolecular reaction after correction for proximity and torsional strain.

adjacent methyl groups were excluded since there was no way at present of calculating the effect of the methyl group on orientation. The benzylic compound was excluded because inductive effects could not be corrected for quantitatively. Sulfhydryl as well as hydroxyl compounds were included, assuming thereby that the preferred angles for SH approach were similar to those for the hydroxyl approach.

The angle chosen for any such correlation is somewhat arbitrary for those compounds in which free rotation at the methylene bond can occur. Therefore, the

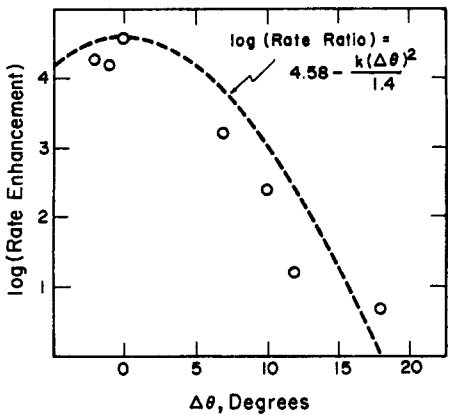


Figure 1. Plot of rate enhancement as a function of an angular dependence of the reacting atoms. The angle ϕ is defined as the angle between the lines joining the α-carbon atom, the carboxyl carbon, and the nucleophile (S or O) when the nucleophile is placed at the distance of closest approach. The deviation $\Delta\theta$ is taken as the difference between the angle ϕ for the compound in question and 98°. The rate enhancement is the increase in rate over the bimolecular rate when both rates are corrected for proximity and torsional strain.

procedure used was to arrange the Dreiding models so that the oxygen or sulfur of the attacking nucleophile was in the position of closest approach to the carboxyl carbon. The angle ϕ is then taken as the angle between the α-carbon atom, the carboxyl carbon, and the nucleophile X (oxygen or sulfur). This is not necessarily the angle of reaction in the transition state nor the angle of the conformer with maximum stability. Nevertheless, it is a systematic relationship between the various compounds.

The variation of the relative rate enhancements with $\Delta\phi$ are given in Table X for a number of lactonizations and thiolactonizations. The rate data have been corrected for proximity and torsional strain and normalized to the bimolecular reaction. An inspection of this data shows that the maximum rate occurred when ϕ = 98° for the Dreiding model of the compound. Moreover, the greater the deviation from the 98° approach, the smaller the relative rate enhancement. The data therefore were plotted as a function of the deviation from this 98° angle as shown in Figure 1. A 15° angle difference results in a change of four orders of magnitude in the relative rate enhancements.

The dashed line in the figure was obtained by a simplified and approximate theoretical procedure. If the orientation deviates from the optimum by some angle $\Delta\theta$, the $\Delta F^{\ddagger}$ would be inversely proportional to the square of this deviation if a simple harmonic oscillator were a good approximation for the system. For normal C–C–C angles with $\Delta\phi$ not much greater than 10° the value of k in eq 2 is 2×10^{-2} kcal deg^{-1}. From this we obtain eq 3. The value 4.58 is the log of the maximum

$$V(\Delta\theta) = k(\Delta\theta)^2 \quad (2)$$

$$\log k_{obsd}/k_{opt} = 4.58 - k(\Delta\theta)^2/1.4 \quad (3)$$

value of relative rate enhancement observed in this study. Considering the approximate nature of all the assumptions the agreement between empirical theory and actual experiment is surprisingly good.

It is reasonable to consider the lactonization and thiolactonization data together in the above treatment since the orientation requirements for these two reactions are probably similar. The reason the rates of thiolactonization do not rigorously parallel the rates of lactonization in equivalent ring systems is that the C–O and C–S bond lengths differ significantly and in some ring systems this affects the orientation between the nucleophilic atom differently for oxygen and sulfur.

From these plots the maximum rate enhancements would occur when the nucleophile was apparently held in an orientation 98° relative to the plane of the carboxyl group. In the transition state leading to the tetrahedral intermediate, ϕ_1 of eq 1 should lie somewhere between 90 and 109°. Thus, the value of 98° is not unreasonable since it is almost exactly half-way between the ground state and tetrahedral intermediate. Nevertheless, one must emphasize the large number of crude estimates involved in this graph and hence the very tentative nature of the conclusions.

Discussion

In previous studies we have examined the rates of lactonization in a number of different ring systems differing in the degree of conformational restriction and proximity between the hydroxyl and carboxyl groups. In order to evaluate the magnitude of the orientation factor it was necessary to evaluate the contribution of proximity and torsional strain from the observed rates. In the present study the uncertainties associated with the proximity calculation or differences in ground-state rotational restriction were avoided by comparing closely related compounds in which corrections for proximity or torsional strain were minor or nonexistent. The finding that these rates also differ by large numbers for small changes in orientation adds support to the basic hypothesis that orientation factors can be large and that orbital steering by a constrained system can introduce large rate effects in intramolecular and enzymatic reactions.

Bruice, Brown, and Harris[17] have claimed that there should be a general increase in reaction rates, regardless of reaction type, of about 160-fold for each internal rotation which is frozen out in the ground state. They apply this to the series of compounds published earlier[1] and there is indeed a rough correlation in the series EtOH + HAc, and hydroxybutyric, 2-hydroxymethyl-3-carboxynorbornane, and 2-hydroxy-6-carboxynorbornane using a factor of 160 per C–C bond frozen. However, this is an extremely restricted series. As Page and Jencks have pointed out, many exceptions to this empirical 160 per bond can be found.[18] The introduction of methyl groups in the compounds reported in this study, based on those arguments, should in each case increase the velocity of reaction or leave it unaffected. As seen above, they sometimes increase and other times decrease the rate. Moreover, the large changes in rate from the [2.2.2] to the [2.2.1] systems would be completely unexplained by this argument since the same freedom of rotation was present in each of these pairs. In the mercapto compounds discussed the corrected rates are intriguing since a factor of 3 rather than 160 was used in Table V. Yet the γ-mercaptobutyric acid thiolactonizes faster than the 2,3-norbornane

(17) T. C. Bruice, A. Brown, and D. O. Harris, *Proc. Nat. Acad. Sci. U. S.*, **68**, 658 (1971).
(18) M. I. Page and W. P. Jencks, *ibid.*, **68**, 1678 (1971).

derivative and the bicyclo[2.2.2], 2,3 derivative. Furthermore, it is seen that the relative rates bear little relationship to freezing of internal rotations.

Variation in rates were obtained in three ways which had minimal effect on properties other than orientation. These ways were (a) change in the supporting superstructure, (b) addition of methyl groups to limit the rotation of the carboxyl, and (c) change of the O group to S with its longer C–S bond length. Not only were large changes in rate observed but within each category the rates sometimes increased and sometimes decreased. This is exactly the type of behavior one might expect for an orientation effect whereas compression, ring strain, solvation, etc., would seem to require a constant increase or decrease for any one agent.

It might still be argued that, although none of the alternatives to orientation are viable as a common explanation for all the results, they can be used in some combination not yet devised to explain these intriguing changes. It is difficult to dispute such a nontheory. One can only say that no satisfactory self-consistent set of alternate explanations has been devised and the orientation factor argument does provide a single and logical explanation for the observations made so far.

The empirical function which relates angles of approach to the velocity of reaction is too crude to be considered a theory as yet. To obtain a reasonable number of points molecules which allowed freedom of rotation (*e.g.*, the 2,3-norbornane derivatives) were included and their correlation using a single angle would lead to the assumption that this conformation was equally filled in the two compounds. Likewise, sulfur and oxygen compounds were included which would involve a tacit hypothesis that the preferred orbital orientations in sulfur were similar to oxygen, the differences in rate coming from the new imposed geometries caused by the longer C–S bond. There is no independent supporting evidence for either hypothesis but both are plausible. The overall fit of data to the dashed curve in Figure 1 is therefore intriguing and perhaps a good point of departure for further studies. The optimum angle of 98° which is derived empirically is also logical since it is midway between a perpendicular initial approach and a tetrahedral transition state. However, this should be taken only as an intriguing correlation at the present.

The hypothesis proposed earlier,[1,2] that reaction rates may be sensitive to orientation by factors of 10^4 even after juxtaposition of the reacting atoms, is given some further support by these experiments. It is perhaps worth emphasizing that the orbital steering concept, *i.e.*, that enzymes and intramolecular structures can achieve accelerated rates by steering the reacting atoms in preferred orientations, defines the factors in empirical terms. The added acceleration is that achieved over an unoriented reaction and its theoretical components may result from bond bending, nonbonded interaction, etc. In other papers we have dealt with some theoretical aspects of the components of this factor.[3,4] Recently Hoare has evaluated a further contribution of solvent orientation.[19] In this paper we record experiments which deal with the orientation factor as a whole and support the order of magnitude postulated. The integration achieved by appropriate experiments is vital since a steering which maximizes overlap in the forming bond while minimizing repulsive interactions involves differences between large forces, none of which is subject to highly precise calculation.

(19) D. G. Hoare, *Nature (London)*, **236**, 437 (1972).

Addition–Elimination and Rearrangement Reactions in Allylic Systems

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Contribution from the Department of Chemistry, Northwestern University, Evanston, Illinois 60201. *Received October 8, 1971*

Abstract: Reactions of 3-(α-halo-α-methylethyl)benzo[*b*]thiophene 1,1-dioxide (**1**) with benzenesulfinate, thiophenoxide, cyanide, and azide salts in suitable solvents resulted in addition–elimination reactions. Evidence is presented to show that the reactions are best classified as ion-pair SN2′ from a mechanistic standpoint.

In earlier papers we have shown that treatment of 3-(α-chloro-α-methylethyl)benzo[*b*]thiophene 1,1-dioxide (**1a**) with piperidine resulted in an addition–elimination (SN2′ or SN2′-like) reaction to form **2** (not isolated), followed by a ring opening–ring closing isomerization to form **3**.[2] The electron pair on nitrogen was visualized as providing the driving force for the ring opening of **2** and the stabilizing factor causing **3** to predominate completely over **2** at equilibrium. It follows that reactions of **1a** with nucleophiles like $C_6H_5SO_2^-$ should stop at the first stage since an electron pair is not present in the addition–elimination product corresponding to **2**. The present paper describes reactions of this type which provide additional information concerning the addition–elimination and rearrangement steps in the above type of reaction sequence.

(1) National Institutes of Health Predoctoral Fellow, 1968–1971.

(2) (a) F. G. Bordwell and D. A. Schexnayder, *J. Org. Chem.*, **33**, 3226 (1968); (b) F. G. Bordwell, D. A. Schexnayder, and R. H. Hemwall, *ibid.*, **33**, 3233 (1968); (c) F. G. Bordwell and D. A. Schexnayder, *ibid.*, **33**, 3236 (1968); (d) F. G. Bordwell and D. A. Schexnayder, *ibid.*, **33**, 3240 (1968).

Results

Preparation of the bromide **1b** was desired in order to test the k^{Br}/k^{Cl} leaving group effect in the addition–elimination reaction. The method used for synthesis