

sented here. Of course, neither could be the hydrogen source with benzene.

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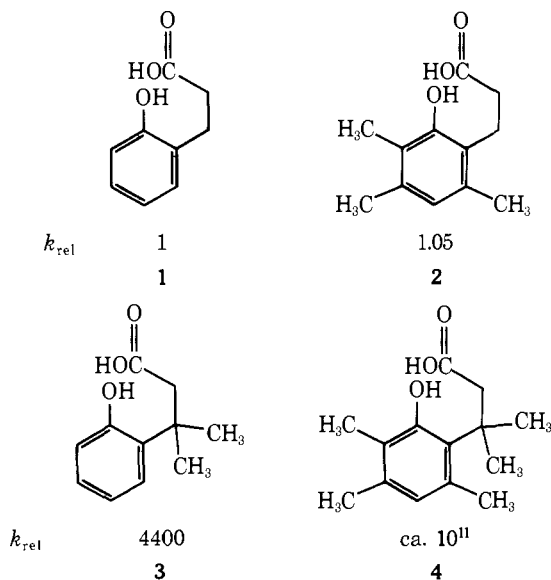
Steric Acceleration of Lactonization Reactions: An Analysis of "Stereopopulation Control"

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Abstract: The rapid lactonization of compounds of type **4** and **5a** relative to **1** (a rate acceleration of about 10^{11}) has been attributed to conformational restriction in the former compounds; the acceleration of rates due to this conformational restriction has been termed *stereopopulation control*. In this paper, we show that conformational restriction can account for a maximum rate enhancement of about 10^4 , leaving a rate factor of at least 10^7 to be accounted for in other ways. Thus, compounds **7a** and **8a** are found to lactonize with rates relative to that of **1** of 1.5×10^2 and 2.4×10^4 , respectively. Consistent with the postulation of a large relief of ground-state strain in the lactonizations of **4** and **5a** is the observation of a secondary deuterium isotope effect in the lactonization of **6a** relative to **5a**: $k_H/k_D = 1.09 \pm 0.02$. Although "stereopopulation control" may lead to sizable rate enhancements in certain cases, its importance in the reactions discussed here has apparently been overestimated.

In 1970, Milstein and Cohen,³ in their study of the lactonization of a series of hydrocoumarinic acids **1–4**, found that the relative rates for hydrogen ion catalyzed reaction showed a dramatic effect of increasing methyl substitution, such that the ratio of rates of **4** relative to **1** was a spectacular 10^{11} . In



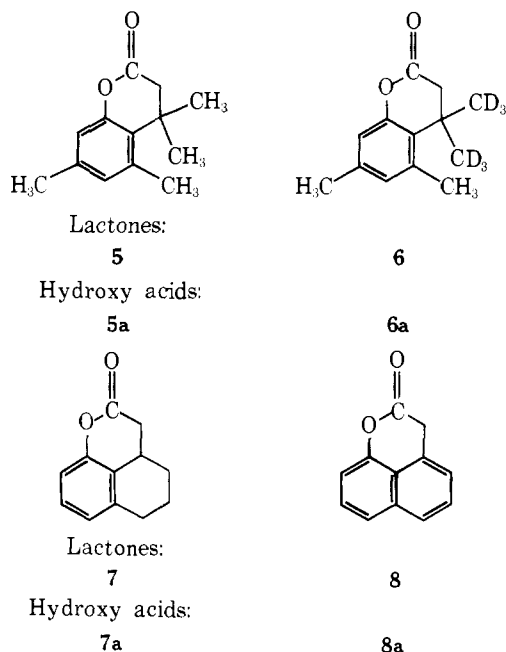
further comparison of their reactions to bimolecular counterparts, they concluded that the rate of lactonization of **4** is accelerated by a factor of about 10^{16} M, an acceleration which certainly approaches that observed for some enzyme-catalyzed reactions over their bimolecular counterparts. These authors recognized these observations as an extension of the well-

known⁴ gem-dialkyl effect, by which rates and equilibria of many ring-closure reactions are enhanced by increasing alkyl substitution on the backbone of the ring. These authors attributed these effects to a restriction of rotational freedom primarily about the bond between the aryl group and the carboxylic acid side chain in the reactive species "... which serves to narrow the distribution of conformational populations, ideally by eliminating nonproductive isomers". This putative restriction of rotational freedom was given the name *stereopopulation control*, and thus was initiated an extensive series of investigations⁵ of similarly accelerated reactions, all of which were postulated to be examples of the operations of this principle. The authors recognized that conformational restriction as a factor in catalysis had been known for some time; their point was that its maximum effect had been grossly underestimated.

In this paper, we report our experimental results which show that (a) the dramatic rate accelerations in the lactonizations of methylated hydrocoumarinic acids can be understood as an effect brought about by relief of the extreme steric compression in these compounds, and (b) the effect of freezing conformations without simultaneously introducing van der Waals repulsions is a rate acceleration of a considerably more modest magnitude than that advocated by the proponents of stereopopulation control, and is more in accord with previous estimates. In the accompanying paper, Winans and Wilcox²¹ provide theoretical support for the importance of relief of steric compression as a significant driving force in these reactions.

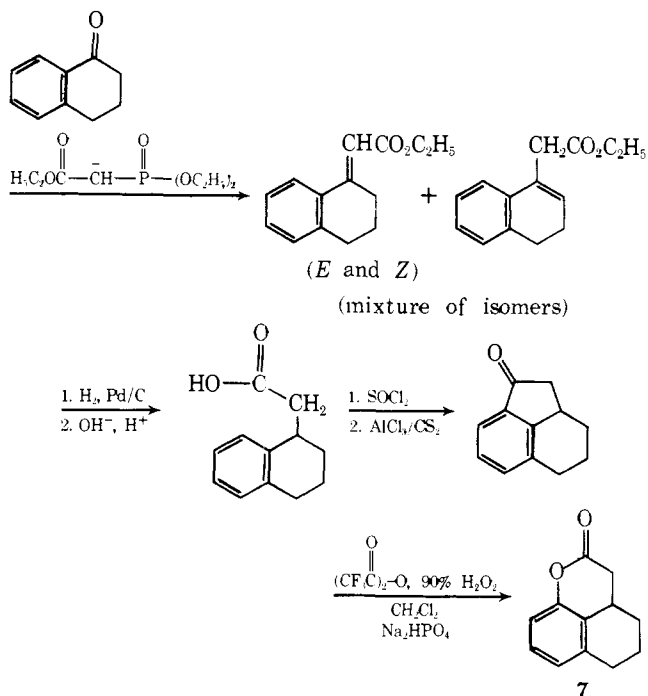
Results

Synthesis of Compounds. Compounds **5**, **6**, **7**, and **8** were used in the investigations reported herein. The synthesis of **6** was completed using a modification of that used for **5**⁶ with the



precautions described in the Experimental Section, yielding material which was 92% deuterated at the ring methyl groups, and not deuterated elsewhere. Compound 7 was synthesized by the route shown in Scheme I in a straightforward manner.

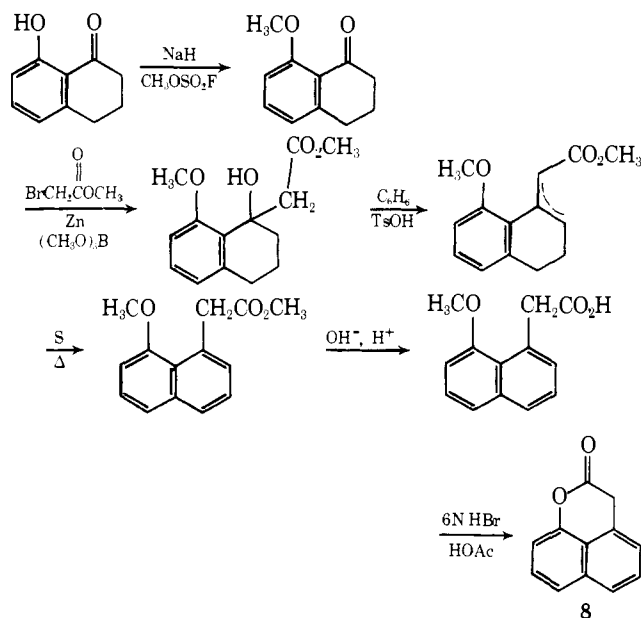
Scheme I



The synthesis of compound 8 followed the basic outlines of that of Legler et al.⁹ but with extensive modification, as shown in Scheme II. Also attempted was a Baeyer-Villiger reaction on acenaphthenone (9) with buffered trifluoroacetic anhydride. Although the only Baeyer-Villiger product was the desired material 8, it was heavily contaminated with starting material and by highly colored substances which were decolorized by dithionite, and which may arise by epoxidation of the enol form of 9.

Kinetic Studies. The conditions of Milstein and Cohen^{3,5a} were duplicated as scrupulously as possible; all kinetic determinations were carried out at 30°, ionic strength $\mu = 0.3$ M (NaCl), and 20% by volume dioxane. Reaction rates were followed spectrophotometrically.

Scheme II



Comparative Lactonization of 5a and 6a. The lactonization of 5a was chosen for a study of the possible presence of a secondary deuterium isotope effect; Milstein and Cohen have shown that rate acceleration of 5a relative to 1 is essentially equal to that of 4.^{5a} Our absolute rate measured for the closure of 5a was in good agreement with that reported by Milstein and Cohen for the same compound. In order to obtain a reliable secondary deuterium isotope effect for lactonization of 5a and 6a, however, the absolute rate is relatively unimportant, but the accuracy of the *relative* rates is crucial. In order to ensure accurate relative rates, triplicate determinations of the rate of lactonization of 5a in a given cuvette and buffer solution were followed immediately by triplicate determinations of the rate for 6a under exactly identical conditions. The results of these determinations are presented in Table I at two pH values and several buffer concentrations. The difference in the rates of the deuterated and undeuterated compounds is well outside the experimental error of the determination, so that there is clearly a secondary deuterium isotope effect for the lactonization of 5a.

Lactonization of 7a and 8a. The lactonization of compounds 7a and 8a were followed in dilute HCl solutions in the same solvent system used for the lactonization of 5a and 6a. Because of the possibility in these compounds of an unfavorable equilibrium for lactonization, the hydrolyses of the corresponding lactones were also followed under identical conditions. In both cases, an equilibrium constant for lactone formation was measured. Furthermore, under a given set of conditions, the observed pseudo-first-order rate constant for approach to equilibrium from the lactone was equal to that for approach to equilibrium from the hydroxyacid, a situation which must hold if the same equilibrium from the lactone was equal to that for approach to equilibrium from the hydroxyacid, a situation which must hold if the same equilibrium is being observed in each case. From the specific rate of approach to equilibrium ($k_{\text{lac}} + k_{\text{hyd}}$, where k_{lac} = the specific rate for lactone formation, and k_{hyd} = the specific rate for lactone hydrolysis) and the relative amplitudes of the changes in each direction ($k_{\text{lac}}/k_{\text{hyd}}$), the value of k_{lac} could be calculated. The appropriate rate and equilibrium constants are given in Table II.

It can be seen from Figure 1 that, in the pH range studied, the reactions are dependent on the concentrations of the hydronium ion, so that the observed rate, k_{obsd} , is given by

$$k_{\text{obsd}} = k_{\text{obsd,H}}[\text{H}^+] \quad (1)$$

Table I. Secondary Deuterium Isotope Effects in the Lactonization of **5a** and **6a**

[Imidazole (total)], M	$k_{\text{lac}}(\mathbf{5a})$, min^{-1}	$k_{\text{lac}}(\mathbf{6a})$, min^{-1}	$k(\mathbf{5a})/k(\mathbf{6a})$ ($=k_{\text{H}}/k_{\text{D}}$)
A. Imidazole-HCl Buffers, pH 7.51, 30°, 20 vol % dioxane, $\mu = 0.3 \text{ M}$ (NaCl)			
0.10	0.287 ± 0.009	0.258 ± 0.004	1.11 ± 0.03
0.15	0.387 ± 0.005	0.357 ± 0.004	1.08 ± 0.02
0.20	0.483 ± 0.008	0.440 ± 0.004	1.10 ± 0.02
0.30	0.683 ± 0.005	0.616 ± 0.012	1.11 ± 0.02
B. Imidazole-HCl Buffers, pH 6.95, otherwise same as above ^a			
0.05	0.299 ± 0.002	0.276 ± 0.003	1.08 ± 0.02
0.10	0.476 ± 0.003	0.437 ± 0.003	1.09 ± 0.01
0.15	0.647 ± 0.003	0.597 ± 0.001	1.08 ± 0.01
0.20	0.810 ± 0.005	0.746 ± 0.008	1.09 ± 0.02
0.30	1.062 ± 0.006	0.997 ± 0.010	1.07 ± 0.02

^a Based on triplicate determinations of each rate constant.

Table II. Rates of Approach to Equilibrium for Lactonization of **7a** and **8a**, and Hydrolysis of **7** and **8**

$-\log [\text{H}^+]$	Starting with lactone $10^2 k_{\text{obsd}} \text{ min}^{-1}$	Starting with acid $10^2 k_{\text{obsd}} \text{ min}^{-1}$
	Opening of 7	Closure of 7a
0.52	5.12 ± 0.04	5.15 ± 0.03
0.75	3.32 ± 0.03	
0.89	2.52 ± 0.03	2.53 ± 0.03
1.00	1.75 ± 0.04	
1.16	1.35 ± 0.01	
1.30	0.87 ± 0.01	
	$K_{\text{eq}} = [\text{lactone}]/[\text{acid}] = 0.69 \pm 0.01^a$	
	$k_{\text{obsd},\text{H}^+} = (1.74 \pm 0.16) \times 10^{-1} \text{ M}^{-1} \text{ min}^{-1}$	
	$k_{\text{lac},\text{H}^+} = (0.71 \pm 0.10) \times 10^{-1} \text{ M}^{-1} \text{ min}^{-1}$	
	$k_{\text{hyd},\text{H}^+} = (1.03 \pm 0.10) \times 10^{-1} \text{ M}^{-1} \text{ min}^{-1}$	
	Opening of 8	Closure of 8a
1.00	67.4 ± 0.7	67.8 ± 0.7
1.10		55.7 ± 0.8
1.15		48.6 ± 0.6
1.22		41.4 ± 0.6
1.40	27.8 ± 0.7	28.4 ± 0.3
	$K_{\text{eq}} = [\text{lactone}]/[\text{acid}] = 1.53 \pm 0.01^a$	
	$k_{\text{obsd},\text{H}^+} = (7.88 \pm 0.25) \text{ M}^{-1} \text{ min}^{-1}$	
	$k_{\text{lac},\text{H}^+} = (4.77 \pm 0.15) \text{ M}^{-1} \text{ min}^{-1}$	
	$k_{\text{hyd},\text{H}^+} = (3.11 \pm 0.15) \text{ M}^{-1} \text{ min}^{-1}$	

^a Determined from relative amplitudes of the reactions in each direction. The stock solution of **8a** in base showed some deterioration over time, which resulted in slightly decreased amplitudes; the first three amplitudes to be determined in the closure reaction were the same, and were averaged. This deterioration did not affect the rate constants or the first-order behavior.

The lactonization equilibria, as expected, were found to be independent of $[\text{H}^+]$, so that the lactonization rate and the hydrolysis rate must have an identical dependence on the hydrogen ion. Therefore, for the lactonization reaction,

$$k_{\text{lac}} = k_{\text{lac},\text{H}}[\text{H}^+] \quad (2)$$

It is the second-order rate constants $k_{\text{lac},\text{H}}$ with which the relevant comparisons to earlier data will be made.

Low-Temperature NMR Experiments. A direct investigation of rotational barriers in **5a** is impractical because of its rapid rate of lactonization. However, we prepared the close analogue **10**, which has the interesting feature that, with the exception of the aromatic protons, its NMR spectrum consists entirely of singlets. Low-temperature NMR at 90 MHz from -60 to -140° in Freon 22 showed no temperature-induced non-equivalencies, although some selective broadening of the up-

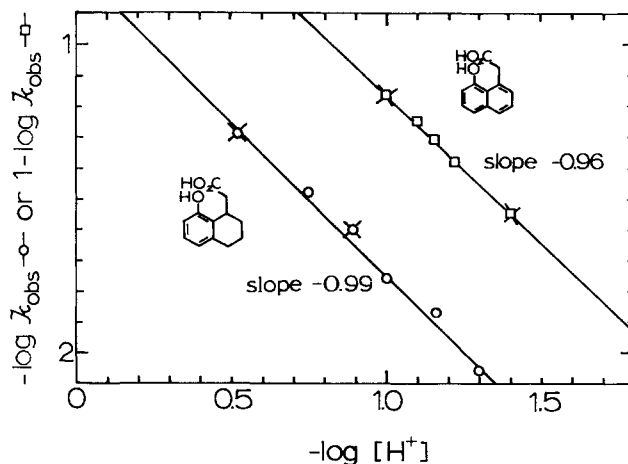
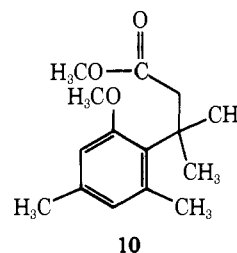


Figure 1. The dependence of k_{obsd} (eq 1) on $-\log [\text{H}^+]$. The points are experimental, and the lines are calculated from a fit of the data to a logarithmic form of eq 1. Crosses indicate points at which determinations were made of the rate of approach to equilibrium from both hydroxy acid and lactone directions.



field aromatic methyl group took place at about -130° . Similar low-temperature examinations of *cis*-1,2-di-*tert*-butylethylene and *tert*-butylmesitylene showed no breaking of the characteristic singlet patterns in these compounds at low temperature.

Discussion

Before quantitative comparisons are made between sets of data, it is important to ascertain that comparisons are being made between reactions of identical mechanism. Milstein and Cohen,¹⁰ arguing from substituent effects on the lactonization reaction, suggested that the rate-determining step of the lactonization reaction is the breakdown of the tetrahedral intermediate. Hershfield and Schmir¹¹ studied the lactonization of a series of coumarinic acids and in these compounds found clear kinetic evidence for a change in the rate-determining step with a change of pH. In the region of their pH-rate profiles in

which breakdown of the tetrahedral intermediate derived from these latter compounds was shown to be rate-determining, the Hammett ρ value was very close to that found by Milstein and Cohen;¹⁰ thus, this work provided independent support for the deductions made in the earlier¹⁰ paper. Since compounds **7a** and **8a** contain functional groups identical with those in compounds **1** and **5a**, and lactonize with rates which are intermediate between those of the extreme cases **1** and **5a**, for which identical mechanisms are implicated, then it is reasonable to suppose that the mechanism of lactonization of these compounds is the same as that postulated by Milstein and Cohen, and this supposition will be made in the analysis to follow.

Does a Trialkyl Lock Exist in 4, 5a, and Related Compounds? Our low-temperature NMR examination of compound **10**, as well as related compounds, produced no definitive evidence which can be used to answer this question. On the other hand, it should be pointed out that extreme conformational restrictions in **4**, **5a**, or related compounds have never been demonstrated experimentally. It seems that arguments concerning the consequences of a conformational lock should be accompanied by evidence that such a lock exists. A further difficulty with the conformational lock hypothesis is how the authors *fortuitously* (their italics; see ref 3, p 1147) synthesized only one conformer of **4** and **5a**, although it must be admitted, if one assumes the existence of the lock, such a synthesis is in principle possible. The measured rotational barrier about the isopropyl-phenyl bond of isopropylmesitylene^{12,13} (12.8 kcal/mol at -35°) and the x-ray crystal structure of Karle and Karle,¹⁵ complicated by intermolecular hydrogen bonding, also do not lead to unambiguous arguments concerning conformational restriction in the specific cases **4** and **5a**. Furthermore, considerations of rotational barriers based strictly on "size" are modified by such considerations as the "gear effect", by which rotational motions of several groups are correlated.^{14a} Finally, the concept of "size" itself is misleading. Thus, if one were to replace the buttressing methyl groups with halogens of progressively increasing molecular weight, it would not be surprising in light of the work of Jensen^{14b} to find little effect on the rate of lactonization.

Thus, it must be recognized that definitive evidence concerning the existence of a conformational constraint in **4** or **5a** does not presently exist. However, in the next section, we shall show that, even if such a lock exists, it does not lead to the immense rate accelerations obtained for the lactonizations of **4** and **5a**.

Kinetic Consequences of Conformational Locking in Lactonization Reactions. Compounds **7** and **8** were synthesized in order to investigate the consequences of conformational locking on lactonization reactions. Compound **7a** evidently possesses several accessible conformational states, two pseudo-chairs and two presumably higher energy pseudo-boats. In both chair forms, the phenolic hydroxyl can easily form a bond to the carbonyl carbon with little perturbation of the remainder of the molecule. The point of this compound is that rotation around the relevant phenyl-carbon bond ortho to the phenolic hydroxyl group is, as a consequence of its inclusion in the carbocyclic ring, highly constrained relative to open-chain **1**. In a crude sense, **7a** can be considered a "partially locked" analogue of **1**. After making a substituent effect correction^{10,16} for the extra alkyl side chain (a factor of only 0.8), the lactonization of **7a** is found to proceed with a rate relative to that of **1** of 1.5×10^2 . The effect of a total lock are provided by compound **8a**. After correcting for the substituent effect due to the presence of the 2,3-naphtho bridge^{10,16} and the absence of the alkyl side-chain (a factor of 1.5), the rate of lactonization of **8a** relative to that of **1** is 2.1×10^4 . This factor is appreciable, but represents only a small fraction of the rate acceleration of **4** and **5a** lactonization.

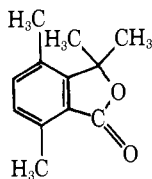
Clearly, the bulk of the tremendous rate acceleration for the

lactonization of **4** and **5a** must be due to some factor other than restriction of the internal degrees of freedom of the open-chain hydroxyacids. Steric repulsions in the ground state of these molecules, largely between the aryl methyl group and the side-chain substituents, are an obvious source of such rate enhancements.⁴ An exploration of the direct *experimental* and theoretical evidence for such ground-state strain is presented in the accompanying paper.²¹ If the conformational effect is evaluated at about 10^4 (compound **8a**), then a factor of about 10^7 remains to be accounted for. Similarly large effects of a steric nature have been accompanied by secondary deuterium isotope effects (often descriptively called "steric isotope effects") when hydrogen is replaced by deuterium at the site of the repulsions; a recent paper references many examples of such effects.¹⁸ Accordingly, we replaced the side-chain methyls with deuterated methyls (compound **6**) and examined the relative lactonization rate of **5a** and **6a**. Table I shows that there is a secondary deuterium isotope effect which is independent of pH (over the two values studied) and buffer concentration. It is expected in this case that electronic effects due to deuterium substitution^{20d} are negligible because of the insulation of the isotopes from the aromatic ring and the carboxyl group. Note that isotope substitution in the ring and α to the carboxyl group was scrupulously avoided (see Experimental Section). How these isotope effects can arise has been thoroughly discussed.¹⁸⁻²⁰ Our effect is somewhat unusual in that it arises from ground-state strain,³⁶ whereas most examples result from constrained transition states.

In the accompanying paper, Winans and Wilcox²¹ report the results of a force field calculation on these lactonization reactions of **1** and a close analogue of **5a**; these authors calculate that the difference in strain energy in the two reactions corresponds to 10.3 kcal/mol, or a factor of about 10^7 in rate, in close agreement with that observed. These authors further explore the relationship of the mechanically descriptive, but statistically mechanically imprecise ideas of "strain energy", "conformational lock", etc., in terms of their relationship to the total free energy of activation, which is of course ultimately the quantity of interest.

In view of the fact that the rate-determining step in lactonization reactions is the breakdown of the tetrahedral intermediate (see above), the steric effects on closure appear as an effect on the ring-forming equilibrium prior to the rate-determining step; the equilibrium constants for this process enter multiplicatively into the observed rate constant. In the reverse, lactone-opening reaction, steric effects on ring opening do not occur until the step in which the phenolate ion is expelled; by microscopic reversibility, this is post rate-determining in the opening reaction, and repulsive effects present in the hydroxy acid will not be reflected in the observed rates of lactone hydrolysis. Assuming the same mechanism holds in basic solution, this analysis is consistent with the general observation that steric effects on the rate of lactone hydrolysis, as one proceeds down the series **1-5**, are not observed.²⁴ This is another way of saying that equilibrium constants for lactonization should reflect the effects of strain relief, and this is observed experimentally. Nevertheless, it should be possible to make the lactone opening so unfavorable sterically that by increased substitution the expulsion of the leaving group in the hydrolytic direction becomes rate-determining. Such a case has evidently been found by Hillery and Cohen,²⁶ who observed that compound **11** was totally stable to ring opening in base, although easily reduced by carbonyl reagents (the latter point demonstrating that the carbonyl attack step is not blocked). These authors attributed such resistance to ring opening to conformational effects; Bruce⁴ has indicated the importance of steric effects in a closely similar case.

The factor of ca. 10^4 in the rate acceleration of **4** and **5a** relative to **1**, which is ascribable to effects other than unfa-



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favorable ground-state strain, although not the major source of rate enhancement in these compounds, is also not a trivial rate acceleration. Conformational "locking" is not necessary to produce these accelerations; if internal rotations are correlated (cf. the "gear effect", above¹⁴) then for each correlation one internal degree of freedom is lost, with the resultant entropic cost. It is further worth pointing out again²⁷ that ground state conformations other than that which looks most like the presumed transition state (often mistakenly called the "productive" conformation) can be highly populated without sacrificing significant rate enhancement. If all such populations are equally destabilized by various factors, and they are all rapidly interconverting, then the transition state is accessible from any one of them. In such cases, the term "reacting conformer", "favorable conformation for reaction", etc., have no meaning, although application of these terms leads to formally correct rate expressions.²⁷

Undoubtedly, enzymes in many cases must use their binding energy in part to restrict torsional and vibrational motions in their substrates, even in the absence of steric repulsions. Such "stereopopulation control" has been recognized in the past,^{3,28} and in the case of a large, flexible molecule (polyene steroid precursors?) could lead to rate accelerations of many orders of magnitude. In the present situation, however, the effect has been highly overestimated, and previous estimates for this effect^{4,22} appear more reasonable. In fact, the rate factor of 10^4 observed for the rigid compound **8a**, combined with the additional factor of 10^4 to 10^5 M observed for acceleration of the lactonization rate of **1** relative to the esterification rate of phenol and acetic acid is quite close to the overall contribution of 10^8 M suggested by Page and Jencks²² for entropic contributions. The use of enzyme binding energy to induce strain in a substrate is perhaps a closer analogy to what appears to be driving these lactonization reactions, but this idea is a well-established feature²⁹ of enzyme catalysis, for which rate accelerations of the magnitude observed here have been well-precedented.

Experimental Section

General Synthetic Procedures. IR spectra were obtained on a Perkin-Elmer 137 instrument in either a KBr pellet or CCl_4 solution. Analytical NMR spectra were obtained in CDCl_3 on a Varian Associates A60A instrument, and low-temperature NMR spectra were obtained on a Bruker HX-90 instrument; chemical shifts are expressed as parts per million downfield from internal tetramethylsilane. Mass spectra were performed on an AEI MS 902 instrument in the electron impact mode at 70 eV. Melting points are corrected, and microanalyses were performed by the Galbraith Laboratories.

The overall synthetic sequence to compound **7** is outlined in Scheme I, and the detailed experimental follows.

Ethyl 1-Tetralylacetate. The ylide derived from ethyl diethylphosphonoacetate (22.4 g, 0.1 mol)⁷ in 125 ml of tetrahydrofuran (THF), generated with NaH (4.63 g, 0.1 mol) was allowed to react with α -tetralone (14.55 g, 0.1 mol); an extensive reflux period was necessary for complete reaction, and an overnight reflux was generally used. Conventional workup yielded a liquid which was distilled at reduced pressure. The fractions collected at 75–100° (0.13 Torr) were analyzed by NMR and appeared to be a mixture of the three possible double bond isomers shown in Scheme I (11.9 g, 55%). This material was hydrogenated in portions at 1 atm in 95% ethanol using 5% Pd on charcoal, employing typically 0.6 g of catalyst per g of substrate. After consumption of the theoretical amount of H_2 , the mixture was filtered and concentrated to give a 98% yield of a residual liquid which showed no evidence of vinyl protons in the NMR.

1-Tetralylacetic Acid. Ethyl 1-tetralylacetate (10.3 g, 47.2 mmol) was saponified in a solution of 90 ml of 10% NaOH and 10 ml of methanol by stirring at reflux for 4.5 h. The usual workup followed by acidification gave 1-tetralylacetic acid (8.2 g, 91%) as an oil (lit. mp³⁰ 35–36 °C) which was treated further without recrystallization.

1,2,3,4-Tetrahydroacenaphthenone. The acid chloride of 1-tetralylacetic acid (6.14 g, 29.4 mmol), prepared by thionyl chloride treatment of 1-tetralylacetic acid, was added dropwise to a mixture of anhydrous AlCl_3 (8.3 g, 60 mmol) in 200 ml of CS_2 . After the mixture was stirred for 1 h, hydrolysis and workup afforded a residue which was recrystallized from hexanes to give 2.22 g (47%) of the desired ketone, mp 101–102 °C (lit.³¹ 102 °C).

8-Hydroxy-1-tetralylacetic Acid Lactone (7). Anhydrous dibasic sodium phosphate (4.3 g) was added to a 100-ml round-bottomed, three-necked flask equipped with an overhead mechanical stirrer, addition funnel, and reflux condenser. 1,2,3,4-Tetrahydroacenaphthenone (1.0 g, 5.8 mmol) and CH_2Cl_2 (15 ml) were added to the flask. Trifluoroacetic anhydride (2.94 g, 14 mmol), 90% H_2O_2 (0.3 ml), and a few milliliters of CH_2Cl_2 were mixed in a small beaker, and when the solution became homogeneous, it was added dropwise to the stirred solution in the flask. After addition, the mixture was refluxed for 1.5 h. The solid salts were removed by filtration and washed with CH_2Cl_2 , and the combined organic layers were washed with 5% NaHCO_3 and water, dried over MgSO_4 , and concentrated in vacuo. Recrystallization of the residue from hexanes afforded white plates (0.74 g, 68%), mp 78–79 °C. The IR showed carbonyl absorption at 1770 cm^{-1} (phenyl acetate, 1770 cm^{-1}) and the NMR, free of absorption from δ 3.3 to 6.6, was δ 1–3.3 (m, 9H) and 6.6–7.4 (m, 3H). Mass spectrum: m/e 188 (P, 85%), 146 (100%), and 131 (36%). Anal. Calcd for $\text{C}_{12}\text{H}_{12}\text{O}_2$: C, 76.61; H, 6.28. Found: C, 76.57; H, 6.43.

The synthesis of **8** follows Scheme II.

1,8-Dihydroxynaphthalene, prepared in 41% yield by the method of Woodward et al.³² was converted to 8-hydroxy-1-tetralone also by the method of Woodward et al.³² The success of this last reaction was found to depend critically on the degree of catalyst activation and H_2 pressure. For freshly activated (base-washed) Raney Ni, 50 psi of H_2 pressure and room temperature provided the best results; higher temperature resulted in overreduction.

8-Methoxy-1-tetralone. The sodium salt of 8-hydroxy-1-tetralone was anticipated to form with difficulty because of the extensive intramolecular hydrogen bonding of the phenolic hydroxyl and the carbonyl which was indicated by the NMR spectrum. Accordingly, to 5.3 g (0.22 mol) of NaH in dry THF, all cooled in an ice bath, was added dropwise with stirring 8-hydroxy-1-tetralone (10.5 g, 65 mmol) and the mixture stirred for 1 h. To the resulting greenish solution was added dropwise 7.5 g (65 mmol) of methyl fluorosulfonate, and stirring was continued for 1 hr. The usual workup followed by concentration afforded 7.1 g (63%) of a yellow liquid which was distilled at 120 °C (1 Torr) to yield a product which solidified on standing: NMR δ 1.8–2.1, 2.4–2.9 (m, 6H), 3.8 (s, 3H), 6.7, 7.1–7.4 (m, 3H).

Methyl 1-hydroxy-8-methoxy-1-tetralylacetate was prepared by the Rathke³³ modification of the Reformatsky reaction using 2.75 g (40 mmol) of Zn dust, 8-methoxy-1-tetralone (7.1 g, 40 mmol), 20 ml of trimethyl borate, and 6.2 g (40 mmol) methyl bromoacetate. Workup afforded 6.7 g (68%) of an orange liquid which was carried through the next procedure: NMR δ 1.7–3.0 (m, 6H), 3.7 (s, 3H), 3.85 (s, 3H), 4.85 (s, broad, 1H, exchangeable with D_2O), 6.6–7.3 (m, 3H).

Methyl 8-Methoxy-1-naphthylacetate. The hydroxy ester from the foregoing procedure was dehydrated in refluxing benzene containing 0.1 equiv of *p*-toluenesulfonic acid (10 h) with concomitant azeotropic distillation of the water produced into a Dean-Stark trap. The resulting material without further purification was subjected to aromatization in the presence of sulfur, as described by Newman,³⁴ entraining the H_2S produced with an argon sweep. Vacuum distillation of the residue (135°, 0.2 Torr) afforded 3.56 g (73%) of an orange liquid which solidified on standing: NMR δ 3.7 (s, 3H), 3.84 (s, 3H), 4.18 (s, 2H) 6.7–7.8 (m, 6H).

8-Methoxy-1-naphthylacetic Acid. Saponification of the product of the previous reaction (3.56 g, 0.015 mol) in 50 ml of 0.1 N KOH made 10% in methanol for 15 min at reflux followed by the usual workup afforded 2.37 g (73%) of a brown solid: NMR δ 3.7 (s, 3H), 4.1 (s, 2H), 6.55–7.6 (m, 6H); the $-\text{OH}$ proton was not located.

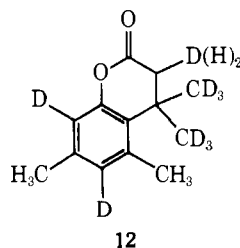
8-Hydroxy-1-naphthylacetic Acid Lactone (8). The crude product from the previous reaction was stirred at reflux for 4 h in a solution

of 50 ml of glacial acetic acid and 50 ml of 48% HBr. After cooling, 50 ml of water was added, and the brown precipitate collected by filtration. The supernatant was concentrated in vacuo to yield an orange sludge. The combined residues were triturated with hexanes and recrystallized therefrom to yield 0.56 g (28%) of **8**, mp 101.5–102.5 °C (lit.⁹ 103–105 °C): NMR δ 4.3 (slightly broadened s, 2 M), 7.0–7.9 (m, 6 H); ir, carbonyl, 1750 cm^{-1} . Anal. Calcd for $\text{C}_{12}\text{H}_8\text{O}_2$: C, 78.25; H, 4.38. Found: C, 78.08; H, 4.22.

4,4,5,7-Tetramethylhydrocoumarin (5) was synthesized by the method previously described.⁶

Methyl 3,3-bis(trideuteriomethyl)acrylate (16) was synthesized by the Emmons⁷ modification of the Wittig reaction using the reaction of the ylide generated from methyl dimethylphosphonoacetate with hexadeuterioacetone in THF; the deuterated ester was obtained in 69% yield after distillation (bp 134 °C) and showed no detectable loss of deuterium relative to the starting deuterioacetone: NMR δ 3.4 (s, 3 H), 5.67 (s, 1 H); the protic material synthesized by esterification of 3,3-dimethylacrylic acid has NMR δ 1.90 (d, 3 H, $J = 1.4$ Hz), 2.17 (d, 3 H, $J = 1.4$ Hz), 3.4 (s, 3 H), 5.67 (septuplet, 1 H, $J = 1.4$ Hz).

4,4-Bis(trideuteriomethyl)-5,7-dimethylhydrocoumarin (6) was synthesized in a manner similar to the protium analogue **5** with the following exceptions. D_2SO_4 (101%) was prepared by distillation of SO_3 (Sulfan, 86.3 g) into 20 g of D_2O cooled with stirring in an ice bath. Titration of the resulting D_2SO_4 with standard NaOH gave a wt % D_2SO_4 of 100.8 ± 0.1 . To 10.0 g of 3,5-dimethylphenol in an 80-ml beaker was added 10 ml of D_2O and ca. 3 ml of the concentrated D_2SO_4 . This mixture was heated with stirring for 30 min, and then poured into 100 ml of ice-water with rapid stirring; ether extraction, washing the ether extracts with 5% NaHCO_3 , and drying (MgSO_4) followed by concentration yielded phenol whose aromatic protons were completely deuterated by NMR. Failure to take this precaution resulted in loss of the desired isotope in the methyl groups of the lactone side chain in the synthesis to follow. In order to prepare **6**, the **3,5-dimethylphenol-2,4,6- d_3** whose preparation was just described, was taken up in anhydrous ether and extensively washed with D_2O containing a trace of D_2SO_4 . Concentration of the ether layer yielded the residue, which was used directly in the preparation of **6** in place of 3,5-dimethylphenol. In this reaction, D_2SO_4 was, of course, substituted for the H_2SO_4 used in preparation of the protium analogue **5**. The product of the reaction was **12**, deuterated as indicated; the position



α to the carbonyl, of course, partially exchanged during the reaction, and the protium previously at that position diluted the isotope pool of the solvent somewhat, but the side-chain deuteriomethyl groups showed a loss of only 8% of their total deuterium during this reaction (92.4% deuteration) by NMR. The final task was to remove the unwanted deuterium, so that only the side-chain methyl groups remained deuterated. This was accomplished by treating the product **12** with 225 g of polyphosphoric acid with mechanical stirring for 2 h on the steam bath. The resulting pink mixture was hydrolyzed over ice and worked up in the usual manner. An NMR of the product indicated complete exchange-out of the previously noted aromatic deuterium, but that at the α position remained. This residual deuterium was removed by treatment of the product with a mixture of 240 ml of absolute ethanol and 180 ml of 6 N NaOH overnight. Neutralization with HCl, collection of the product by filtration, and recrystallization from hexanes yielded 4.8 g of the product **6** (mp 93.5–94.5 °C) which, by NMR, had no deuterium at the side chain methylene or aromatic positions, and 92.4% deuterium in the deuteriomethyl positions.

Methyl 3-Methyl-3-(2,4-dimethyl-6-methoxyphenyl)butyrate (10). The lactone **5** (102 mg, 0.5 mmol) was dissolved in methanol and treated with 1.1 ml of 1 M methanolic NaOH. The solvent was removed and the residue dissolved in 5 ml of acetone; 400 mg of K_2CO_3 , and 0.172 ml (1.5 mmol) of dimethyl sulfate were added. The mixture

was stirred for 1 h at room temperature and added to ice. Conventional workup followed by flash distillation at 0.1 Torr afforded a small sample of the desired product: NMR δ 1.56 (s, 6 H), 2.23 (s, 3 H), 2.5 (s, 3 H), 2.93 (s, 2 H), 3.47 (s, 3 H), 3.75 (s, 3 H), 6.56 (broad s, 2 H), and a small impurity (unaffected by temperature) at δ 1.22.

cis-1,2-Di-tert-butylethylene was prepared by hydrogenation of 419 mg di-tert-butylacetylene (a gift of Mr. Rick Grossman) in the presence of 55 mg of Pd/ BaSO_4 catalyst and 7 μl of quinoline. The product was about a 70:30 ratio of the cis:trans olefin, but the former was obtained pure by preparative GLC on a $\frac{1}{4}$ in. \times 8 ft DC-10 column at 110°.

tert-Butylmesitylene was prepared by the method of Burgstahler et al.,³⁵ and purified by preparative GLC on a $\frac{1}{4}$ in. \times 8 ft SE-30 column: NMR δ 1.5 (s, 9 H), 2.18 (s, 3 H), 2.5 (s, 6 H), 6.8 (broad s, 2 M).

Kinetic methods were those described by Milstein and Cohen, except that a Cary Model 1605 spectrometer was used. The kinetics of all compounds were carried out at 30° in 20 vol % dioxane, 0.3 M ionic strength maintained with NaCl, and all kinetic traces showed excellent pseudo-first-order behavior. Despite the small amount of protium in the side-chain methyls of **6a**, no obvious deviations from first-order kinetics could be detected. Reactions were followed at 285 (**5a** and **6a**), 279 (**7** and **7a**), and 274 nm (**8** and **8a**).

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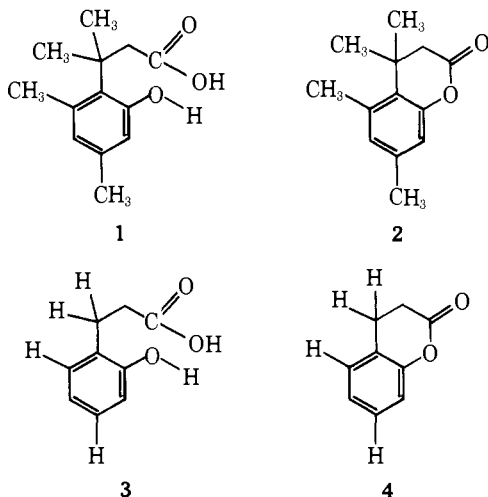
Comparison of Stereopopulation Control with Conventional Steric Effects in Lactonization of Hydrocoumarinic Acids

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Abstract: Milstein and Cohen have observed exceptionally large rate enhancements in the acid-catalyzed lactonization of hydrocoumarinic acid on substitution of sterically interacting methyl groups to the acid. They have interpreted these rate increases in terms of stereopopulation control (conformational locking) rather than a conventional ground state relief of strain. Estimation of the importance of conventional steric strain relief by a empirical force field model leads to the conclusion that the conventional strain relief is the dominant factor. The calculational model is described and the results are analyzed in some detail.

Milstein and Cohen have observed² that the tetramethylated *o*-hydroxyhydrocinnamic acid **1** lactonizes to give **2** at an acid-catalyzed rate 8.5×10^{10} faster than the analogous demethylated acid **3** gives **4**. It was proposed that this large rate

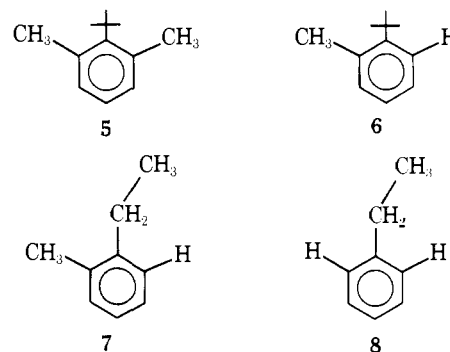


enhancement resulted from restriction to rotation of the side chain in **1** so that the carboxylic acid group was effectively frozen into a conformation favorable for lactone production. The contribution of conventional steric effects such as relief of ground state strain in **1** was rejected as minor.³

This proposal of *stereopopulation control* is potentially important to the high reactivity and specificity of enzyme reactions. It seemed essential to verify that conventional steric effects truly were unimportant. On the face of it, a reasonable alternative to stereopopulation control is that **1** is severely crowded, but that this strain is largely relieved on forming lactone **2**. Since **3** would be relatively unstrained, a steric acceleration could result. This simple hypothesis⁴ could be embroidered with further contributions from electronic effects of the four extra methyls in **1** and secondary steric effects such as differential solvation, but these should be, by common ex-

perience, small compared to the large rate differences of **1** and **3**. And, of course, stereopopulation control could be contributing as well.

A rough estimate of the magnitude of steric acceleration to be expected comes from consideration of the strains in hydrocarbons **5-8**. The change in strain energy of the reaction



of **1** \rightarrow **2** is approximately the difference in strain of **5** and **6**. In making this analogy, the repulsion of a phenolic OH by the $\text{CH}_2\text{CO}_2\text{H}$ group has been equated to the repulsion of a CH_3 by a methyl on the *tert*-butyl group. It is known that OH is effectively smaller than CH_3 ; however, this is partially compensated by the $\text{CH}_2\text{CO}_2\text{H}$ group being larger than CH_3 .⁵ In parallel fashion the change in strain energy of the reaction of **3** \rightarrow **4** is approximately the strain difference between **7** and **8**.⁶

For the latter pair, the change in strain is about 1.1 kcal/mol, which is the difference in heats of formation of gaseous 2-ethyltoluene and 4-ethyltoluene. Thermochemical data for hydrocarbons **5** and **6** are not available. However, the required strain energy difference has been estimated by Brown⁷ to be about 24 kcal/mol in **5** and 4-6 kcal/mol in **6**.

With the strains given above one can estimate a range of steric accelerations of 10^{12} - 10^{14} . As crude as this estimate is, it strongly suggests that the observed lactonization rate enhancement of 5×10^{10} can indeed be accommodated by a