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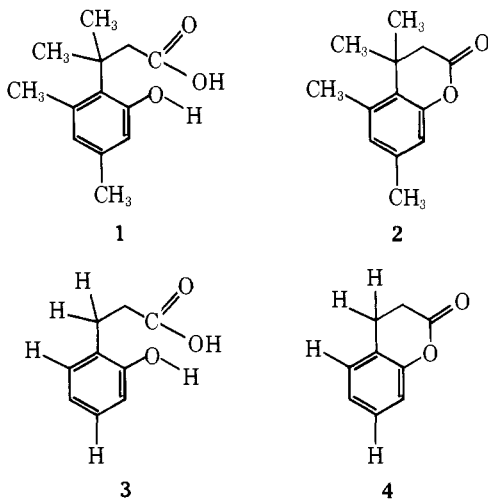
Comparison of Stereopopulation Control with Conventional Steric Effects in Lactonization of Hydrocoumarinic Acids

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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

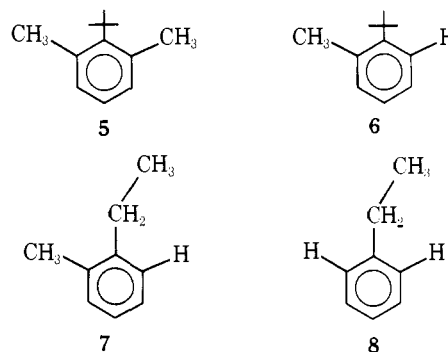


enhancement resulted from restriction to rotation of the side chain in **1** so that the carboxylic acid group was effectively frozen into a conformation favorable for lactone production. The contribution of conventional steric effects such as relief of ground state strain in **1** was rejected as minor.³

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

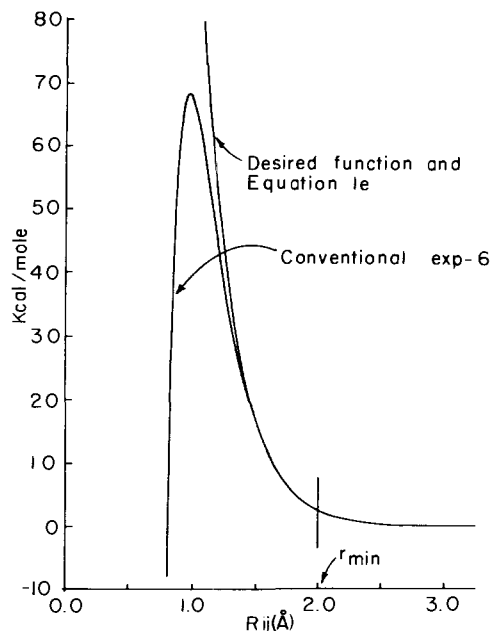


Figure 1. Comparison of H...H van der Waals interactions.

conventional steric effect. The remainder of this paper is concerned with improving the estimate of steric acceleration in the lactonization of **1**. The technique is an empirical force field calculation of the strain present in **1** and **3**, as well as the presumed intermediates in the lactonization reaction.

The Theoretical Model

Empirical force field calculations were carried out on the lactonization reactants and intermediates as well as several related aromatics using a model essentially like that described by Boyd.⁸ The potential function, eq 1, included bond

$$\left. \begin{aligned} E(r) &= 1/2K_r(r - r_0)^2 & (a) \\ E(\theta) &= 1/2K_\theta(\theta - \theta_0)^2 & (b) \\ E(\delta) &= 1/2K_\delta(\delta)^2 & (c) \\ E(\phi) &= 1/2E_0(b + \cos 3\phi) & (d) \\ E(nb) &= A \exp(-Br) - C/(r^6 + 1) & (e) \end{aligned} \right\} (1)$$

$$\text{"strain energy"} = \sum E(r) + \sum E(\phi) + \sum E(\delta) + \sum E(\phi)$$

stretching (1a), bending (1b), out of plane bending (1c), torsional (1d), and nonbonded interactions (1e).

The nonbonded interactions were modified from Boyd in three ways. First, it has been noted that the electron density in a carbon-hydrogen bond is located closer to the carbon than expected from the internuclear distance. This alters the apparent center of polarizability and affects the calculated van der Waals forces. This effect can be included by shortening the carbon-hydrogen bond by 10% for the nonbonded interactions.⁹ This shortening applies *only* to the *nonbonded interactions*.

Second, because of the severe steric crowding in these molecules, initial coordinate estimates sometimes placed atoms so close together that the conventional Buckingham exponential-6 approximation to the van der Waals potential assigned large negative potential values. This error arises because the attraction term, $1/r^6$, becomes large at very small r . The addition of the term 1.0 allows the exponential repulsion to remain dominant at small values of r . As Figure 1 shows, this adjustment does not affect the value of the potential at separations attainable in the minimum energy configuration.

The third change in the Boyd program was to substitute a full pivoting simultaneous equation-solving routine¹⁰ for the simple Gauss elimination method used by Boyd. The full pi-

Table I. Assumed Force Fields

Stretch	K_r , mdyn/Å	r , Å	
C _{sp} ² -H	5.1	1.09	
C _{sp} ³ -H	4.55	1.09	
C _{sp} ³ -C _{sp} ³	4.4	1.54	
C _{sp} ² -C _{sp} ³	4.6	1.54	
C _{sp} ² -C _{sp} ²	7.62	1.398	
C-O	5.2	1.364	
O-H	5.0	0.96	
C=O	11.6	1.245	
Bending	K_θ , mdyn/Å	θ , deg	
C _{sp} ² -C _{sp} ² -C _{sp} ² (C _{sp} ² O)	1.0	120.0	
C _{sp} ³ -C _{sp} ³ -C _{sp} ³ (C _{sp} ²)	0.8	111.0	
C _{sp} ² -C _{sp} ² -H	0.75	120.0	
C _{sp} ² -C _{sp} ³ -H	0.608	109.0	
H-C _{sp} ³ -H	0.508	107.9	
C _{sp} ³ -C _{sp} ³ -O	1.0	109.4	
O-C _{sp} ³ -O	0.9	109.4	
C _{sp} ³ -O-H	0.65	109.0 (107.8, acid)	
C _{sp} ³ -C=O	0.59	116.2	
O=C-O	1.58	124.0	
Out of plane	K_δ		
C _{sp} ² -C _{sp} ² (H)-C _{sp} ²	0.29		
C _{sp} ² -C _{sp} ² (C _{sp} ²)-C _{sp} ²	0.70		
C _{sp} ² -C _{sp} ² (O)-C _{sp} ²	0.50		
Torsional	K_ϕ	b	
C _{sp} ² -C _{sp} ² -C _{sp} ² -C _{sp} ²	-0.08	-1.0	
(H)C _{sp} ³ -C _{sp} ³ -C _{sp} ³ -C _{sp} ³ (H)	0.0146	1.0	
C _{sp} ² -C _{sp} ² -O-H	-0.022	-1.0	
O=C-C _{sp} ² -C _{sp} ³	-0.13	-1.0	
H-O-C=O	0.03	1.0	
Nonbonded	A	B	C
C C	104.0	3.09	4.45
C H	30.0	3.415	0.96
H H	18.4	3.74	0.19
O H	148.6	4.34	0.545
O C	104.0	3.09	4.45
O O	104.0	3.09	4.45

voting scheme solves the ill-conditioned equations that can arise (we have noted this particularly with molecules containing flexible side chains). With the simpler elimination scheme there was a tendency for the calculated atom displacements to oscillate.

The values of force constants and other parameters used in the present calculation are given in Table I. The carbon and hydrogen values are essentially those of Boyd.⁸ The oxygen force constants are obtained from spectroscopic data on carboxylic acids.¹¹ The bond lengths and angles are from microwave data on acetic acid¹² and phenol.¹³ The unstrained OH distance was taken to be a constant for all molecules; the C-O distance was taken as that found in alcohols and phenol. The angle bending constants at the orthoacyl carbon were estimated from carbon analogues. The nonbonded interaction parameters for carbon and hydrogen are those of Boyd.^{8a} The H...O nonbonded interaction was approximated as an H...F interaction using the values reported by DeCoen et al.^{8c} This choice was suggested by the similar sizes of fluorine and oxygen and by the similar magnitudes of their nonbonded interactions employed in the Hill scheme.^{8d} The O...C and O...O interactions were set equal to the C...C values. The calculated energies do not appear to be sensitive to the choice of oxygen parameters, as they are dominated by H...H and to a lesser extent the C...H interactions.

It has been shown that small errors in force constants do not make significant differences in the overall calculated energy. This is especially true in **2**, where the main source of strain is the interaction between the methyl groups and does not involve

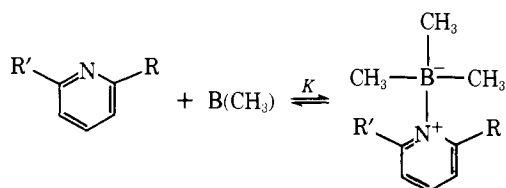
the oxygen functionalities to a significant degree. Because of the good agreement with experimental results that Boyd had with calculating strain energy in cyclophanes,^{8a} such discrepancies as using 1.54 Å instead of ca. 1.49 as the equilibrium C_{sp²}-C_{sp³} bond length were retained. To adjust these values would probably require extensive adjustments in the rest of the force field, which is not the objective of this investigation. It was demonstrated that the differences in strain energy were not overly sensitive to small variations in the assumed force field.

Methodology

For these highly strained molecules, a typical calculation involved several steps. Two Fortran programs were used to assemble the data required for the complete minimization of the strain energy. The first program calculated a set of starting Cartesian coordinates from the assumed bond lengths, bond angles, and torsional angles. A second program assigned the force constants for each of the potential functions according to the atom connectivity and type. Next, (and this is a critical step!) the initial strain energy was calculated and checked for any exceptionally strained interactions. If any unusually large interactions were found, the starting coordinates were altered so as to relieve these strains as much as was practical. Finally, the strain was minimized using the Boyd program, which typically converged to a root mean square displacement in bond lengths of less than 0.001 in 12–20 iterations. With very strained molecules such as *o*-di-*tert*-butylbenzene the atom position increments calculated by the Boyd program were too large to allow convergence and had to be reduced by factors of 0.5–0.1. With highly strained molecules where the strain arises mostly from nonbonded interactions the potential surface can have many local minima. The Boyd program may not find the lowest of these except by starting in the vicinity of that minimum. Since there are a large number of conformations available to these molecules, another critical step was to use models to determine the best conformations for the initial geometry estimates. In the results to be reported later, an attempt was made to allow any reasonable geometry a chance to compete for being the lowest energy minimum.

Results and Discussion

The two pairs of isomers **5**, **9** and **10**, **11** were analyzed to see how well strains calculated with the present model agree with experimental values. The values for **5** and **9** are not available from thermochemical measurements but they have been estimated. Many years ago, H. C. Brown introduced the concept of steric homomorphs. By measuring the variations in equilibrium constants of the following reaction the strain in **5** was estimated⁷ to be about 17 kcal/mol and that in **9** to be 4–6 kcal/mol. For **10** and **11**, using the same technique they



estimated a minimum strain of 25 kcal/mol. As shown in Table I the calculated values are 14.2 and 22.6 kcal/mol, respectively. Arnett and co-workers have indirectly measured the difference in strain energy between **10** and **11** and found it to be 22 kcal/mol.¹⁴ Interestingly enough, this value is 3 kcal/mol less than Brown's estimate and the calculated difference between **5** and **9** is also about 3 kcal/mol below his estimate. The generally good agreement between the calculated and observed strain energies lends great confidence to the theoretical model as a predictor of strain energy differences.

Table II. Comparison of Calculated and Observed Structures of Tetra-*tert*-butylbenzene

	Tetra- <i>tert</i> -butylbenzene x-ray	Allinger & Sprague calcd	Present calcd
1–2	1.416 ± 0.005	1.427	1.424
2–3	1.395–1.398 ± 0.005	1.402–1.405	1.408
1–7	1.566–1.568 ± 0.006	1.539–1.566	1.577
7–8	1.49–1.57 ± 0.006	1.546–1.559	1.554–1.561
	Angle, deg		
1–2–3	115.1–115.4	114.8–118.7	117.7
7–1–2	129.9–131.0	126.5–132.8	126.2–126.3
1–7–8	110–116	107.0–124.7	109.0–114.0

As a further test of the model it is interesting to note that Allinger and Sprague have calculated, with their force field, the structure of *o*-di-*tert*-butylbenzene (unfortunately, they do not report strain energies).¹⁵ Also, the x-ray structure of tetra-1,2,4,5-*tert*-butylbenzene has been reported.¹⁶ Table II compares the present results with the previously calculated bond lengths and angles, and with the x-ray results. Although structure alone is not a rigorous test of a force field,¹⁷ it is satisfying that the structure calculated here fits well with both the calculations using a different force field and with the experimental x-ray results.

Before discussing the results on acids **1** and **3** one last point must be made. In strain energy calculations using force fields that include van der Waals interactions between all pairs of atoms, the calculated energies include both (repulsive) strains and a portion of the (attractive) bond energy terms. To remove these latter contributors it is essential not only to calculate differences in "strain energies" of isomers (species with identical *atoms*) but, as discussed by Schleyer,¹⁷ to compare isologous pairs (species with identical *bonds*). Clearly, comparison of the ortho and para di-*tert*-butylbenzenes satisfies these conditions.

The situation is less satisfactory with the lactonization reactions of **1** and **2** and **3** to **4**, since **1** is not isomeric with **2**, nor is **3** with **4**. If the lactones **2** and **4** are replaced by the hydrates **2a** and **4a**, then the desired isomeric relationship is obtained. This is fortunate since these hydrates are undoubtedly the actual high energy intermediates in the lactonization reaction and thus, in fact, lie energetically closer to the transition states than do the product lactones. Using them in the strain calculation should give a better approximation to any steric acceleration present in these reactions. Unfortunately, neither the pair **1** and **2a** nor the pair **3** and **4a** is isologous since in each transformation a C=O π bond is replaced by two C–O σ bonds. The calculated strain in each pair would contain a small residual bond energy contribution. As shown in eq 2, however, the bond energy difference term (BE') is the same for both

$$\begin{aligned}
 (SE_1 + BE_1) - (SE_2 + BE_2) &= \Delta SE_{12} + BE' \\
 (SE_3 + BE_3) - (SE_4 + BE_4) &= \Delta SE_{34} + BE' \\
 \Delta \Delta SE &= \Delta SE_{34} - \Delta SE_{12}
 \end{aligned} \quad (2)$$

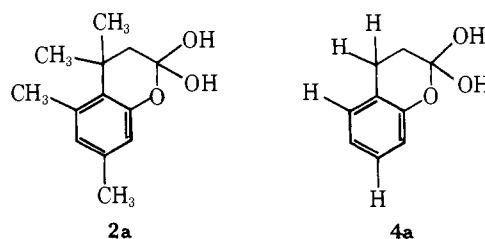
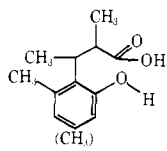
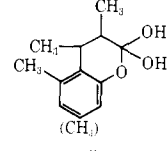
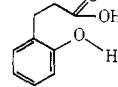
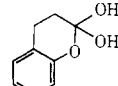






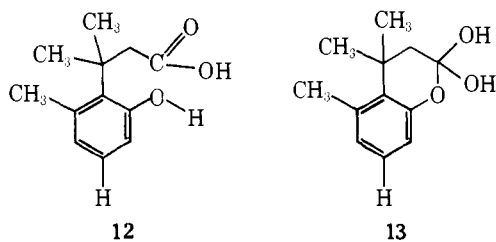
Table III. Calculated Strain Energies (SE)

	Molecules	Strain energy, kcal/mol	Δ SE, kcal/mol
12 (1)		23.86 ^a	-8.45 ^a
13 (2a)		15.41 ^a	
3		6.75	+1.89
4a		8.64	
5		22.09	-14.17
9		7.92	
10		31.73	-21.55
11		10.18	

^a See text for identification of structure.

pairs and therefore cancels when the second difference is taken.

The results of the strain calculations on acids **1** and **3** and the presumed reaction intermediates **2a** and **4a** are given in Table III. Actually the values quoted for **1** and **2a** are values computed for the monodemethylated acid **12** and lactone hydrate **13**. The extra methyl of **1** and **2a** was deleted because of



local restrictions on computer core size; it was felt that such an isolated methyl group would have a trivial effect on the strain and that the estimated strain difference would be indistinguishable from that for **1** and **2a**. The available experimental results of Milstein and Cohen on methyl substitution are fully in accord with this position.

The strain energy differences in Table III correspond to a lactonization rate enhancement of **1** over **3** of 10^7 . This is still only a crude estimate of the expected rate enhancement because the calculated strain is only a potential energy quantity. Real molecules and transition states are governed by free energy changes. It is here that the Boyd approach has an advantage since this program includes the capability of calculating molecular vibration frequencies and hence enthalpic,

Table IV. Calculated Thermodynamic Strain Contributions^a

	12 (1) ^b	13 (2) ^b	3	4a
$H_{298}^{\circ} - H^{\circ}_0$	13.01 ^c	11.09 ^c	9.06 ^c	6.99 ^c
Z.P.E.	161.77	161.20	111.04	111.08
S_{298}°	132.13 ^d	140.27 ^e	100.83 ^e	97.23 ^f
$\Delta H_{298}^{\circ} - \Delta H^{\circ}_0$		-1.92		-2.07
Δ Z.P.E.		-0.57		+0.04
$\Delta H^{\circ}_0 - \Delta$ Z.P.E.		-8.45		+1.89
ΔS_{298}°		+8.14		-3.60
$\Delta\Delta H_{298}^{\circ}$		+10.80		
$\Delta\Delta S_{298}^{\circ}$		-11.74		
$\Delta\Delta G_{298}^{\circ}$		14.25		
k_{1-2a}/k_{3-4}		3×10^{10}		

^a Energy quantities are in kcal/mol; entropies are in entropy units. ^b See text for explanation of structures. ^c Includes classical contributions for very low frequencies. ^d Does not include two low-frequency contributions, see text. ^e Does not include one low-frequency contributions, see text. ^f Includes all low-frequency contributions.

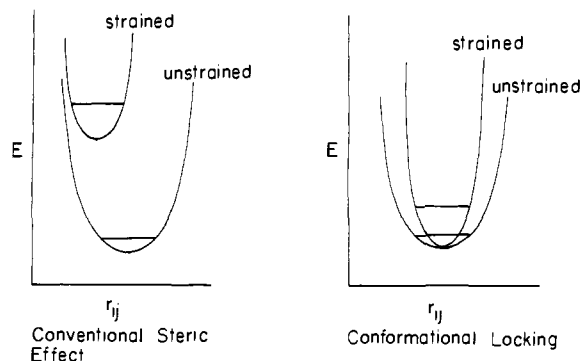


Figure 2. Comparison of conventional steric effect with conformational locking.

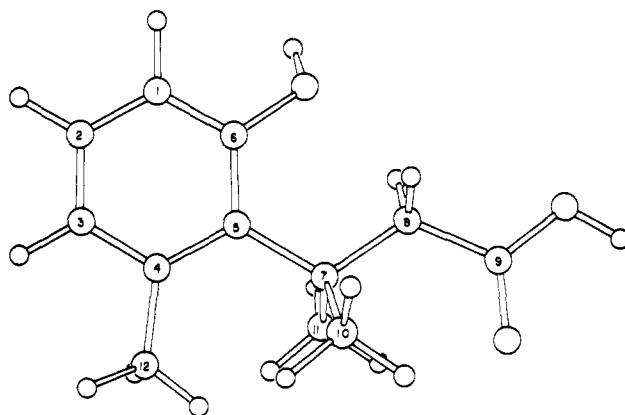


Figure 3. ORTEP/2 drawing of calculated ground-state conformation of acid **12**.

entropic, and zero point energy contributions. The full thermodynamic results are summarized in Table IV.

The last entry of Table IV gives a predicted rate enhancement of 3×10^{10} , which is in striking agreement with the observed value of 8.5×10^{10} . The agreement is, in fact, better than one should expect in light of the approximations made in the model. An inherent problem⁸ is the contribution of low frequency vibrations to the thermodynamic functions, which are particularly unreliable. As noted in the footnotes to Table IV certain of the very low frequency vibrations have been left out of the thermodynamic calculations. Since they enter in a symmetrical fashion the calculated $\Delta\Delta H$ should be reliable. It can be estimated that the proper $\Delta\Delta S$ value is in error by about 1–2 eu. This corresponds to an uncertainty in the rate ratio of a factor of 0.5 to 1.0. In spite of these limitations the

rate ratio comes close enough to the observed value to confidently proceed with the analysis in molecular terms.

The immediate question is how to dissect this rate ratio into the two rate factors having to do with a conventional steric effect and the Cohen proposal of stereopopulation control. The conceptual basis for these two interpretations is illustrated in Figure 2. The most significant difference between them is that for conformational locking the bottom of the potential well is at the same energy for both the strained and unstrained situation. With conventional steric effects a major part of the "strain" arises from an increase in potential energy, i.e., a raising of the bottom of the potential well. For both types of steric effects the narrowing of the potential well is accompanied by an increase in zero point energy, a lowering of the heat capacity contributions, and a lowering of the entropy. Since there is no quantitative relationship between the potential energy increase and the enthalpic and entropic contributions to the conventional steric effect, there is no way to dissect the calculated (or observed) entropy change into the component contributions of the two steric effects. Qualitatively, however, it is apparent that the total free energy steric effect of 14.25 kcal/mol is dominated by the potential energy contribution calculated to be 10.34 kcal/mol. This dominant contribution is unambiguously assignable to a conventional steric interaction and the conclusion is inescapable that it is the dominant source of the rate acceleration. If one arbitrarily *defines* the conformational lock contribution to be the entropic component, then it is responsible for a factor of less than 10^3 in rate acceleration. Either way one concludes that Milstein and Cohen are correct in principle but that they have grossly overestimated the magnitude of the conformational lock on rate enhancement.¹⁸

Finally, it is instructive to examine more closely the sources of strain relief. As with the di-*tert*-butylbenzenes the van der Waals repulsions between the methyl groups are reduced by lengthening and bending the aromatic-alkyl bonds. This energetically expensive path to strain relief is compelled by the repulsions between the phenolic O-H and carboxylic acid side-chain. Closing the lactone ring eliminates this constraint so that the van der Waals repulsions can be reduced by less strenuous angle bends and torsional twists. An additional favorable factor in the lactone is the shortness of the two C-O bonds, which pulls the quaternary carbon and the attached methyl groups back away from the adjacent ortho-methyl group. These changes in underlying geometry are revealed in the ORTEP/2 drawing of **12** and **13**. The position of the C(12) methyl relative to the benzene ring is the same in both molecules. In the lactone the absence of the carboxylic acid group allows the C(10) methyl to pull away from the repelling C(12)

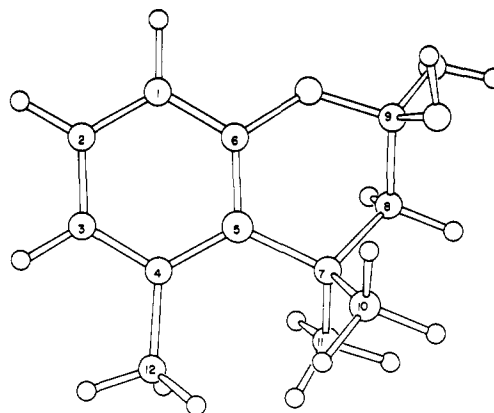


Figure 4. ORTEP/2 drawing of calculated tetrahedral intermediate **13**.

methyl. Also, in the lactone C(8) has moved away from C(10) and C(11). These distortions can be extrapolated to suggest further ways of testing the importance of conformational locking and the balance between it and conventional strain effects.

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