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Molecular mechanics (MM3) study of the lactones of *endo*-bicyclo[2.2.2]oct-5-ene-2-carboxylic acid

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ABSTRACT: *endo*-Bicyclo[2.2.2]oct-5-ene-2-carboxylic acid, in acidic solution, cyclizes to give a mixture of three isomeric lactones. These three isomers have different stabilities and are partly interconvertible, but their simultaneous decomposition makes the experimental study of these equilibria difficult. In the present work, these three lactones were studied using MM3. The relationship between the O—C(O)—C bond angles and the C=O stretching frequencies of these compounds was investigated. Based partly on the thermodynamic data calculated by MM3, the mechanism of the interconversion of the three lactones was proposed. Copyright © 1999 John Wiley & Sons, Ltd.

KEYWORDS: molecular mechanics; MM3; lactonization; *endo*-bicyclo[2.2.2]oct-5-ene-2-carboxylic acid; heat of formation; free energy of formation

INTRODUCTION

Molecular mechanics is an efficient tool for studying and understanding a variety of structural problems in chemistry. The importance of molecular mechanics is enhanced when the experimental study of the problem is either tedious or impossible. One such case is the lactonization of *endo*-bicyclo[2.2.2]oct-5-ene-2-carboxylic acid. Under acidic conditions, this carboxylic acid is converted to a mixture of three isomeric lactones.[1,2] When these lactones rearrange from one to another, the process is accompanied by decomposition.[3,4] Therefore, the experimental study of their interconversion has been difficult. A previous molecular mechanics study reported[5] that calculations carried out using the MM2 molecular mechanics program,[6] which was the precursor of MM3,[7] could not explain either the stabilities or the interconversion process of these lactones. Therefore, we believed that it would be worthwhile to investigate these lactones using MM3. In addition, with the help of MM3, unlike MM2, one can calculate the vibrational spectrum of a molecule. It is well known[8] that in cyclic ketones the C=O stretching frequency is inversely related to the number of atoms in the ring. It would be interesting to examine this relationship in the present lactones. In the present work, the three lactones obtained experimentally from *endo*-bicyclo[2.2.2]oct-5-ene-2-carboxylic acid were studied using MM3. Several additional lactones that are possible isomerization products, but that are not observed experimentally, were also studied.

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RESULTS AND DISCUSSION

The structures of the lactones from *endo*-bicyclo[2.2.2]oct-5-ene-2-carboxylic acid that were reported by Moriarty *et al*,[4] are shown in Scheme 1. The lactones **3, 4** and **5** were studied using MM3 and their C=O stretching frequencies were compared with the experimental values. However, the experimental infrared spectroscopic analysis was carried out in chloroform solvent, whereas MM3 calculates values that correspond to the isolated, gas-phase molecules. It was observed that the C=O stretching frequencies of esters in general (and methyl acetate in particular) are about 32 cm^{-1} higher in the gas phase than the corresponding frequencies in chloroform solution, mainly as a result of hydrogen bonding.[9] Therefore, the experimental frequencies were adjusted for this solvent effect. From Table 1, it is clear that the vibrational frequencies calculated by MM3 are comparable to the adjusted experimental values.

It is well known[8] that for cyclic ketones, as the number of atoms in the ring increases the C=O stretching frequency decreases. The same phenomenon is also observed for lactones and lactams.[10] This observation led to the belief that the C=O stretching frequencies are dependent on, and inversely related to, the number of atoms in the ring. The following explanation was provided for this phenomenon. As the number of atoms in the ring decreases below six, the carbonyl carbon deforms from its ideal sp^2 geometry. Therefore, the p

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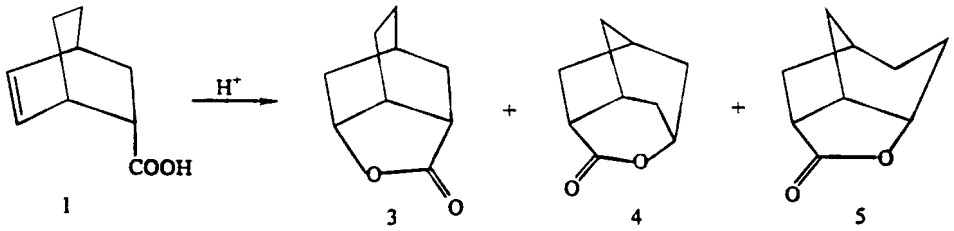


Scheme 1. Lactonization of *endo*-bicyclo[2.2.2]oct-5-ene-2-carboxylic acid to **3, 4** and **5**[4]

Table 1. Relationship between the O—C(O)—C bond angle and C=O stretching frequency of lactones **3, 4** and **5** (all have C_1 symmetry)

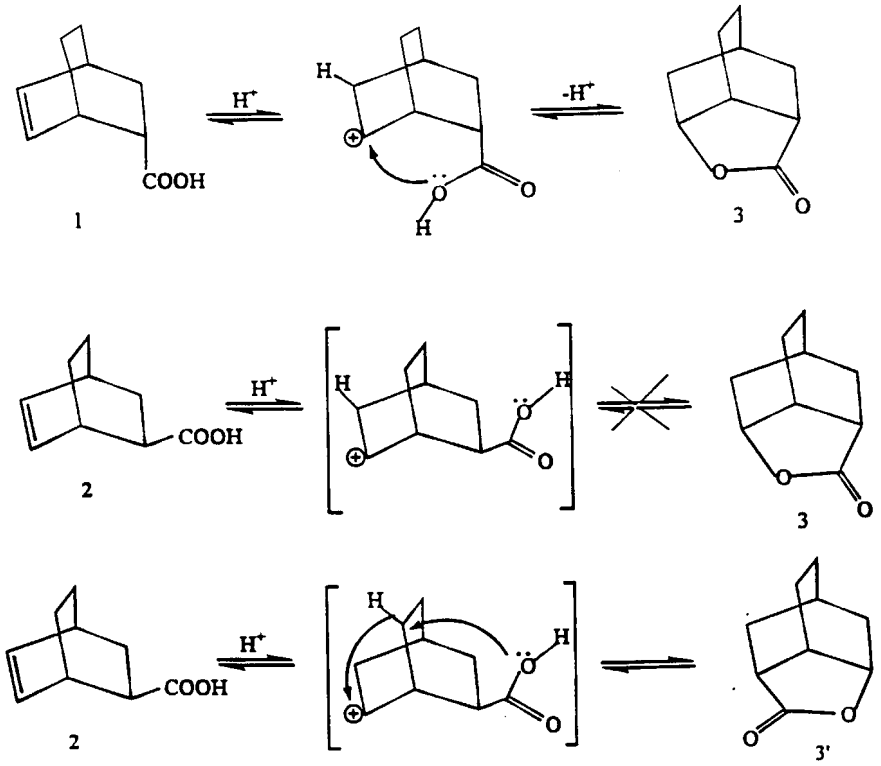
Parameter	3	4	5
O—C(O)—C bond angle (°)	108.66	114.39	110.33
C=O stretching frequency (cm^{-1}):			
Exptl[4] ($CHCl_3$ solution)	1760	1730	1755
Exptl (corrected to gas phase)	1792	1762	1787
MM3	1786	1766	1783

character in the two C—C bonds increases and the *s* character in C=O bond must therefore increase. The increased *s* character leads to a stronger C=O bond, resulting in a higher C=O stretching frequency.[8] However, the study of more complicated ketones revealed that it is not the number of atoms in the ring that dictates the C=O stretching frequency but the angle made by the carbonyl carbon with its neighboring atoms in the ring.[11] Even though the increase in the *s* character of the C=O bond may contribute to the increase in C=O stretching frequency, it is only a minor contribution.[12] The actual phenomenon is more physical than chemical. The C=O stretching and O–C and C–C stretchings act analogously to the pendulums connected to a common point. Each influences the vibrations of the other, and depending on the O—C(O)—C angle, the vibrations couple with one another to varying degrees. As the C—C(O)—C angle becomes smaller and the O—C and C—C bonds become more colinear with the C=O, and there is an increased coupling of C=O stretching with the other stretchings. When such a coupling increases, the higher frequency is expected to increase and the lower frequency to decrease. As a result, the C=O stretching frequency, which is higher than the C–O C–C stretching frequencies, increases.[11,12] In the case of the lactones under study, the O—C(O)—C angle has a strong influence on the C=O stretching frequency. From Table 1, it can be seen that the values for the O—C(O)—C angles in the lactones increases in the order $\mathbf{3} < \mathbf{5} < \mathbf{4}$, and the values for the C=O stretching frequencies decrease correspondingly, $\mathbf{3} > \mathbf{5} > \mathbf{4}$. The smaller the O—C(O)—C angle, the greater is the O—C and C—C bond coupling with the C=O bond, and hence the higher the C=O stretching frequency.

The experimental study of the acid-catalyzed cyclization of *endo*-bicyclo[2.2.2]oct-5-ene-2-carboxylic acid over a wide range of acid concentrations revealed that the reaction yielded three lactones (**3, 4** and **5**) in varying amounts, and no other identifiable products were detected. Lactone **3** was found to be the kinetic product initially produced, its concentration decreasing as the acidity of the reaction mixture was increased.[5] In the acidic medium, lactone **3** partially rearranged to lactone **4.** Lactone **5** was found to be the minor product and was readily interconvertible with lactone **4** in acidic medium.[4] However, all these reactions were accompanied by a simultaneous decomposition of the lactones, so the kinetic studies of these interconversions were tedious and the results only qualitative.

In order to carry out MM3 studies on these lactones, the following strategy was adopted. First, it was reported by Moriarty *et al.*[4] that the *exo*- and *endo*-bicyclo[2.2.2]oct-5-ene-2-carboxylic acids do not interconvert via a keto–enol tautomerism under the experimental conditions, and that both the *endo*- and *exo*-acids give lactone **3.** From Scheme 2, the formation of lactone **3** from acid **1** is evident. However, once the possibility of the interconversion of acids has been excluded, acid **2** would not give lactone **3**, as the position of the carboxyl group makes such a reaction sterically impossible. We believe that the carbocation formed undergoes rearrangement as shown in Scheme 2 to yield lactone **3′,** which is in fact the enantiomer of lactone **3**. The structure identification techniques reported by Moriarty *et al.*[4] did not include the measurement of optical rotation. None of the techniques that they reported could distinguish between the two enantiomers.

We considered the rearrangement of lactone **3** to lactones **4** and **5** using a physical model, but the process involved considerable twisting of the bonds which we believe to be improbable. However, if we start from lactone **3,** the formation of **4′** and **5′,** the mirror images of lactones **4** and **5,** appeared to be straightforward, as shown in Scheme 3. The mechanism involves hydride and C—C bond shifts. Similarly, lactone **3′** could be rearranged to lactones **4** and **5.** Once again, the identification techniques reported by Moriarty *et al.*

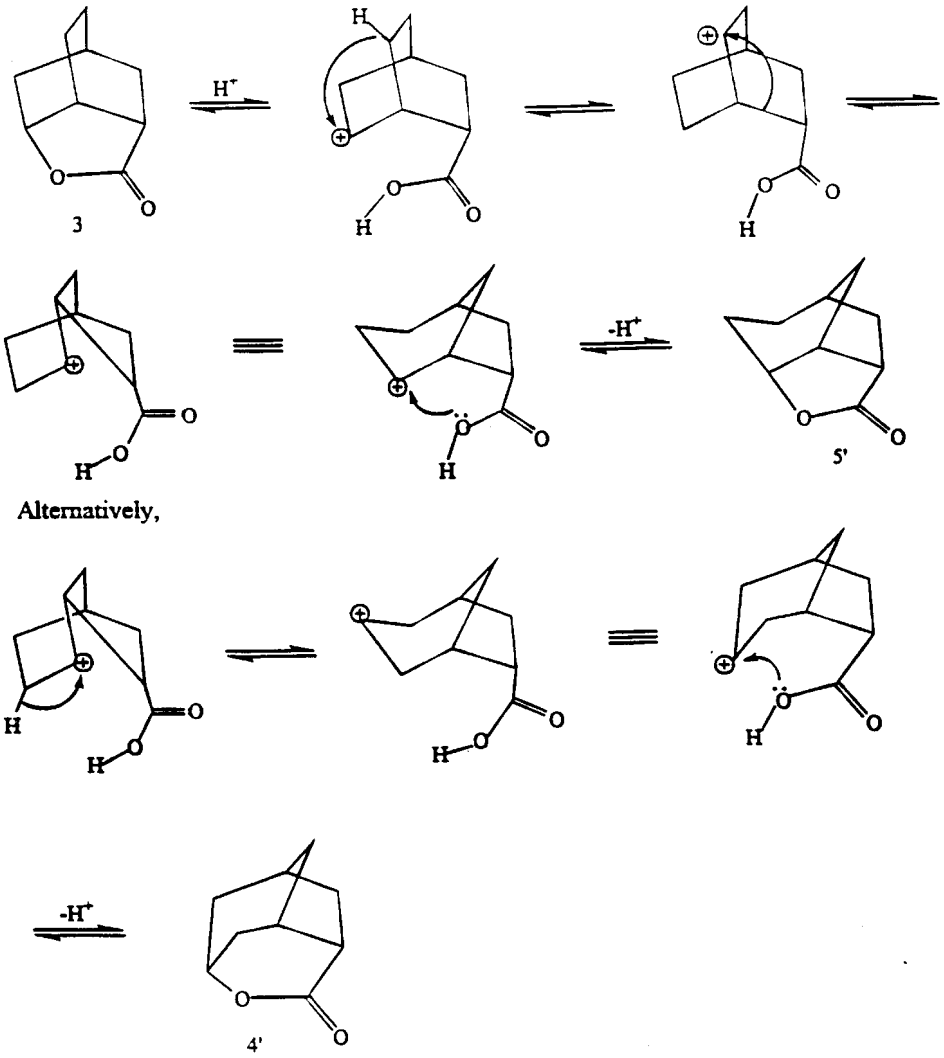


Scheme 2. Mechanism of formation of lactones **3** and **3′**

could not distinguish between lactones **4** and **4′** or between lactones **5** and **5′**. We suggest that, in the future, the experimental study of the interconversion of these lactones should consider the fact that all of these lactones are chiral and can exist as enantiomers. The *endo*- and *exo*-acids can be synthesized[1,4] and, if these acids are not spontaneously interconvertible, then the enantiomers should be separable.

Brecknell *et al.*[5] reported a study of these lactones using the MM2 force field. They compared the final steric energies of the lactones and concluded that these values did not reflect the relative stabilities of the lactones. We repeated the MM2 calculations of the steric energies of these compounds but could not reproduce the relative final steric energies reported by them.[5] Our MM2 program calculated the final steric energies of the lactones **3, 4** and **5** as 25.27, 27.89 and 24.56 kcal mol^{-1} and the heats of formation as -100.0, -97.4 and -100.7 kcal mol^{-1} (1 kcal = 4.184 kj) respectively, indicating a stability order of $5 \geq 3 > 4$. As MM3 is a better force field than MM2, in the present work similar calculations were carried out using MM3. With MM3, in addition to the final steric energy and the heat of formation, one can calculate other thermodynamic quantities such as enthalpy, entropy and free energy. MM3 analysis of the three lactone structures revealed that **3, 4** and **5** have final steric energies 38.26, 37.22 and 43.11 kcal $mol,^{-1}$ respectively, and these convert to heats of formation of -89.76, -90.79 and -90.42 kcal $mol,^{-1}$ respectively, as shown in Table 2. The final steric energy values in any molecular mechanics calculations are relative to a somewhat arbitrary zero point. For these lactones, the zero point of reference is different for lactone **5** than for lactones **3** and **4**. The connectivity of the atoms in lactone **3, 4** and **5** is different, which makes them constitutional isomers. Lactone **5** contains one more five-membered ring than do **3** and **4**. Therefore, their final steric energies cannot be directly compared to determine the relative stabilities of these compounds. The correct way to compare their stabilities would be by calculating and comparing their heats of formation.

A more exact analysis of the thermodynamics of this system can be performed as follows. First, the MM3 calculations are for an isolated (gas-phase) molecule, whereas the experiments were conducted in strongly acidic solutions. Under these conditions, the molecules are largely protonated; however, since lactones **3, 4** and **5** are all unhindered bicyclic lactones, we might hope that protonation and solvation problems will largely cancel out, and the relative calculated energies should be close to the experimental values, if the experiment could be conducted without causing the product decomposition. In order to determine whether the reaction is favorable to the formation of lactones, MM3 calculations were also carried out on acid **1**. Lactones **3, 4** and **5** are compact structures lacking rotatable bonds, so each has only one



Scheme 3. Rearrangement of lactone **3** to lactones **4**′ and **5**′

conformation. However, various conformations of acid 1 are possible, owing to the rotation of the carboxyl group. There are two rotatable bonds, namely, the C—C(O) bond and the C(O)—OH bond. MM3 calculations (using the double angle driver) revealed that in the case of the latter, the hydrogen atom preferred to be eclipsed by the carbonyl oxygen by more than 5.0 kcal mol^{-1}. Hence there is only one conformation about the C(O)—OH bond with a significant equilibrium concentration, which is the *trans* conformation. On the other hand, the C—C(O) bond can assume various conformations. A plot of the final steric energy versus $C_{bridgehead}$—C—C(O)—O torsional angle is shown in Fig. 1. This graph revealed two conformations, one with a $C_{bridgehead}$—C—C(O)—O torsional angle of about 180°, which is the global minimum, and the other of about 310°. The graph also showed a very small dip at about 70°. However, we believe that the well depth here is too small for the well to contain a vibrational level, thus excluding the possibility of a stable conformation with this geometry. Our study of the saddle points of this particular minimum revealed that for the conformation with the $C_{bridgehead}$—C—C(O)—O torsional angle of 50°, the distance between C(2) and O(11) was 2.844 Å, indicating a significant repulsion between these two atoms. This saddle point showed a higher van der Waals energy by about 0.42 kcal mol^{-1} for this specific interaction. In an effort to minimize this

Table 2. Comparison of MM3 energies (kcal mol^{-1}) of lactones **3, 4** and **5** at 298.16 K

Parameter	3	4	5
Final steric energy	38.26	37.22	43.11
Total enthalpy	165.97	165.21	170.59
Total entropy (eu)	89.13	87.55	89.33
Relative entropy (eu)	1.58	0.0	1.78
Heat of formation	−89.76	−90.79	−90.42
Relative heat of formation	1.03	0.0	0.37
Free energy of formation	−116.33	−116.89	−117.05
Relative free energy of formation	0.72	0.16	0.0

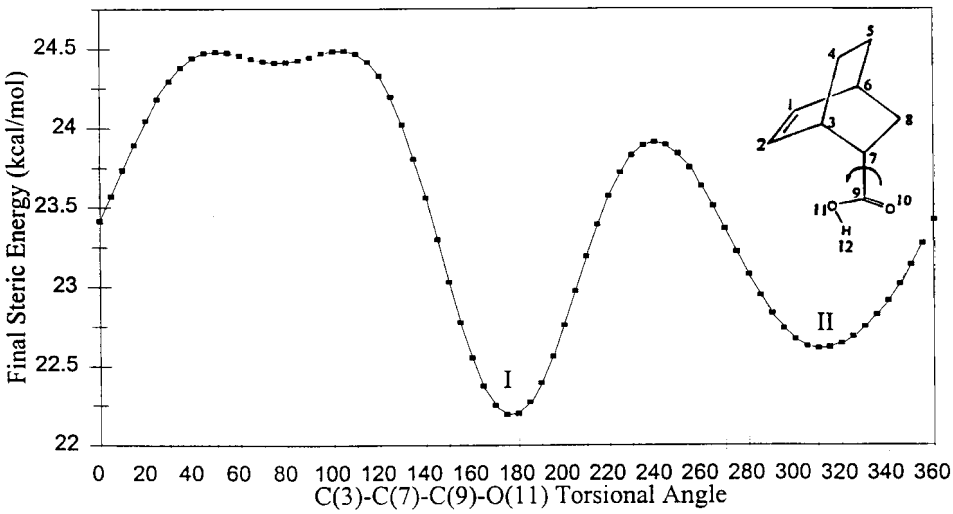


Figure 1. Torsional energy porfile of acid 1

strain, the C(3)—C(7)—C(9) bond angle widened by about 2.5°. Similarly, for the conformation with $C_{bridgehead}$—C—C(O)—O torsional angle of 105° (the other saddle point), the distance between O(11) and H(22) was 2.270 Å, indicating a repulsion between these two atoms. Here the van der Waals repulsion energy corresponding to the O(11)—H(22) interaction was about 0.37 kcal mol^{-1} for the saddle point. In this case, the C(7)—C(9)—O(11) bond angle widened slightly (by about 0.4°). We believe that the interactions of O(11) with C(2) and H(22) are the major contributors to the high energy of this minimum.

Each of the lactones and each conformer of acid 1 has a symmetry number of 1 and exists as a pair of enantiomers. When the entropy values are mentioned in tables or otherwise, they are the total entropy values for the enantiomeric mixtures. We carried out MM3 calculations on the two real conformers of acid 1, and the results are shown in Table 3. The free energy values were used to calculate the Boltzmann populations of the respective conformers. The heat of formation for acid 1 was calculated to be −81.37 kcal mol.$^{-1}$ The entropy of acid 1 was calculated using the equation

$$S = \sum N_i S_i - R \sum N_i \ln N_i$$

where N_i is the Boltzmann population and S_i is the entropy of conformer *i*. The last term is the entropy of mixing and R is the universal gas constant. Using the above equation, the entropy of acid 1 was calculated as 98.09 eu. Using the entropy and heat of formation values, the free energy of formation was calculated from the equation

$$\Delta G_f^\circ = \Delta H_f^\circ - T\Delta S^\circ$$

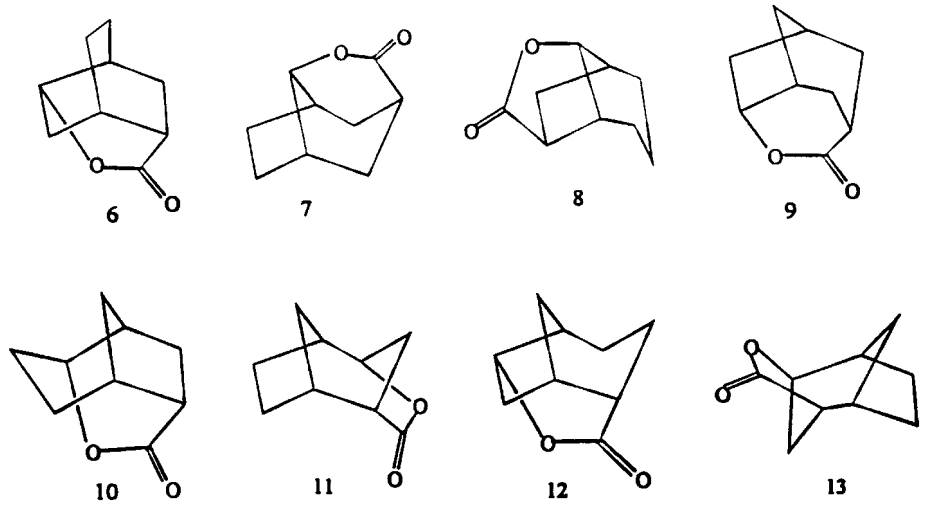
and had the value −110.62 kcal mol^{-1} at 298.16 K. This value is 6–7 kcal mol^{-1} more positive than the free energies of formation of the lactones **3, 4** and **5,** so the lactonization of acid 1 is thermodynamically favored.

Next, we tried to understand the relative stabilities of the lactones **3, 4** and **5**. From Table 2, it can be seen that with respect to the heats of formation, lactone **4** has the lowest value and lactone **5** is 0.37 kcal mol^{-1} higher. Lactone **3** is still higher, 1.03 kcal mol^{-1} above lactone 4. The numbers and kinds of bonds in these isomers are similar, and each has C_1 symmetry, so we expected that, at a given temperature, they would have similar entropies, which was found to be the case. The calculated values for the total entropies for the lactones **3, 4** and **5** were 89.13, 87.55 and 89.33 eu, respectively. If we wish to compare the equilibrium data, only the relative entropies of the compounds need to be considered, and these are 1.58, 0.00 and 1.78 eu, respectively, at 298.16 K. The relative free energies of formation calculated by MM3 are thus 0.72, 0.16 and 0.0 kcal mol^{-1} for lactones **3, 4** and **5,** respectively. Even though these values indicate that lactone **5** is more stable than lactone 4, they are actually indistinguishable within the computational limits of MM3. These calculations are

Table 3. MM3 energies (kcal mol^{-1}) of acid 1 at 298.16 K

	Conformer[a]	
Parameter	I	II
$C_{bridgehead}$—C—C(O)—O angle	175.70	313.60
Final steric energy	22.19	22.61
Enthalpy	148.80	148.95
Free energy	120.14	119.96
Boltzmann population	0.423	0.577
Entropy (eu)	96.10	97.23
For the equilibrium mixture:		
Molar entropy (eu)	98.09	
Heat of formation	−81.37	
Free energy of formation	−110.62	

[a] See Fig. 1.



Scheme 4. Structures of some of the possible lactones

consistent with the experimental observation that lactones **4** and **5** are readily interconvertible. Lactone **3** is higher in free energy but by less than 1 kcal mol^{-1}. In addition, when we compare the free energy of formation of acid 1 with those of the lactones **3, 4** and **5,** it is evident that all of the lactones have more negative ΔG_f values than acid 1 (by 6–7 kcal mol^{-1}; actually this amount may be reduced by solvation). Hence the reaction certainly is in favor of the formation of the lactones from the acid.

The thermodynamic stabilities of **3, 4** and **5** parallel their heats of formation. Furthermore, the isomers **3, 4** and **5** all have the same number and kinds of substitutions (primary, secondary, etc.), so that the differences in their heats of formation should give approximate estimations of their stabilities. Moriarty *et al.*[4] concluded that lactone **4** was the most stable, and that lactone **3** is a kinetic product which rearranged to lactone **4**. The free energies of formation of these lactones calculated by MM3 support those conclusions. Lactone **3** has a higher free energy of formation than lactone **4**, which is why lactone **3** is rearranged to lactone **4** in acidic medium. Lactone **5** has a similar free energy of formation to lactone **4,** which is the reason for their interconvertibility under acidic conditions. Based on their free energies of formation, we calculated the equilibrium concentrations of **3, 4** and **5** to be 14, 37 and 49%, respectively, at 298 K.

Lactonization of *endo*-bicyclo[2.2.2]oct-5-ene-2-carboxylic acid can proceed by multiple pathways. If the reaction were to follow all of these pathways, it might be expected that several cyclized lactones could be formed,

Table 4. Comparison of MM3 energies (kcal mol^{-1}) of lactone structures 3–13 at 298.16 K

Parameter	**3**	**4**	**5**	**6**	**7**	**8**
Final steric energy	38.26	37.22	43.11	40.18	38.62	51.19
Total enthalpy	165.97	165.21	170.59	167.76	166.08	178.75
Total entropy (eu)	89.13	87.55	89.33	86.98	88.36	88.92
Relative entropy (eu)	1.58	0.00	1.78	−5.70	0.81	1.37
Heat of formation	−89.76	−90.79	−90.42	−82.32	−88.62	−82.34
Relative heat of formation	1.03	0.0	0.37	8.47	2.17	8.45
Free energy of formation	−116.33	−116.89	−117.05	−108.25	−114.96	−108.85
Relative free energy of formation	0.72	0.16	0.0	8.64	1.93	8.04
	9	**10**	**11**	**12**	**13**	
Final steric energy	38.52	49.72	61.40	49.44	55.69	
Total enthalpy	166.44	177.14	188.27	176.83	182.73	
Total entropy (eu)	87.59	87.26	87.48	87.21	87.05	
Relative entropy (eu)	0.04	−0.29	−0.07	−0.34	−0.50	
Heat of formation	−88.72	−78.30	−72.12	−78.58	−77.83	
Relative heat of formation	2.07	12.49	18.67	12.21	12.96	
Free energy of formation	−114.87	−104.31	−98.20	−104.58	−103.78	
Relative free energy of formation	2.02	12.58	18.69	12.31	13.11	

in addition to those discussed above. Some of these lactone structures are shown in Scheme 4. While designing these hypothetical structures, we followed only the simplest mechanisms and also avoided any structures with extreme steric strain, such as those containing four-membered rings, or those whose formation involved an exocyclic carbocation. It should be noted that this list is not exhaustive and, theoretically, many more different structures are possible. However, experimentally only lactones **3, 4** and **5** have been found. In order to understand why these lactones are preferred over the rest, we carried out MM3 calculations on structures **6–13**. The various thermodynamic quantities for these compounds are shown in Table 4. It can be seen that all of these lactones (**6–13**) have much more positive free energies of formation than lactones **3–5.** In other words, lactones **3–5** are more stable than any of the lactones **6–13**. Only lactones **7** and **9** have energies that are anywhere near those of **3–5**, being about 2 kcal mol^{-1} higher (the others are 8–18 kcal mol^{-1} higher). These two should be formed in small amounts, *ca* 2%, and might be found if kinetically stable, and if searched for). However, the previous failure to find **6–13** appears to have been essentially a thermodynamic, not a kinetic, matter.

Lactonization of *endo*-bicyclo[2.2.2]oct-5-ene-2-carboxylic acid can lead directly to either lactone **3** or lactone **6** depending on to which carbon atom the initial proton is added. Lactone **3** is a γ-lactone and lactone **6** is a δ-lactone. Traditionally, γ-lactones are observed to be more stable than δ-lactones,[5] so this case is unexceptional. The heats of formation from MM3 indicate that lactone **3** is more stable than lactone **6** by 7.44 kcal mol^{-1}. This led us to conclude that between the two expected kinetic products, lactone **3** is greatly favored over lactone **6**. Lactone **3** then further rearranges to lactone **4′,** which is the thermodynamic product. As shown in Scheme 3, the formation of **4′** and **5′** from lactone **3** involved a common intermediate, which supports the ready interconversion of **4′** and **5′.** Similarly, *exo*-bicyclo[2.2.2]oct-5-ene-2-carboxylic acid cyclizes to lactone **3′**, which undergoes further rearrangement to more stable lactone **4**. Since the experiment started with **3**, and **4′** is the most stable structure which is readily convertible to **5**, the mechanism for interconversion must be **3**→**4′** ⇌ **5′**, which is in accord with the mechanism suggested by Moriarty *et al.*[4]

CONCLUSIONS

MM3 is a very helpful tool for the study of problems in structural chemistry, especially those which are challenging to study experimentally. The lactonization of *endo*-bicyclo[2.2.2]oct-5-ene-2-carboxylic acid is one such problem. In this work, with the help of the calculations carried out using MM3, we could study the relationship between C=O stretching frequencies and the O—C(O)—C bond angles. In addition, the energies calculated by MM3 were used to explain the mechanism for interconversion of these lactones.

Acknowledgements

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