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An Experimental and Theoretical Study of a Bicyclic Acetal Equilibrium

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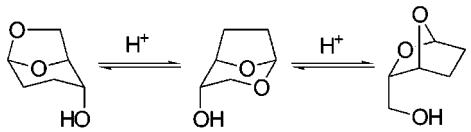
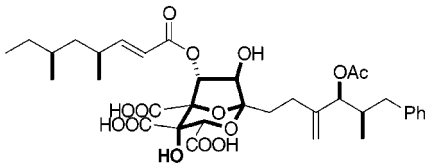
ABSTRACT



The position of equilibrium for competitive acetal formation can be hard to predict. This example, the core of zaragozic acid, is finely balanced, but an experimental investigation has proved that the left-hand isomer is preferred. Molecular mechanics force fields are unable to cope with such systems, because there is competition between five- and six-membered rings. Results from these calculations should not be used to estimate the position of equilibrium in such cases.

The zaragozic acids[1] (squalestatins[2]) are a series of natural products containing a densely functionalized 4-hydroxy-2,8-dioxabicyclo[3.2.1]octane core, **2**, which can, in principle, isomerize to give two other bicyclic structures (Figure 1).



Zaragozic Acid A (Squalestatin S1)

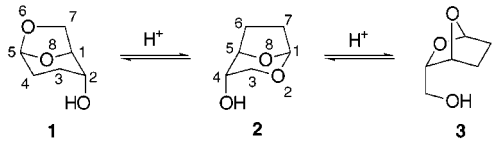


Figure 1. Zaragozic acid and the isomers of its core.

Synthetic studies toward the zaragozic acids[3,4] have been reported, and in a few cases,[4e,5] structures isomeric to the desired 2,8-dioxabicyclo[3.2.1]octane **2** are observed, such as **1** and **3**. This rearrangement is unpredictable. If this isomerization could be modeled reliably by using computational methods, then a synthetic strategy toward analogues can be planned confidently to result in the desired core.

We have performed conformation searches on a large number of reported analogues, using MacroModel and the MM2* force field,[6] and found that, in every case, the 6,8-dioxabicyclo[3.2.1]octane **1** is calculated as the preferred

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(2) Dawson, M. J.; Farthing, J. E.; Marshall, P. S.; Middleton, R. F.; O'Neill, M. J.; Shuttleworth, A.; Stylli, C.; Tait, R. M.; Taylor, P. M.; Wildman, H. G.; Buss, A. D.; Langley, D.; Hayes, M. V. *J. Antibiot.* **1992**, *45*, 639.

(3) For a review, see: Nadin, A.; Nicolaou, K. C. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1622.

(4) Total syntheses: (a) Evans, D. A.; Barrow, J. C.; Leighton, J. L.; Robichaud, A. J.; Sefkow, M. *J. Am. Chem. Soc.* **1994**, *116*, 12111. (b) Carreira, E. M.; Du Bois, J. *J. Am. Chem. Soc.* **1995**, *117*, 8106. (c) Nicolaou, K. C.; Yue, E. W.; La Greca, S.; Nadin, A.; Yang, Z.; Leresche, J. E.; Tsuri, T.; Naniwa, Y.; De Riccardis, F. *Chem. Eur. J.* **1995**, *1*, 467. (d) Caron, S.; Stoermer, D.; Mapp, A. K.; Heathcock, C. H. *J. Org. Chem.* **1996**, *61*, 9126. (e) Sato, H.; Nakamura, S.; Watanabe, N.; Hashimoto, S. *Synlett* **1997**, 451. (f) Armstrong, A.; Jones, L. H.; Barsanti, P. A. *Tetrahedron Lett.* **1998**, *39*, 3337.

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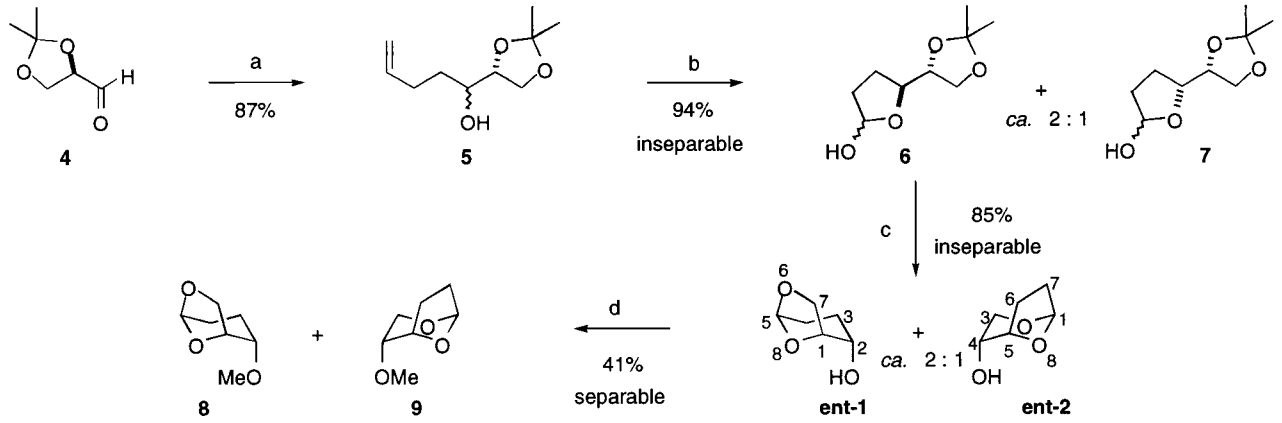
Scheme 1[a]



[a] Reagents and conditions: (a) $CH_2{=}CHCH_2CH_2MgBr$, THF, −10 °C to rt, 3.5 h; (b) (i) O_3, CH_2Cl_2, −78 °C, 0.25 h; (ii) PPh_3, CH_2Cl_2, 3.75 h; (c) 2% concentrated HCl, THF, 20.5 h; (d) KH, MeI, THF, 0 °C to rt, 23 h.

product under thermodynamic control. This contradicts the experimental results, in most cases. Our findings are supported by Evans,[4a] who comments that molecular modeling predicted the undesired isomer to form, while recently Myles has made a more detailed computational study[7] and invoked both thermodynamic and kinetic arguments to explain the calculations. In this Letter we report the synthesis of simpler bicyclic core structures and demonstrate how great care must be exercised in analyzing calculations on such systems.

The equilibration of **ent-1** and **ent-2** was chosen for study because these molecules are sufficiently small that exhaustive conformation searches and ab initio calculations may be performed, together with detailed analysis of the output data. They were synthesized from 2,3-*O*-isopropylideneglyceraldehyde[8] **4** as shown in Scheme 1. Their equilibration was monitored by NMR with 0.1% triflic acid in a range of solvents. Computational modeling of these molecules is easiest to carry out as if the equilibrium occurs in a vacuum, and this approximation may be valid if the equilibrium is not significantly solvent dependent. The equilibrium ratios are presented in Table 1. In every case equilibrium was reached within an hour, and it was demonstrated that equilibrium had been reached by taking the ca. 2:1 ratios obtained in the higher relative permittivity solvents and observing a rapid change to the 52:48 ratio in chloroform, which remained constant over several weeks. Similarly, the ca. 1:1 ratios obtained in the lower permittivity solvents could be equilibrated back to 70:30 in DMSO.

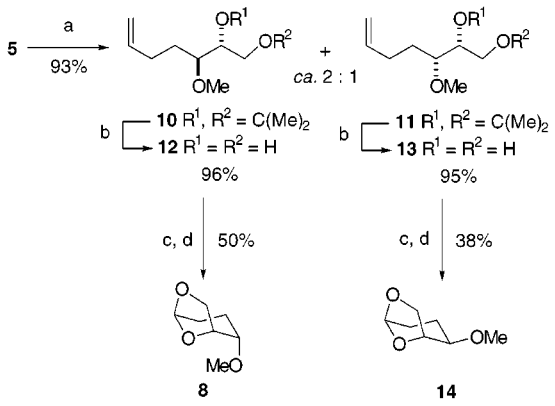
Only these two structures were ever observed during equilibrium studies. Structure **ent-3** was never observed. The structure of **ent-1** was proved by methylation to give **8**, which was correlated by a synthesis using an independent route (Scheme 2). Identification of axially substituted **8** and equatorially substituted **14** also allowed *anti* **6** and *syn* **7** to be distinguished. Structure **ent-2** was distinguished from **ent-3** by NOE studies. Irradiation of the methine proton attached to carbon 5 (**ent-2** numbering) caused no enhancement of the methylene protons on carbon 3.

Table 1. Solvent Dependency of the Equilibrium

solvent	ratio **ent-1**:**ent-2**[a]	solvent	ratio **ent-1**:**ent-2**[a]
C_6D_6	53:47	DMF-d_7	69:31
$CDCl_3$	52:48	DMSO-d_6	70:30
THF-d_8	58:42		

[a] Ratios determined by analysis of the ^{1}H NMR spectrum and are judged accurate to ±3%.

Scheme 2[a]



[a] Reagents and conditions: (a) KH, MeI, THF, 0 °C to rt, 22.5 h; (b) 1.0 M HCl in Et_2O, MeOH; (c) (i) O_3, CH_2Cl_2, −78 °C ; (ii) PPh_3, CH_2Cl_2; (d) 1.0 M HCl in Et_2O, THF, 4 Å sieves.

(6) MM2: Allinger, N. L. *J. Am. Chem. Soc.* **1977**, *99*, 8127. Implemented in MacroModel 5.5: Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440.

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(8) Schmid, C. R.; Bryant, J. D. *Org. Synth.* **1993**, *72*, 6.

As expected, these experimental results could not be reproduced by MM2*, which predicts isomer **ent-1** to lie ca. 25 kJ mol^{-1} lower in energy than **ent-2**; hence **ent-2** would not be observed. MM2* even predicts structure **ent-3** to be lower in energy than **ent-2**. We have found no other force field that gives more reliable results. The equilibrium was modeled rather well using ab initio methods, however (Table 2).[9] They confirm that structure **ent-3** should not be observed, and they correctly predict that **ent-1** will be preferred at equilibrium. These calculations do not allow for solvent effects, and so the calculated ratios should be closest to the experimental results in nonpolar solvents.

Table 2. Calculated Equilibrium Ratios **ent-1**:**ent-2**

calculation	ratio **ent-1**:**ent-2**[a]	calculation	ratio **ent-1**:**ent-2**[a]
MM2*	100:0	RHF/6-31G*	86:14
RHF/3-21G	71:29	MP2/6-31G*	63:37

[a] Ratios are calculated from the sum of the Boltzmann factors of each conformation at 300 K.

It was clear, therefore, from calculations on these and on other published systems, that the MM2* force field has a bias favoring acetals in five-membered rings. This bias renders comparisons between five- and six-membered ring acetals meaningless using MM2*.

Examination of the energy breakdown for the global minimum structures of **ent-1** and **ent-2** reveals the largest discrepancy to be in the electrostatic contribution. The global minimum energy difference is 25 kJ mol^{-1}, and the difference between the electrostatic contributions for the two isomers is 8 kJ mol^{-1}. We chose to focus on this contribution, because electrostatic interactions are only considered by the force field if atoms are in a 1,4 or more distant relationship. Atoms 1,2 or 1,3 apart are considered to have more important stretch, bend, and torsion terms. This appears to be a rather bad approximation for the system under study. Furthermore, partial positive charge is only allocated to the oxygen and adjacent atoms (negative partial charge is found in the lone pairs); hence large, repulsive transannular interactions are present between atoms 2 and 5 and 3 and 8 in **2**. These interactions account for 33 kJ mol^{-1}, while the analogous interactions in **1** (1 and 6, 7 and 8) are in a 1,3 relationship. Coulomb's law can be used to calculate that these interactions would contribute 40 kJ mol^{-1} to the total energy if they were included.

It is very striking that this electrostatic energy discrepancy is close to the total energy difference between the two isomers and that this large error prevents the simple calculation of the position of equilibrium for these systems. We are currently developing a method to modify the electrostatic contribution to the MM2* force field so that it may become predictive for these and related bicyclic acetals.

In conclusion, our synthesis of **ent-1** and **ent-2** and the study of the equilibrium between them shows that the preference of zaragozic acid itself is not maintained in this less-substituted system. We can find no simple qualitative explanation for this. Our evidence strongly indicates that force field calculations tend to give misleading results when comparing five- and six-membered rings with transannular electrostatic effects, and so they should only be used to predict the behavior of systems of this sort with great caution.

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Supporting Information Available: Full experimental details and characterization data for compounds **5**−**14**. This material is available free of charge via the Internet at http://pubs.acs.org.

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