# THEORETICAL STUDIES OF THE CONFORMATIONAL CONTROL
OF ADDITIONS TO BICYCLO[m.1.0]ALKAN-2-ONES.
APPLICATION AND VALIDATION OF THE WIZARD TECHNIQUE

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Abstract The conformational spaces of some bicyclo[m.1.0]alkanes were examined utilizing WIZARD. These results were validated by Monte' Carlo techniques, MM2, and AMPAC. The results were used to explain experimentally observed diastereoselectivity of nucleophilic addition to the carbonyl. In medium and large ring systems ($m \geq 6$) the acyl-cyclopropyl subunit adopts a conformation which causes the protons on the γ and δ carbons (not the cyclopropyl) to shield the carbonyl from nucleophilic attack. In smaller systems ($m < 6$) the rings are flattened, and selectivity is lost.

Mash *et al*, have demonstrated that nucleophilic additions to bicyclo[m.1.0]alkan-2-ones were highly diastereoselective[1] (ratio $\geq$ 20:1) when $m \geq 6$, but less selective when $m \leq 5$ (ratio $\leq$ 5:2). In this paper we present preliminary theoretical studies which provide a possible explanation for this observation.
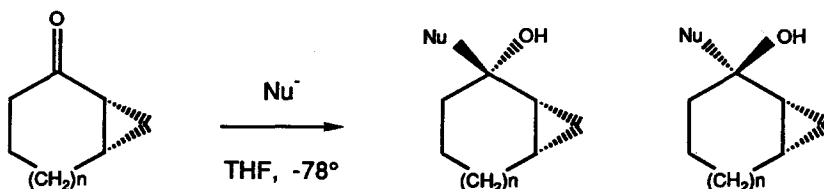
By examining entries 1 - 8 in Table 1 of the previous paper[1], it can be seen that the diastereoselectivity of the reaction is essentially independent of the nucleophile utilized. This and other considerations[2] have led us to tentatively assume that this reaction exhibits a "starting material like" transition state, and that the stereochemical outcome of the reaction is controlled by the conformations of the starting material. Thus, we wished to consider *all* conformations of 1 - 3. To do this, we utilized our logic based conformational search program called WIZARD[3] to provide initial geometries, which were then refined by MM2. These results were checked by using Monté Carlo search techniques, MM2's "Dihedral Driver" option, and AMPAC[4]. No new conformations were found by any other technique, indicating that WIZARD had exhausted the conformational population. A RMS comparison of the structures generated by WIZARD with those refined by MM2 and AMPAC showed essential agreement ($\leq$0.2 Å RMS difference). The results are summarized in Table 1 for those conformations which will constitute >99.9% of the starting material population[5].

Table 1. Lowest Energy Conformations of bicyclo[m.1.0]alkan-2-ones

	(Strain Energy in Kcal/mol).					Torsion Angle (C_3 C_2 C_1 C_{m+2})	
	1 (m=4)	2 (m=5)	3(m=6)	1 (m=4)	2 (m=5)	3(m=6)	
a	121.129	123.053	125.352	19	68	89	
b	121.558	123.556	125.417	-8	66	87	
c	---		126.278	127.409	---	48	78
d	---		126.956	128.265	---	61	-86
e	---		127.053	128.267	---	-59	85
Total Generated	2	7	21				
Maximum Strain	121.558	129.411	137.400				

The structures of the lowest energy conformations are shown in Figure 1. The hindrance to approach to both faces of the carbonyl of each conformation was examined utilizing a number of techniques: visual examination of CPK like graphic representations; calculations of distances and angles; insertion of a "dummy nucleophile" at a given distance from the carbonyl carbon and calculation of the van der Waals strain[6]. These studies led to the following observations about the accessibility of the carbonyl to nucleophilic attack in the preferred conformations. Reasons for these preferences are proposed afterwards.
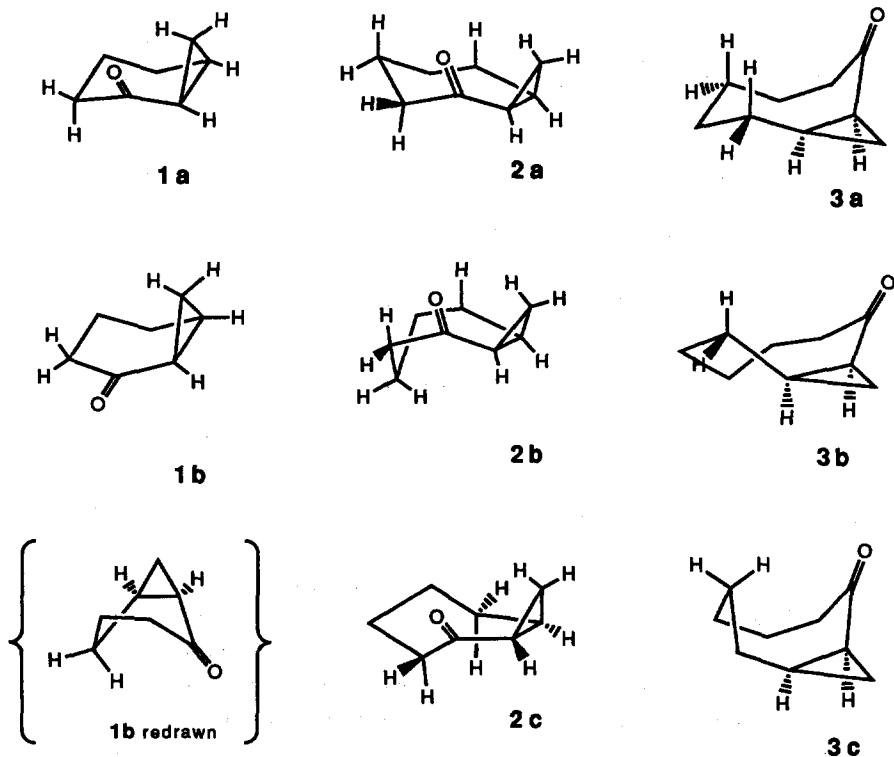
Figure 1. Conformations of **1, 2,** and **3** that lie within 3 Kcal/mol of the most stable conformation.

In compound **1** (m=4) the cyclopropyl ring will be constrained to be essentially axial, and the cyclohexanone ring will adopt either a flattened chair (**1a**) or boat (**1b**) form. In **1a** nucleophilic attack will be axial, leading to *trans* addition, while in **1b** the attack should come from the "outside" of the boat, leading to *cis* addition. The experimental ratios agree with the predicted **1a** : **1b** equilibrium based on a 0.43 Kcal/mol difference in strain energy. Similarly, in compound **2** (m=5) the cycloheptanone ring could exist in a slightly flattened chair (**2a**), boat (**2b**), or twist (**2c**) form. Only **2a** and **2b** should contribute significantly to the equilibrium mixture, and the theoretical analysis shows that the course of the attack by a nucleophile should parallel the previous series, in agreement with the experimental results.

With bicyclo[6.1.0]nonan-2-one (**3**) the total number of low energy conformations increases to 21, but three (**3a-c**) will comprise > 99% of the equilibrium mixture of starting materials. In all three conformers the cyclopropyl ring assumes a pseudo equatorial position with the median planes of the two rings being nearly parallel, while the carbonyl is canted strongly upwards from the median plane of the ring (**3a** $\theta = 116°$, **b** $\theta = 123°$, **c** $\theta = 103°$). In these conformers, steric hindrance to nucleophilic attack does not come from the cyclopropyl hydrogens, <u>but from protons attached to carbons γ or δ to the carbonyl carbon</u>. The PLUTO plot of **3a** shown in Figure 2 emphasizes how the smaller ring lies out of the way.
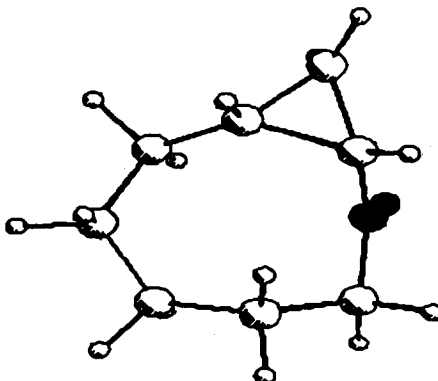

Figure 2. PLUTO plot of **3a**, as seen from the α-face, with the carbonyl (shaded) pointed away.

To help understand the reasons why this occurs, an MM2 Torsional Driver study was done on *cis*-1-acetyl-2-methylcyclopropane, the results of which are shown in Figure 3. It can be seen that there are two deep minima at approximately +90° and -90°. If a ring is then constructed by "connecting a methylene chain between the methyl grou as shown above each minima, the syn and anti conformations shown are obtained. Nucleophilic attack on these two conformations should respectively lead to predominantly *trans* and predominantly *cis* products. Since the syn conformation corresponds to the deeper minimum, we would expect that this conformation would be preferred in those rings which are large enough to be able to span these terminii without strain. Table 1 also shows the torsion angle of the corresponding bonds in **1**, **2**, and **3**.

The 6 and 7 membered ring systems of **1** and **2** are clearly not large enough to bridge the terminii without strain, and thus the angles are substantially closed. This leads to an overall flattening of the ring system and decreased selectivity. The effect is stronger in the [4.1.0] system ($8 \leq |\tau| \leq 19$) than in the [5.1.0] system ($48 \leq |\tau| \leq 68$), which is mirrored in the selectivity (2:1 *vs* 5:2).

Conversely in the 8 membered and larger ring systems the cyclopropyl-acyl section can approach the desired ±90° torsion angle which leads to the syn or anti forms shown in Figure 3. The strain in these conformers will come from a mixture of the torsional strain of the 1-acyl-2-methyl-cyclopropyl section, transannular strain between the methylene bridge and the cyclopropyl bridge, and the internal strain of the methylene bridge. The syn form is preferred by the first and second terms. The third term will always be proportional to the first term (if either portion of the molecule is more strained, the other portion will deform until they are roughly isoenergetic). *Thus, we expect the syn form to*

predominate in all such rings. Consequently we would expect to see selective attack from the outer face of the carbonyl of the more stable syn conformer(s) to give predominantly the *trans* product, in agreement with experimental results.
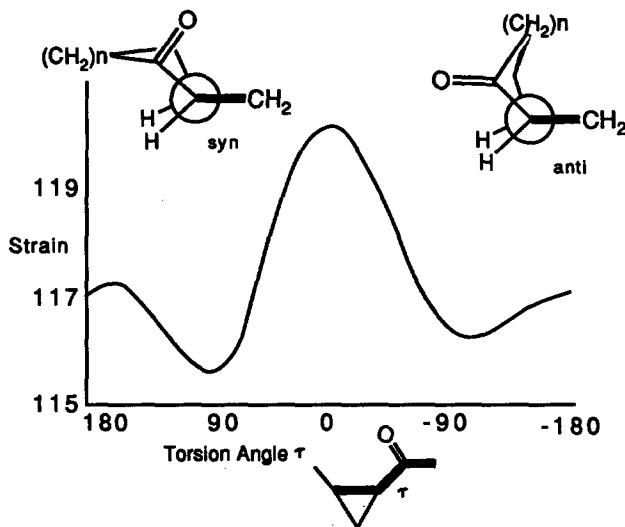

Figure 3. MM2 Torsion Angle Driver Results for *cis*-1-acetyl-2-methylcyclopropane, and the rings systems which correspond to the minima. (Note that the Newman projections are along the 1,2 bond of the cyclopropyl ring. The cyclopropyl ring is shown as a bold line).

Confirmatory evidence for this hypothesis comes from two sources: In the [6.1.0] compound (3) we do find a parallel series of anti conformations, beginning at 128.265 Kcal (< 1% S.M. equilibrium) interleaved with those syn conformations which possess a higher degree of internal strain. Secondly, although we cannot use WIZARD to systematically study the larger ring systems at this time, partial studies *via* Monté Carlo methods show similar trends with interleaved syn and anti conformations, and hindrance to nucleophilic attack due to γ and δ annular protons instead of the cyclopropyl protons. Extensions to WIZARD to allow it to predict conformations of large ring systems are now underway, and will be reported when complete.

1) Mash, E.A., Kaczynki, M.A., Dolata, D. P., *Tetrahedron Lett.,* **1990**, *31*, 0000.
2) Full details of these other considerations, which include AM-1 calculations of heats of formations, will be published in a more comprehensive paper.
3) a) Dolata, D.P., Carter. R.E.; *J. Chem. Inf. and Comp. Sci.,* **1987**, *27*, 36.
   b) Leach, A.R., Prout C. K., Dolata, D. P.; *J. Comp Chem.,* **1990**, *11*, 680.
4) Monté Carlo - Dolata. D. P.; Manuscript in Prep.
   MM2 - Burkert,U.; Allinger, N.L. *Molecular Mechanics*; American Chemical Society: Washington DC, 1982.
5) We recognize that this is an oversimplification based on ΔH rather than ΔG. This will be covered in a later paper.
6) The position of the dummy nucleophile was chosen to be commensurate with the transition state as predicted by Houk, *et al.* We are currently modeling the actual reaction path utilizing MOPAC/PM3, and will report that in a later paper.
   a) transition states - Houk, K., N., *et al,* Science, **1986**, *231*, 1108, and references therein.
   b) MOPAC/PM3 - Stewart, J.J.P, FJSRL-TR-88-0007, US Air Force Academy, 1988.