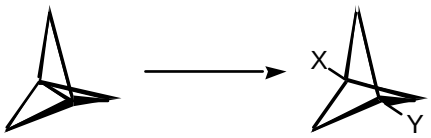
Determination of the *A*-value for the Bicyclo[1.1.1]pentane Ring

Dr. Kathleen R. Mondanaro, R.N., Ph.D., Saint Michael's College

Background and Significance Strained-ring compounds (SRCs) have significant deviations from preferred molecular geometries. This gives rise to unusual chemical reactivity and spectroscopic properties.[1-2] The driving force for much of the increased reactivity is the relief of strain which is often manifested as unusual reactivity of the carbon-carbon bonds. The extra energy of the hydrocarbon is derived from the bond-strain energy which is built into molecules with small ring systems. Molecules containing strained rings are often highly symmetric and have higher densities than less symmetric compounds. The high density and strain energy increases the heat of formation which leads to an increase in combustion energy. Adding these highly energetic hydrocarbons to conventional fuels can lead to improved performance as fuels, propellants and explosives.[1-2] Thus, strained-ring compounds have a broad range of applications in materials chemistry. Most of our work has focused on the synthesis of strained bicyclo[1.1.1]pentanes (BCPs, **2**) for these applications. BCPs are most conveniently synthesized from [1.1.1]propellane (**1**, Figure 1)[3].

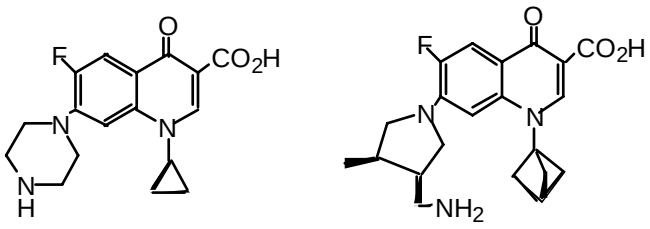


1 **2**

Figure 1

Recently, however, we have turned our attention to biological applications of strained-ring compounds. While our recent publication investigated the energy content of new diazeniumdiolates[**4**], these compounds also are known to have biological activity which, among other things, affects vasodilation and vasoconstriction. In addition, antibiotic resistance and the threat of biological warfare have stimulated researchers to incorporate non-natural rings like the BCP ring into analogs of pharmaceutical agents. For example, Barbachyn and co-workers found that replacing the cyclopropane ring of ciproflaxacin (**3**) with a bicyclo[1.1.1.]pentane ring, along with a modification of a distal amine ring produced an analog (**4**, U-87947-E, Figure 2) of ciproflaxacin (cipro) which was very effective against a

variety of both gram-positive and gram-negative bacteria, and was particularly effective against cipro-resistant strains of *Staph.* aureus.[5] Thus, replacing small rings in natural products with more strained, non-natural rings like bicyclo[1.1.1]pentane has the potential to be very effective in addressing concerns about antibiotic resistance. Cipro also is one of the most potent antibiotics used to treat anthrax which has generated much concern with regard to its potential as a biological warfare agent.



Ciprofloxacin **U-87947E**

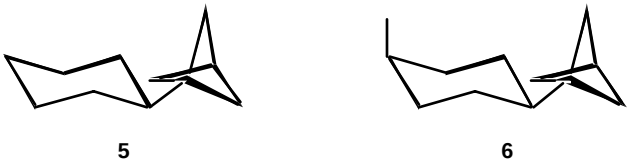
3 **4**

Figure 2

In these contexts, we have investigated more convenient synthetic routes into bicyclo[1.1.1]pentanes.[6] More efficient and convenient access to **1**, and thus to BCPs (**2**) in general, will benefit our on-going research in materials science and our relatively recent foray into investigating biological applications of SRCs. Our results will also enable others to investigate various medicinal agents to combat problems of drug-resistance; since little is known about how the bicyclo[1.1.1]pentane ring affects conformational stabilities and molecular energetics, a better understanding of how the strained BCP ring affects these parameters may be very helpful in drug design and synthesis.

Specific aims For the VGN project, we propose to determine the *A*-value[7] for the BCP group as a substituent on a cyclohexane ring. Our synthetic approach to the target molecules, bicyclo[1.1.1]pentylcyclohexane (**5**) and *cis*-1-bicyclo[1.1.1]pentyl-4-methylcyclo-hexane (**6**), is presented in Scheme 1. After optimization of the yield and purification of **6**, a variable temperature NMR study will be done to determine the difference in energy (*A*-value) between cyclohexane conformers with an axial- vs. equatorial- substituted

bicyclo[1.1.1]pentane (BCP) ring (Figure 4). The funds requested from VGN will provide supplies and 6.5 weeks of summer salary for the PI.



5 6

Figure 3

Chemical background and plans to address the specific aims It is well known that the lowest energy conformation of cyclohexane is the chair in which all of the carbon-carbon bonds are staggered. Conformers of alkyl-substituted cyclohexanes interconvert through a boat or twist boat conformation. Equilibrium concentrations of the conformers favor the one which has the largest substituent in the equatorial position so as to minimize unfavorable steric interactions between the substituent and the methylene carbons of C-3 and C-5 (Figure 4). Generally, the larger the substituent, the greater the preference for the equatorial conformer.[7]

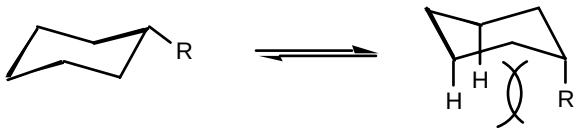


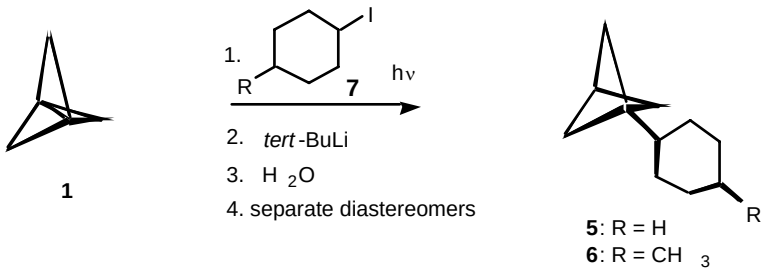
Figure 4

The free-energy difference between the conformers that have the substituent in the axial versus the equatorial position is called the *A*-value.[7] The *A*-values for several mono-substituted cyclohexanes have been measured by NMR.[7] The accepted *A*-values for the methyl, ethyl, isopropyl and *tert*-butyl groups are 1.74, 1.80, 2.15, and 4.9 Kcal/mol respectively.[7]

Molecular mechanics calculations have shown that bicyclo[1.1.1]pentane is closer in size to the isopropyl and cyclopropylmethyl groups, than to the *tert*-butyl group.[8,9] Interestingly, it has been shown that the reactivity of bicyclo[1.1.1]pentanes is more similar to the *tert*-butyl analogs than the corresponding isopropyl compounds.[8,9] These data, in addition to the aforementioned reasons for undertaking this study, piqued our interest in determining the *A*-value for the bicyclo[1.1.1]pentane ring as a substituent on cyclohexane.

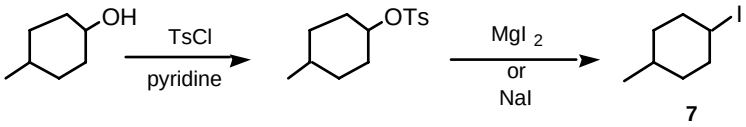
Calculations predicted the free-energy difference between the axial and equatorial conformers of 1-bicyclo[1.1.1]pentylcyclohexane (**5**, Figure 4, R = BCP) to be 3.4 Kcal/mol.[8] That suggests the ratio of conformers to be *ca.* 1:5000 at 200 K, favoring the equatorially-substituted conformer, and making it unlikely to be observable by NMR. The compound was synthesized and only one conformer was observed. The calculated data for *cis*-1-bicyclo[1.1.1]pentyl-4-methylcyclohexane (**6**), however, were more encouraging; the free-energy difference for **6** is predicted to be only 1.1 Kcal/mol, suggesting the ratio of conformers will be ~1:16 at 200 K.[8] The presence of a methyl group *cis* to the bicyclo[1.1.1]pentane should allow both conformers to be observed. We plan to do low temperature NMR studies to investigate the equilibrium. While several experiments are possible, we first will integrate the peak corresponding to the BCP ring to determine the percentage of each conformer present. Then variable temperature NMR studies will be done to see at what temperature the two peaks for the 'frozen out' conformers coalesce into one peak. The *A*-value will be abstracted from these data, taking into account the additivity of the methyl group (1.74 Kcal/mol).[7,8] Saint Michael's College currently does not have variable temperature NMR capability so these studies will be done at the University of Vermont.

Synthesis Our synthesis for **6** is illustrated in Scheme 1, and is based on the known synthesis of **5**.[6,8]



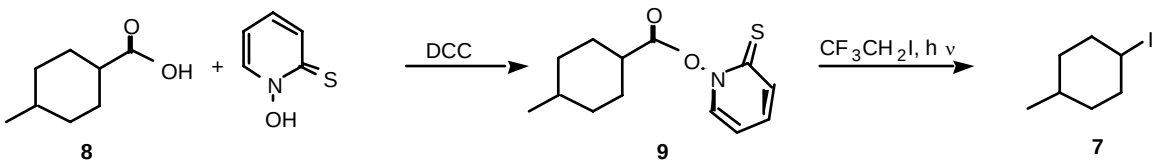
Scheme 1

Because 1-iodo-4-methylcyclohexane (**7**, R = CH_3) is not commercially available, it was necessary to synthesize this compound. Even with several attempts, we were unable to obtain sufficient quantities of **7** via either substitution method shown in Scheme 2.[10] Both procedures reported a low yield of **7**. Few experimental details were given so our results were not surprising.



Scheme 2

Recently, we have investigated an alternative method based on Barton's decarboxylation of bridgehead carboxylic acids.[11] We prepared the thiohydroxamic acid **9** of 4-methylcyclohexanecarboxylic acid (**8**), and irradiated it in the presence of 2-iodo-1,1,1-trifluoroethane according to the method of Della and coworkers[12] to afford **7** (R = CH_3) in 65% crude yield (Scheme 3). The reaction has not been optimized but is highly reproducible. We were delighted to find that the photochemical addition of **7** to **1** proceeded on the crude material as readily as we expected based on the synthesis of **5** (Scheme 1).



Scheme 3

Subsequent transformation of the photoadduct, as noted in Scheme 1, afforded a mixture of the expected *cis* and *trans* stereoisomers of **6**. Presently, we need to repeat the synthesis in order to make enough of **6** to permit preparative GC separation of the *cis* and *trans* isomers. Once purification of *cis*-**6** is accomplished, the VT-NMR studies will be done to determine the *A*-value for the bicyclo[1.1.1]pentyl group as a substituent on cyclohexane.

Time table and role of undergraduate research students The work described herein will be the project for one summer (2004) undergraduate research student during the VGN funding period. Starting from [1.1.1]propellane, an undergraduate can make a gram (or more) of the target molecule in about a week. The remainder of the funding period will be devoted to purification of the compound, the NMR experiments, and completing the manuscript for publication of this study.

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