ENERGIES OF ORGANIC COMPOUNDS

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Abstract

The enthalpy of reduction of lactones to the corresponding diols has been determined, allowing the enthalpies of formation of the lactones to be determined. The results of this study agree well with the data we have obtained for the enthalpies of hydrolysis of the lactones. We have begun the measurement of the enthalpies of reduction of norbornanones, and we have shown that it is possible to determine the difference in energy between the exo and endo forms of the product alcohols by measuring the equilibrium constant as a function of temperature. The study of the enthalpies of hydration of carbonyl compounds has continued, and the enthalpies of hydrolysis of the corresponding ketals is being determined. The study of the enthalpies of hydration of alkenes is nearly completed, and the rearrangement reactions which were uncovered are being investigated.

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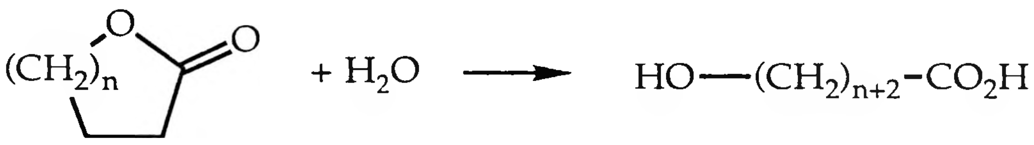
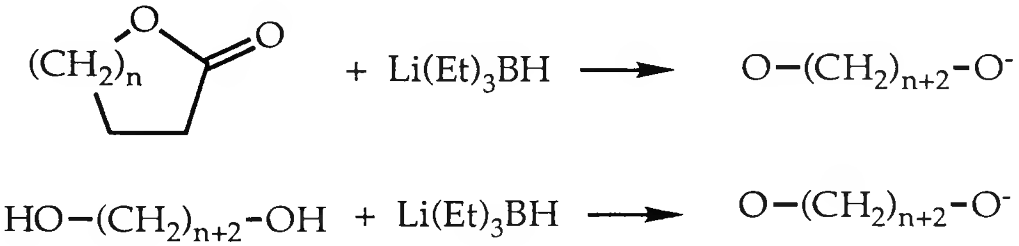
Progress Report

a. **Enthalpy of reduction of lactones.** We have been particularly interested in lactones because this type of ring system occurs in a wide variety of important naturally occurring compounds. There is considerable interest in being able to model these compounds in a reasonably accurate fashion. We have recently completed a study of the enthalpies of hydrolysis of the 5-14 membered ring lactones to the corresponding hydroxyacids:

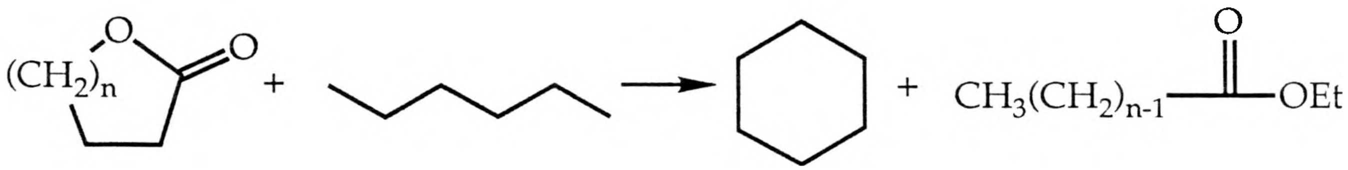


Here, we measure the enthalpy of reaction of the lactone with base in aqueous dioxane, and of the hydroxyacid with the same solvent. From these data, and the enthalpies of hydrolysis of ethyl esters with the same number of carbons (which we also have measured), we have been able to make estimates of strain energies.

Since the enthalpies of formation of the hydroxyacids were not known, it was not possible to derive enthalpies of formation. Our new ability to measure the enthalpies of reduction of carbonyl compounds vis reaction with lithium triethylborohydride in triglyme made it possible to study the enthalpies of reduction of the lactones. All but two of the above lactones have been studied in this fashion, and the remaining ones are currently being studied. Here, the enthalpies of formation of the product diols are in many cases known, and the data for the remaining compounds may be estimated by interpolation from the available data.



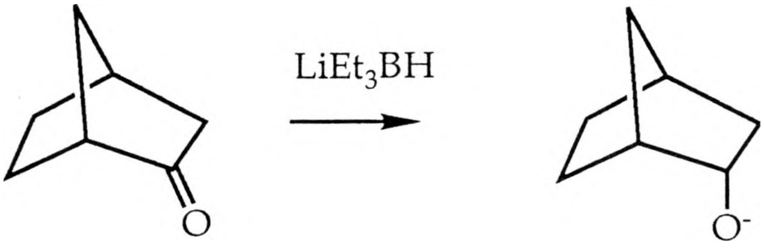
Having the enthalpies of formation, the strain energies may be derived in a straightforward fashion via the use of reactions such as:



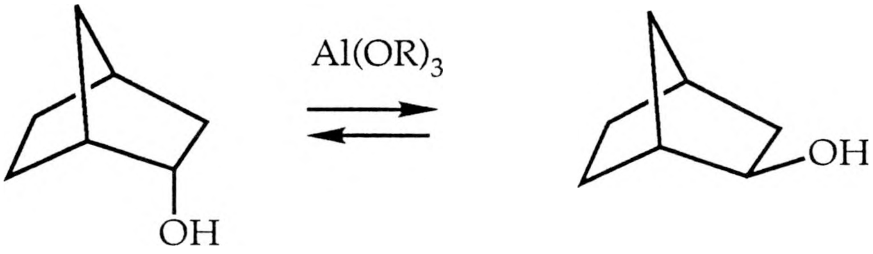
Here, all the compounds are conventionally considered as strain free, except for the lactones. The enthalpies of formation of the ethyl esters are available from our measurements of their enthalpies of hydrolysis. We anticipate that this project will be completed by the end of this calendar year.

b. **Enthalpy of reduction of carbonyl compounds.** A number of our measurements of the enthalpies of reduction of aldehydes and ketones have been repeated by a second student, using different batches of reagents and solvents, giving results in good accord to those previously obtained. This gives us confidence that our procedure gives reliable results, despite the several points of disagreement with the data in the literature. MM3 calculations have been carried out for all of the compounds studied, and for the open chain compounds, there is generally good agreement. Somewhat larger differences were found with some cyclic compounds. The results of this investigation are being prepared for publication, and should be submitted by the end of summer.

We have now turned to the norbornyl compounds previously studied via measurement of the enthalpies of hydrolysis of the ketals. We chose these compounds for study since they have rigid, well defined conformations, and allow a variety of substitution patterns. This should allow us to gain a better insight into the modes of interaction of alkyl groups with carbonyl groups.



We have carried out the reduction of 2-norbornanone, and it proceeds well. The product is mainly the endo alcohol. The relative energies of the exo and endo alcohols may be determined by equilibration in the presence of an aluminum alkoxide, and determining the equilibrium constant as a function of temperature. We have shown that the two alcohols can be separated by gas chromatography, and that we can determine their ratio with good precision.



Having both the enthalpies of reduction, and the difference in enthalpy between the two epimeric alcohols, we will be in a position to make detailed comparisons with the predictions of MM3 and other force fields.

c. **Enthalpies of hydration of carbonyl compounds.** We have studied the enthalpies of hydration, and the enthalpies of hemiketal and ketal formation by direct nmr measurements as a function of temperature. Some of the values thus obtained appeared to be somewhat unusual, and therefore we are determining the enthalpy changes for the ketal formation directly via measurements of the enthalpy of hydrolysis of the ketals.

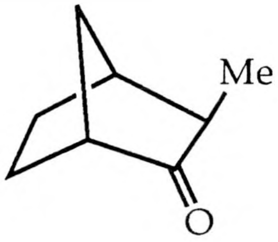
We are carrying out an extensive set of calculations for these equilibria in order to try to understand the factors which contribute to the wide, range of observed equilibrium constants. There is a significant change in dipole moment as a result of the reactions, and therefore one would anticipate a significant solvent effect. We have recently begun modelling solvent effects in the context of ab initio molecular orbitals theory via the use of the reaction field model, and it will be applied to some of these cases also.

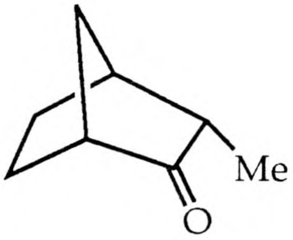
The wavefunctions which result from the calculations are being analyzed in terms of Bader's theory of atoms in molecules in order to obtain physically meaningful electron populations and atom energies.

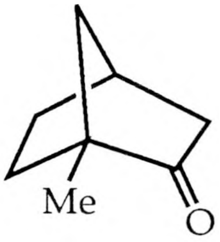
d **Enthalpies of hydration of alkenes.** We have essentially completed our experimental work on this reaction, and the results are being prepared for publication. We have had some difficulty with the measurement of the enthalpies of hydration of methylcyclobutene and methylenecyclobutane. In order to obtain a better measure of the difference in energy, we are determining the equilibrium constant as a function of temperature. We have found that sodium on alumina is a very effective agent for achieving equlibration.

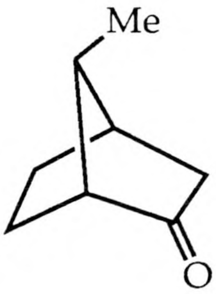
Proposed Studies

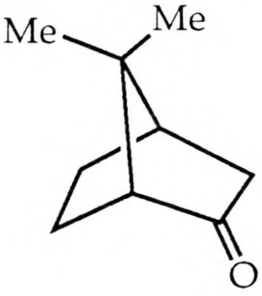
a. **Enthalpies of reduction of carbonyl compounds.** Now that we have shown that norbornanone can be satisfactorily studied, we plan to determine the enthalpies of reduction of the following norbornane derivatives:

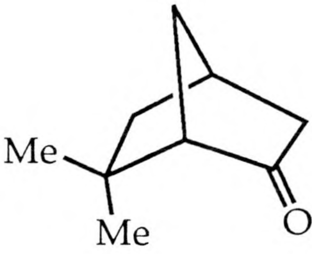


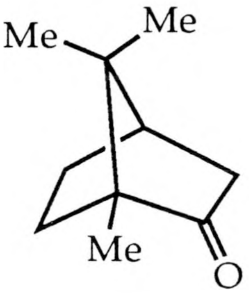


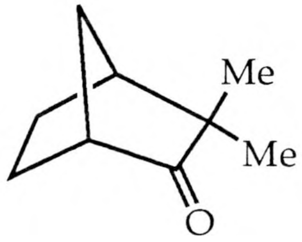


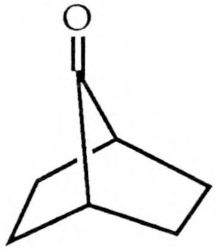








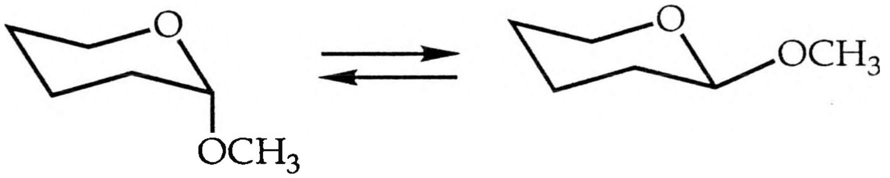




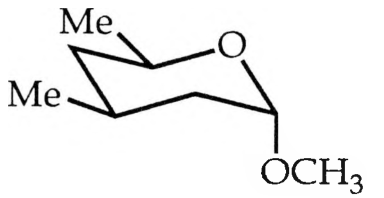
They are the compounds we previously studied via measurement of the enthalpies of hydrolysis of the corresponding ketals. The interaction of the methyl group with the carbonyl should disappear in the product alcohols, and therefore the differences in enthalpies of reduction will be quite interesting. The difference in energy between the exo and endo alcohols will in each case be determined via equilibration experiments. The set of data thus obtained will provide a very good test of force field for molecular modelling.

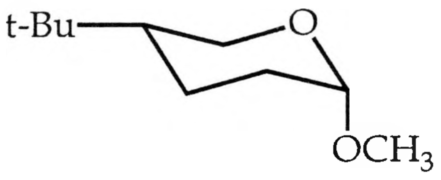
It should be noted that most of the compounds will have to be prepared, and so this investigation represents a considerable undertaking.

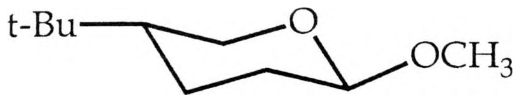
b. **The enthalpy component of the anomeric effect.** The anomeric effect has a direct effect on the energies and conformation of molecules with two oxygens attached to a given carbon, and also appears to have some importance for nitrogen and sulfur substituents. In our theoretical study of the anomeric effect, we found a difference in energy between axial and equatorial methoxytetrahydropyran of 1 kcal/mol in good agreement with the experimental ΔG value. The axial form was the more stable in contrast to cyclohexane derivatives where the equatorial form would be favored at equilibrium. However, the ΔH reported was close to zero and it was believed that the effect was entropy controlled. We calculated the entropy change, and found it to be essentially zero. Thus, theory and experiment lead to opposite conclusions for the origin of the conformational difference.



In order to have a better experimental value for the energy difference, we are planning to prepare the following compounds, and to determine their enthalpies of hydrolysis. The substituents will lock the conformations and so the two forms may be isolated and studied separately. The difference in enthalpy of hydrolysis will directly give the enthalpy difference between the conformers.

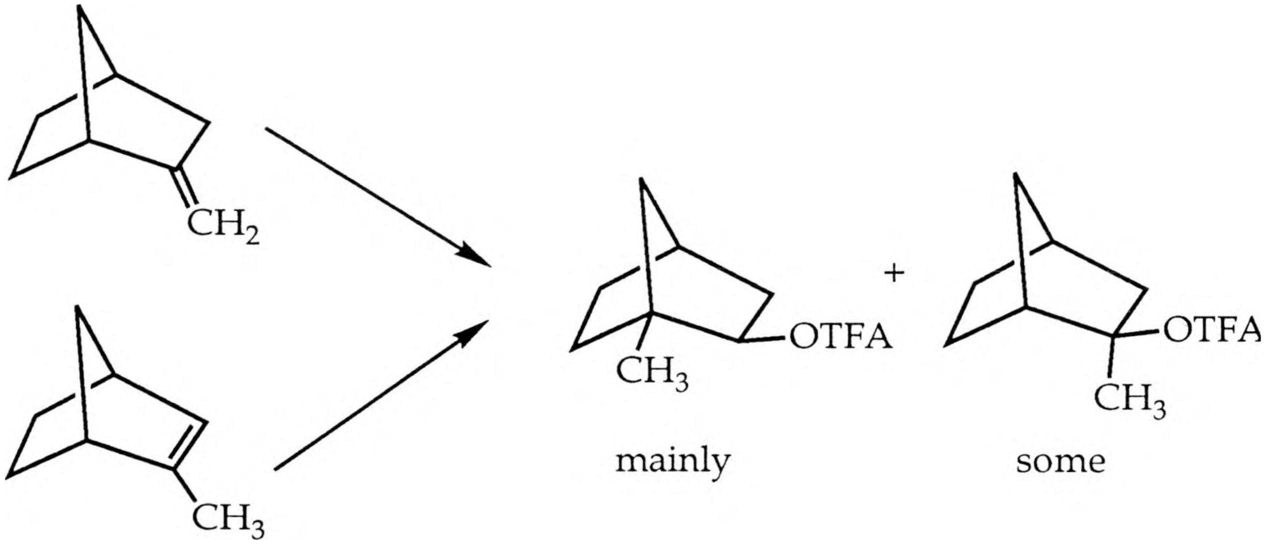






This study will provide one of the first direct determinations of the energetic component of the anomeric effect.

c. **Rearrangements in alkene hydration.** We should like to complete our study of alkene hydration by clarifying the nature of some of the rearrangements which we observed. In the case of 2-methylenenorbornane and 2-methyl norbornene, we observed that the major product was the 1-methyl-2-norbornyl trifluoroacetate, rather than the expected 2-methyl-2-norbornyl trifluoroacetate.



We plan to try to determine the energy difference between the products via equilibration experiments, and we will carry out other experiments along with MM3 calculations in order to try to gain an understanding of the nature of this reaction.

Whereas the hydration of methylenecyclopentane and of methylene cyclohexane proceeded well and gave single products and very reproducible results, the corresponding reactions of methylenecycloheptane and of methylenecyclooctane were irreproducible and gave mixtures of products. We plan to determine the structures of the products and their ratios, and then to carry out additional studies designed to show why these reactions are so different from the others we have studied.

d. **Enthalpies of hydration of carbonyl compounds.** We have determined the enthalpy of hydrolysis of cyclohexanone dimethyl ketal, and we plan to prepare and study the ketals from the following ketones: cyclobutanone, cyclopentanone, cyclohexanone, cyclooctanone, and 7-norbornanone so that they may be compared with the results of direct measurement of the equilibrium constant for the formation of the ketals from the ketones and methanol. Similar measurements for some key acetals also are planned.

The calculations for these compounds will be completed and analyzed so that we may achieve an understanding of the origin of the differences in equilibrium constants.